Treatment of Children and Adolescents with Schizophrenia

The evidence base pertaining to the pharmacotherapy of schizophrenia in children and adolescents (C&A) is tiny compared to what is available for adults. Only 5 studies are double-blind, randomized, prospective investigations, all with small numbers of patients.(1,2) Nevertheless, the literature in aggregate suggests important areas of agreement with practices supported in the adult literature, although there are some nuances where practice should perhaps differ.

Key Findings, with Recommendations

1. The available data support using two or more monotherapy antipsychotic trials with typical or atypical antipsychotics before prescribing clozapine.(2,3)
2. Adolescent and early onset young adult patients have a lower rate of adherence to antipsychotic medications compared with adults.(4) Though there are many factors contributing to non-adherence, careful attention to side effects seems particularly important in C&A patients.
3. Although children (age 10-19) seem more susceptible to extrapyramidal side effects (EPS) of typical antipsychotics than adults(5,6), many studies have demonstrated that second generation antipsychotics cause a low rate of EPS in the C&A population.(2,3,7,8) The risk of tardive dyskinesia also appears to be lower with the atypicals, possibly because of the lower risk of EPS. In one study, patients with a history of EPS on an atypical had a higher risk of later tardive dyskinesia.(9)
4. As in adults, risperidone seems to have a higher rate of EPS than the other second generation antipsychotics in C&A patients. However, in adults, there is good evidence that using lower doses to minimize EPS is the optimum approach with this antipsychotic, *and moreover* it produces a better clinical outcome.(6) *A review of 10 C&A studies with risperidone (unpublished manuscript) found comparable efficacy at doses from 2 mg to 6 mg per day, but the rate of EPS was 4% when the mean dose was 2 mg per day (N=195), 15% with a mean of 3 mg (N=93), 60% with 4 mg (N=33), and 50% with 6 mg (N=26).* It is recommended that better efforts to avoid these side effects be made, such as by employing initial doses of risperidone as low as 0.125 mg twice a day in patients age 10 or less (10), *and 1-2 mg with others.* Furthermore, it is suggested that any dose of risperidone that produces EPS may be too high a dose for that patient and should be lowered. Note that when compared to adults, C&A patients have increased cytochrome P450 activity in all phase I enzymes *except* 2D6.(11) Risperidone is a 2D6 substrate, and therefore C&A patients do not metabolize risperidone as efficiently as they do other atypicals. This may explain the apparent sensitivity of C&A patients to risperidone.
5. Dosing with olanzapine in C&A should be closer to adults, typically about 10 mg per day(12): high levels of cytochrome P450 1A2 enzyme activity is probably the reason for the relatively higher dosage requirement in young patients.(11)
6. Weight gain is a very common and important side effect of risperidone and olanzapine in C&A patients.(13,14) "Extreme" weight gain that has been

observed with both medications, although one prospective comparative study did find significantly more weight gain with olanzapine vs. risperidone,(13) as has been noted in several adult studies.(6) Quetiapine has also been associated with large weight gains over the long term, but other factors could have contributed to the weight gain in this study.(15)

7. Quetiapine doses should also probably be closer to adult levels when treating C&A patients: quetiapine is mainly a substrate of the cytochrome 3A4 enzyme, which was also found to have increased activity in C&A patients.(11) Supporting this, a study of 10 adolescents with schizoaffective disorder responding well to quetiapine over one year found that the mean dose was 600 mg per day.(15)
8. Ziprasidone has been used in C&A patients with Tourette's syndrome and appeared safe and efficacious,(16) but there has been no significant literature in schizophrenia as yet. It is metabolized in part by the 3A4 enzyme, so doses should be closer to adults. A recent report indicates that the QTc measurements from routine EKGs in C&A patients are valid and appropriate to use in monitoring safety when using this antipsychotic.(17)
9. Clozapine is effective in treatment-resistant schizophrenia but seems to have a very high rate of side effects in C&A patients including sedation (80%), seizures, and neutropenia.(3), especially when compared with experience in adults using low doses.(18) This may be due to high 1A2 enzyme activity in C&A patients: Clozapine is metabolized in part by 1A2, and levels of the metabolite norclozapine have been found to be high in C&A patients, and norclozapine levels correlated with side effects.(19)
10. Amisulpride has been reported to be effective and well tolerated in 10 adolescents in a study from Germany.(20) *Aripiprazole was reportedly used in 12 children and 11 adolescents with behavior disorders at doses from 1 to 10 mg per day.(21) Neither has significant evidence of use in schizophrenia as yet.*

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References

1. Weisz JR, Jensen PS. Efficacy and effectiveness of child and adolescent psychotherapy and pharmacotherapy. Mental Health Services Research 1:125-158, 1999 Decades of intervention research have produced a rich body of evidence on the effects of psychotherapies and pharmacotherapies with children and adolescents. The authors summarize and critique that evidence. In general, the large body of evidence on efficacy contrasts sharply with the small base of evidence on effectiveness.
2. Campbell M, Rapoport JL, Simpson GM. Antipsychotics in children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry 38;537-545, 1999 This is a critical overview of the available evidence for the efficacy and safety of antipsychotic agents in children and adolescents and to identify knowledge gaps and needs for further research. It was concluded that currently available standard antipsychotics have a definite role in the treatment of children and adolescents, but the use of these agents is limited mainly by tardive and withdrawal dyskinesias and, in some patients, by excessive sedation. The atypical antipsychotics should be critically assessed and compared with psychosocial interventions.
3. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. Archives of General Psychiatry 55:1090-1097, 1996 In this study, the efficacy and adverse effects of clozapine and haloperidol were compared for 21 children and adolescents with early-onset schizophrenia. Clozapine has striking superiority for positive and negative symptoms in treatment-refractory childhood-onset schizophrenia. However, due to possibly increased toxic effects in this pediatric population, close monitoring for adverse events is essential.
4. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatrica Scandinavica 106:286-90, 2002. Two hundred admissions to an Early Psychosis Program were evaluated for medication adherence. In their first year in the program 39% were non-adherent, 20% inadequately adherent, and 41% adherent. It was concluded that non-compliance has to be anticipated and relationships maintained with patients and families to intervene as soon as possible to minimize the consequence of non-compliance.
5. Keepers GA, Clappison VJ, Casey DE. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. Archives of General Psychiatry 40;1113-1117, 1983. 215 psychotic inpatients were reviewed. Initial prophylaxis with anticholinergic drugs significantly reduced the occurrence of EPS. Efficacy depended on a complex interaction of variables, including the patient's sex and age, antipsychotic drug type and dose, and treatment phase.
6. Osser DN, Sigadel R. Short-term inpatient pharmacotherapy of schizophrenia. Harvard Review of Psychiatry 9:89-104, 2001 This paper reviews the literature to determine the optimal strategies for using the various antipsychotics, especially the atypicals available at that time. Risperidone was found to work best at doses

that minimized extrapyramidal side effects. Head-to-head comparisons were evaluated, and olanzapine produced more weight gain than risperidone.

7. Armenteros JL, Whitaker AH, Welikson M, et al. Risperidone in adolescents with schizophrenia: an open pilot study. Journal of the American Academy of Child and Adolescent Psychiatry. 36:694-700, 1997 OBJECTIVE: This paper assessed the short-term efficacy and safety of risperidone in 10 adolescents with schizophrenia. Clinically and statistically significant improvement was seen on the PANSS, BPRS, and CGI at a mean dose of 6.6 mg/day. There were no major adverse reactions.
8. McConville BJ, Arvanitis LA, Thyrum PT, et al. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. Journal of Clinical Psychiatry 61;252-60, 2000. Ten patients with DSM-IV chronic or intermittent psychotic disorders (ages 12.3 through 15.9 years) participated in an open-label, rising-dose 3-week trial and received oral doses of quetiapine starting at 25 mg b.i.d. and reaching 400 mg b.i.d. by day 20. Quetiapine was well tolerated and effective. The most common adverse events were postural tachycardia and insomnia.
9. Connor DF, Fletcher KE, Wood JS. Neuroleptic-related dyskinesias in children and adolescents. Journal of Clinical Psychiatry 62:967-974, 2003. This prospective study was completed to test whether clinical use of atypical antipsychotics is associated with less risk for developing neuroleptic-related dyskinesias than clinical use of typical neuroleptics in an unselected heterogeneous population of seriously emotionally disturbed youths admitted to acute residential treatment. Of 102 antipsychotic-treated youths, 5.9% had probable tardive dyskinesia, a rate less than the prevalence of tardive dyskinesia in chronic neuroleptic-treated adults. Use of typical neuroleptics was significantly ($p = .03$) associated with dyskinesia compared with use of atypical antipsychotics.
10. Baldessarini RJ. Dosing of antipsychotic agents in pediatric populations. (editorial). Journal of Child and Adolescent Psychopharmacology 5:1-4, 1995.
11. Leeder JS, Kearns JL. Pharmacogenetics in pediatrics: implications for practice. Pediatric Clinics of North America 44:55-77, 1997. Drug biotransformation phenotype may be influenced by disease (e.g., infection), environmental factors (e.g., diet and environmental contaminants), concurrent medications, and developmental stage. Knowledge of these factors is essential for optimum treatment.
12. Grothe DR, Calis KA, Jacobsen L**,** et al. Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. Journal of Clinical Psychopharmacology 20:220-225. Eight inpatients (ages 10-18 years) with treatment-resistant childhood-onset schizophrenia received olanzapine (2.5-20 mg/day) over 8 weeks. Olanzapine concentrations were of the same magnitude as those for nonsmoking adult patients with schizophrenia but may be as much as twice the typical olanzapine concentrations in patients with schizophrenia who smoke. The usual dose recommendation of 5 to 10 mg once daily with a target dose of 10 mg/day is likely a good clinical guideline for most adolescent patients.

13. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. Journal of the American Academy of Child and Adolescent Psychiatry 41:337-343, 2002. Hospitalized adolescents treated with olanzapine (n = 21), risperidone (n = 21), or haloperidol (n = 8) were prospectively monitored on a weekly basis for the first 12 weeks of treatment. Average weight gain was significantly higher for the olanzapine group (11%) than for the risperidone (7%) and haloperidol (1.5%) groups. Extreme weight gain (>7%) was recorded in 19 patients (91%), 9 patients (43%), and 1 (13%) patient, respectively.
14. Martin A, L'Ecuyer S. Triglyceride, cholesterol and weight changes among risperidone-treated youths: a retrospective study. European Child and Adolescent Psychiatry 11:129-133, 2002. Twenty-two patients with mean age 13 were treated with risperidone, mean dose 2.7 mg, for an average of 5 months. Weight gain averaged 15 lb. No significant changes in serum triglyceride or cholesterol levels were seen in the group as a whole.
15. McConville B, Carrero L, Sweitzer D, et al. Long-term safety, tolerability, and clinical efficacy of quetiapine in adolescents: an open-label extension trial. Journal of Child and Adolescent Psychopharmacology 13:75-82, 2003. This is an 88 week extension of a previously cited study of 10 adolescents with diagnoses of schizoaffective disorder (n = 7) or bipolar disorder with psychotic features (n = 3). The results indicated that quetiapine is a well-tolerated antipsychotic agent that is efficacious for the treatment of symptoms of selected psychotic disorders in adolescents.
16. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's Syndrome: a pilot study. Journal of the American Academy of Child and Adolescent Psychiatry 39:292-299, 2000. Twenty-eight patients aged 7 to 17 years were randomly assigned to ziprasidone or placebo for 56 days. Ziprasidone was initiated at a dose of 5 mg/day and flexibly titrated to a maximum of 40 mg/day. The mean final dose was 28 mg. Ziprasidone was safe and effective for this indication.
17. Hassan F, Richards MP, Quinlan PE, Alessi NE. QTc values in children and adolescents: machine versus hand-derived values. New Research Abstracts NR155, American Psychiatric Association Annual Meeting, San Francisco, CA, May 19, 2003. Some have proposed that machine-derived QTc measurements are inaccurate in the pediatric population. QTc's on EKGs of 15 ziprasidone-treated C&A patients were evaluated manually with calipers and compared with the machine calculations. There was no significant difference. See also abstract NR186 for more data on this study.
18. Naber D, Holzbach R, Perro C, Hippius H. Clinical management of clozapine patients in relation to efficacy and side-effects. British Journal of Psychiatry 160(suppl. 17):54-59, 1992. Medical charts of 480 schizophrenic in-patients were analyzed to evaluate the efficacy and side-effects of clozapine (mean 49 days). Clozapine treatment lasted for mean 49 days and the mean final dose was 215 mg/day. 11.0% showed worsening or no change, 31.5% slight improvement, 53.0% marked improvement and 4.5% almost total reduction of symptoms. Clozapine treatment had to be discontinued because of severe side-effects in 8.6%

of patients. This study indicates a satisfactory benefit/risk ratio and compliance in most of the patients.

19. Frazier JA, Cohen LG, Jacobsen L, et al. Clozapine pharmacokinetics in children and adolescents with childhood-onset schizophrenia. Journal of Clinical Psychopharmacology 23:87-91, 2003. Clozapine (mean dose 200 mg) and its metabolites, norclozapine, and clozapine-N-oxide were studied in six youth, ages 9-16 years, with childhood onset schizophrenia. Clinical improvement seen in 5/6 patients correlated with serum clozapine concentrations. In addition, clinical response and total number of side effects correlated with norclozapine concentrations.
20. Gopel C, Marcus A. Initial experiences with amisulpride, an in Germany novel, atypical neuroleptic drug in treatment of adolescents with psychiatric disorders. [article in German]. Z Kinder Jugendpsychiatr Psychother. 29:230-8, 2001. Ten adolescent cases were treated with amisulpride. Results were promising and the rate of side effects was tolerable. Controlled studies are warranted.
21. Findling R. Preliminary data suggest that aripiprazole improves symptoms of conduct disorder in both children and adolescence. New Research Abstract 33. 16th U.S. Psychiatric & Mental Health Congress. Orlando, Florida, November 6, 2003. The investigators gave 1 mg if patients were under 25 kg, 2 mg if 25-50 kg, 5 mg if 50-70 kg, and 10 mg if over 70 kg. Similar pharmacokinetics were found as in adults. Some vomiting and somnolence occurred, that tended to improve with dosage optimization.