

Decision Making About Children With Psychotic Symptoms: Using the Best Evidence in Choosing a Treatment

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A school guidance counselor contacts your office worried about an 11-year-old boy, Peter, initially referred to her for declining school performance. Along with the counselor you meet with the child and his sole parent, Susan, who is a 34-year-old part-time nursery school teacher. Throughout the interview, Peter appears perplexed and frightened and is extremely evasive, giving monosyllabic answers to nearly all questions. His mother tells you he had rather late developmental milestones and little interest in his peers, but was managing at a mainstream school with support until a year ago, when he began to complain that the children were "really out to get me," and at times would appear terrified when left at the school gates. Twice during the past month, he has claimed that he heard a group of "bad boys" screaming insults at him, although the mother was certain there was no one else present. Despite these changes in Peter, his mother does not feel he has been unusually sad, and although he lacks drive, he stills retains some of his interest in computer games and has been sleeping and eating well. He is in good health and recently had a normal physical examination by a pediatrician. In addition, the mother gives a history

of bipolar affective disorder in her brother and states that Peter's biological father had a psychotic episode shortly before he left the family. What is the likely differential diagnosis?

Peter presents with brief self-limited hallucinations and persecutory ideation (if not frank delusions) on a background of a gradual deterioration in overall functioning. Affective symptoms are not prominent, and there is little to suggest an organic contribution. This raises the possibility that Peter has, or is on the verge of developing, a psychotic disorder, perhaps childhood-onset schizophrenia (COS), defined by the presence of symptoms before the 13th birthday. Although this must be considered in the differential, it is important to remember that COS is extremely rare. For example, a Canadian study of diagnoses on drug prescriptions indicates that the rate of schizophrenia at an age younger than 15 is 1/50th the rate in adults (Beitchman, 1985). A study of hospital admissions of 312 psychotic youth during a 13-year period in Denmark found only 4 patients were younger than 13 years (Thomsen, 1996).

The National Institute of Mental Health (NIMH) Cohort

Our experience at the NIMH would indicate that 95% of 1,500 children referred because of a high clinical suspicion of COS did not meet unmodified *DSM-IV* criteria for schizophrenia. By far the most common final diagnosis, reached after inpatient observation off all medication, was a mood disorder. Hallucinations are relatively common in pediatric bipolar disorder and major depression (Chambers et al., 1982; Varanka et al., 1988). However, the psychotic symptoms in these conditions tend to be mood congruent, and follow-up studies on this population generally suggest a stable

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The patient described in the article is not based on any individual, but rather reflects the breadth of clinical experience obtained during the research program into childhood onset schizophrenia at NIMH over the past 15 years.

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clinical outcome (Garralda, 1984b; McClellan and McCurry, 1999; McClellan et al., 1999; Ulloa et al., 2000). Such results support the adage that an atypical presentation of a common disorder is more likely than a typical presentation of an extremely rare illness.

Atypical psychosis, usually classified as psychosis not otherwise specified, is another common diagnosis. NIMH researchers have used the term *multidimensionally impaired* to capture the mix of stress-related transient episodes of psychosis, emotional lability, impaired interpersonal skills, and information-processing deficits that these children exhibit (Frazier et al., 1994; Kumra et al., 1998). Pervasive developmental disorders and childhood disintegrative disorder can often be mistaken for psychosis because they show severe impairment in reciprocal communication, social interactions, and odd stereotyped behaviors. Finally, rarely conduct disorder and various other behavioral disturbances can be associated with hallucinations (Garralda, 1984a, b)

PETER AT RISK

You meet with Peter several times, and his mental state remains unchanged over a month. His mother is extremely worried that he is "becoming psychotic like my brother" and asks your opinion as to how likely it is that he is developing schizophrenia. She also asks whether there are any medications that might help.

Peter thus certainly fits the profile of a child at ultrahigh risk of developing psychosis, and this raises the difficult question of how to manage and possibly treat him. Treatment may be justified because the prodromal or prepsychotic state is itself problematic for Peter, and interfering with his progress at school. In addition, there is the hope that treatment at this stage may avert psychosis entirely; the evidence of this is considered below. Weighed against intervention are several ethical and pragmatic concerns. First, even the best current criteria of ultrahigh risk are far from perfect and carry a high rate of false positives. Thus, many subjects will be potentially exposed to medications or other treatments without any clear evidence that they would have developed psychosis if left untreated. Second, intervention entails contact with psychiatric services and the label of being at risk of developing psychosis, both of which are likely to carry some social stigma.

To evaluate the evidence that treatment at this stage can avert psychosis entirely, you decide to look at the literature. You do a search on the open-access database

PubMed using the terms "high risk AND psychosis" and limit the search to randomized, controlled trials. You get 17 hits and find two papers that look relevant (McGorry et al., 2002; Morrison et al., 2004). You are puzzled at finding so few reports and so search again with the terms "prodrome AND schizophrenia," again limiting the search to randomized, controlled trials. This gives you one more clearly relevant study (Woods et al., 2003). Final searches using other combinations of your key terms (psychosis, schizophrenia, high risk, prodrome) yield no more trials except a descriptive summary of an ongoing trial in Germany, but the reporting is not complete (Ruhmann et al., 2005). Also, there are reports from the New York High Risk Project and Hillside Recognition and Prevention Program that you have heard a lot about (Cornblatt, 2002), but the pharmacological studies are not controlled.

You decide to start with the randomized, controlled trials as the evidence with the least bias. You summarize the studies (Table 1) and prepare to discuss the evidence with Peter and his mother: There is good evidence from the available studies that low-dose antipsychotics and cognitive therapy may reduce the intensity of the prodromal psychotic symptoms. Whether the interventions also decrease the risk of progression to full psychosis is less clear. On the basis of the raw figures, there seem to be striking reductions in the rate of transition to psychosis. Yet, given the small numbers in the trials, these results often do not reach significance. Also, it is not clear how long benefits are sustained, and side effects, like weight gain with the olanzapine group, need to be considered. You also mention to Peter's mother that few of these studies have included patients as young as Peter.

CHOOSING PETER'S TREATMENT

You and his mother, with Peter's assent, decide together that medication is not the best choice and choose to monitor his mental state closely while arranging additional support at school. He remains about the same with this plan for many months, but then shows a rapid decline in mental state shortly before his 13th birthday: Peter describes a constant voice of a boy insulting him and increasingly complex delusions about persecution from other children orchestrated by teachers at his school. There is now little doubt that Peter has a psychotic illness and would meet criteria for a schizophreniform disorder (and may well eventually meet criteria for schizophrenia).

Evidence of treatment of first-episode psychosis in children includes only one randomized, double-blind trial comparing outcomes in children treated with olanzapine, risperidone, and haloperidol (Sikich et al., 2004). This 8-week study included 75 children and adolescents with psychotic symptoms stemming from a wide range of underlying diagnoses. All three treatments were associated with significant reductions in the total symptom scores at baseline (using the Brief Psychiatric Rating Scale for Children) of 50% for risperidone, 44% for olanzapine, and 67% for haloperidol. The categorical response rates, like most outcome measures, did not

differ significantly, but there was a trend to better response for the atypicals: 74% (14/19) with risperidone, 88% (14/16) with olanzapine, and 53% (8/15) with haloperidol. The findings of the study are congruent with those of an 8-week, open-label, unrandomized comparison of olanzapine, risperidone, and haloperidol in 43 adolescents with schizophrenia that found all three agents were equally efficacious (Gothelf et al., 2003).

Although the study by Sikich and colleagues provides perhaps the best evidence of the treatment of psychosis in adolescents, two factors limit its applicability to Peter. First, the study included a diagnostically heterogeneous

TABLE 1
Randomized Trials of Interventions for Patients at High Risk of Developing Psychosis

Study	Interventions	N	Outcome Measures	Results	Is this relevant to Peter? Is this important for Peter?
McGorry et al., 2002	Needs based intervention vs. specific preventive intervention (risperidone 1.3 mg/day and CBT; single blind)	59	Development of definite psychotic symptoms (based on PANSS)	10/28 in NBI developed psychosis at 6 mo vs. 3/31 in SNI; patients who were fully adherent to risperidone had lower rate of development of psychosis (2/14 vs. 7/17); difference not sustained at 12 mo	Outcome was any form of psychosis, not just schizophrenia; subjects were older than Peter (14–30 yr); only 14 participants were fully adherent to antipsychotic treatment, so numbers are small; no reporting on adverse side effects; unclear whether it was medication, CBT, or both that were effective in the short term; unclear what the CBT involved; 74% of subjects enrolled in trial did not transition to psychosis
Morrison et al., 2004	TAU vs. CT (single blind)	58	Development of definite psychotic symptoms (based on PANSS)	2/35 in CT developed psychosis vs. 5/23 in TAU; low overall rate of transition to psychosis (12%); 96% reduction in odds of making a transition to psychotic in CT group (after adjustment for potential moderating variables)	Outcome was any form of psychosis not just schizophrenia; excluded subjects <16 yr; unclear which component of CBT was therapeutic; CI for the reduction in odds are large, so there may not be much reduction at all; 88% of subjects enrolled in trial did not transition to psychosis
Woods et al., 2003	Placebo vs. olanzapine (double blind)	60	Development of psychosis (using Scale of Prodromal Symptoms)	10/29 placebo vs. 5/31 olanzapine developed psychosis; significant group difference at 8 wk using linear mixed-models analyses (detects difference in rate of change)	Outcome was any form of psychosis not just schizophrenia; included subjects >12 yr; no data on outcome after 8 wk; marked weight gain in olanzapine wing (10 lb)

Note: CBT = cognitive behavioral therapy; PANSS = positive and negative syndrome scale; SNI = specific needs intervention; NBI = needs based intervention; TAU = treatment as usual; CT = cognitive therapy.

group, and only half of the subjects had a diagnosis of a schizophrenia spectrum disorder. Second, a large proportion of youths in the study were receiving other psychotropic medications and may have had some degree of treatment resistance. Despite these caveats, it is likely that the atypical antipsychotics olanzapine and risperidone are at least as effective as typicals, such as haloperidol, and are appropriate as first-line agents in the treatment of COS.

As you try a wide range of medications with Peter, there are problems. Haloperidol is oversedating; olanzapine is excellent in abating symptoms but he gains 8 kg and refuses to continue taking the drug; and risperidone, quetiapine, and low-dose perphenazine are ineffective despite more than adequate trials over a period of 3 months each. What are the remaining treatment options? Given the malignant course of very early onset schizophrenia, such a scenario is sadly not unusual. In adult-onset schizophrenia, most but not all meta-analyses suggest that clozapine is more efficacious than typical and possibly most atypical antipsychotics in the short-term treatment of patients who are treatment resistant (Davis et al., 2003; Geddes et al., 2000; Leucht et al., 2003; Moncrieff, 2003). Is this true for very early onset schizophrenia also?

You do a literature search again using PubMed and entering the terms "childhood schizophrenia AND clozapine" with the limit of "randomized controlled trial." This gives you three hits, and the first refers to a double-blind comparison of haloperidol and clozapine (Kumra et al., 1996). This NIMH study randomized 21 children for 6 weeks of treatment and found clozapine to

be markedly superior on all components of the Brief Psychiatric Symptom Scale and overall ratings of clinical improvement, a striking finding given the small sample and the severity of illness at baseline. The mean dose of haloperidol used was 16.8 mg/day, which is at the upper end of the contemporary treatment range. This study did not find a significant increase from baseline in either arm in the rates of extrapyramidal side effects, whereas most other studies find rates of between 58% and 80% in patients with COS treated with typical antipsychotics such as haloperidol (Engelhardt et al., 1973; Pool et al., 1976; Spencer et al., 1992).

Knowing that the NIMH is studying childhood schizophrenia and thinking Peter may benefit from and contribute to the study, you quickly find their Internet site and call. While talking about Peter with the intake research social worker, you discover the NIMH group has recently completed a direct comparison of olanzapine, one of the most widely used atypical agents, with clozapine. In a double-blind randomized, controlled, 8-week trial, 25 patients with COS were randomized (12 to clozapine and 13 to olanzapine). Using intent-to-treat analyses, clozapine was associated with a significant reduction in all outcome measures, with olanzapine showing a rather less impressive improvement, as shown in Figure 1 (Shaw et al., 2006).

A direct comparison of treatment efficacy showed that for most measures there was no significant difference between the groups. The only exception was in the alleviation of negative symptoms of schizophrenia, with clozapine producing a 45% greater reduction in the

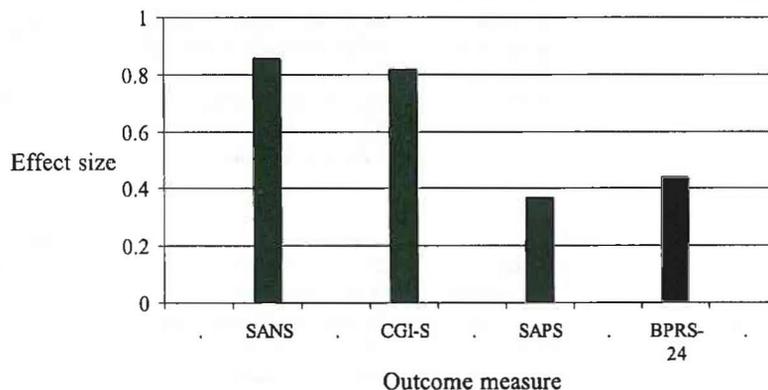


Fig. 1 A visual summary of data comparing clozapine to olanzapine in reducing symptoms in childhood-onset schizophrenia from an antipsychotic-free baseline. The effect size is calculated by comparing the change scores in each outcome measure associated with clozapine and olanzapine. An effect size of ≥ 0.8 indicates that the superiority of clozapine over olanzapine is large; an effect size between 0.5 and 0.8 indicates moderate superiority for clozapine, and between 0.2 and 0.5, a minimal superiority for clozapine. Olanzapine was not associated with greater improvement in any of these outcome measures. SANS = Scale of Negative Symptoms; CGI-S = Clinical Global Impressions-Severity score; SAPS = Scale of Positive Symptoms; BPRS-24 = Brief Psychiatric Symptom Scale, 24-item version.

Scale for the Assessment of Negative Symptoms from an antipsychotic-free baseline ($p = .04$; effect size, 0.89). The size of the differential effect on negative symptoms is thus large and stands in marked contrast to studies of adults with schizophrenia that report no significant difference between olanzapine and clozapine in treating negative symptoms, despite a larger sample size and power to detect smaller effects (Bitter et al., 2004; Tollefson et al., 2001; Volavka et al., 2002). Unfortunately, clozapine was also associated with significantly more overall side effects including hypertension, tachycardia, and enuresis. Both treatments were associated with substantial weight gain of 4 kg. The double-blind studies are complemented by uncontrolled studies showing good clinical response to clozapine in youth with COS who have not responded to other antipsychotics (Frazier et al., 1994; Turetz et al., 1997).

Overall, the evidence from the NIMH studies certainly suggests clozapine is superior to haloperidol for patients like Peter who have either failed other antipsychotics or developed intolerable side effects. There is evidence for superiority of clozapine over olanzapine with a general pattern of superior clinical response for clozapine, which needs to be balanced against its increased side effects.

Attention to psychosocial factors that may contribute to his lack of response to treatment is also important, especially the level of expressed emotion within the family (indexed by degree of criticism, hostility, and overinvolvement). Behavioral family therapy is often highly effective in reducing the level of such expressed emotion and in adult-onset schizophrenia has been found to reduce the rates of relapse (Pharoah et al., 2003).

Given these data, you and his mother choose treatment with clozapine. Peter has an excellent response, with resolution of his positive symptoms and a marked increase in his level of motivation. Unfortunately, he also develops a range of side effects, including drooling and a marked weight gain of 6 kg. On a positive note, Peter has not developed some of the other side effects associated with clozapine such as neutropenia or seizures, problems with glucose regulation, including diabetes mellitus, or myocarditis. You manage his hypersalivation with a low dose of an anticholinergic. You find that there is some evidence for managing weight gain associated with clozapine through behavioral techniques, and refer Peter to a dietician and physical therapist who has experience in this area (Faulkner et al., 2003).

Such a severe and complex disorder as childhood schizophrenia is well served by an approach based on evidence with the least bias. Although patients such as Peter present complex treatment issues, in our experience, a multidisciplinary team approach, which matches optimal pharmacotherapy with attention to educational needs and the family environment, is a highly effective intervention that can ameliorate the course of this devastating illness.

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