Children With Schizophrenia: Diagnosis, Phenomenology, and Pharmacotherapy

by Elizabeth Kay Spencer and Magda Campbell

Abstract

This article presents data on the diagnosis and phenomenology of schizophrenia in 16 hospitalized children, ages 5.5 to 11.75 years. These 16 subjects are the first to complete an ongoing double-blind, placebo-controlled study of haloperidol in children with schizophrenia diagnosed by *DSM–III–R* criteria. We describe the pharmacologic treatment response of this subsample and compare our diagnostic, phenomenologic, and treatment findings with those of other investigators. Our results show that children under age 12 can be diagnosed with schizophrenia by the same criteria used for adults, that they show comparable clinical symptoms, and that on haloperidol they show improvement in target psychotic symptoms, at least in a short-term inpatient setting.

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Childhood-onset schizophrenia is a rare disorder, estimated to occur 50 times less frequently than adult-onset schizophrenia (Karno and Norquist 1989). Its rarity, in combination with changes over the years in nomenclature and diagnostic criteria for schizophrenia as it presents in childhood, has led to a paucity of data about children who meet currently recognized criteria (Beitchman 1985; Campbell et al. 1991). On the Bellevue Hospital Center's Children's Psychiatric Inpatient Unit, three studies have examined hospitalized children with schizophrenia who met *DSM–III* (American Psychiatric Association 1980) (Green et al. 1984; Green and Padron-Gaylor 1986) and, more recently, *DSM–III–R* (American Psychiatric Association 1987) diagnostic criteria (Spencer et al. 1992). The third study, which is ongoing, is assessing the efficacy and safety of haloperidol in a carefully diagnosed sample of children who have schizophrenia. We will present some of these data and compare them to the findings of some other investigators.

Diagnosis and Phenomenology

Before 1980 the literature on early-onset schizophrenia often described diagnostically heterogeneous groups of patients, because "childhood schizophrenia" included patients who today would be diagnosed as having a psychotic disorder other than schizophrenia, or autistic or pervasive developmental disorders. However, some researchers, such as Kanner (1949) and Rutter (1972), regarded autism and schizophrenia as two distinct entities.

There was a great need to define this disorder in children and to use operational criteria, to be able to compare results across studies and to generalize, and to apply results from clinical drug trials to daily clinical practice. Before studies by Kolvin (1971*a*, 1971*b*), Kolvin et al. (1971*a*, 1971*b*, 1971*c*, 1971*d*, 1971*e*), and Green et al. (1984), the literature was not clear on what was meant by schizophrenia in childhood or childhood schizophrenia. In the above studies, children with schizophrenia (or late-onset psychosis) were

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compared to children with autism. In a retrospective chart review of children hospitalized between 1977 and 1982, Green et al. (1984) reported on 24 (15 male and 9 female) children with schizophrenia diagnosed by *DSM–III* criteria, ages 6.7–11.11 years (mean = 9.96 years). The children with schizophrenia were compared to 25 children diagnosed with infantile autism, ages 5.2–12.10 years (mean = 9.10). The children with schizophrenia differed from those with autism on several parameters, including phenomenology and IQ, confirming that these disorders are distinct clinical entities, and thus replicating Kolvin's findings (Kolvin 1971*a*, 1971*b*; Kolvin et al. 1971*a*, 1971*b*, 1971*c*, 1971*d*, 1971*e*). Green and Padron-Gayol (1986) reported on 16 children (13 male and 3 female, ages 5.7–12.6 years), who were hospitalized in Bellevue Hospital Center after 1982. This study confirmed that children can meet the *DSM–III* diagnostic criteria of schizophrenia.

These studies show that schizophrenia can develop before age 12, meeting the diagnostic criteria for schizophrenia in adults. During the past decade, others found that children can fulfill the criteria for schizophrenia, as specified by *DSM–III* (Kydd and Werry 1982; Watkins et al. 1988; Russell et al. 1989) and by *DSM–III–R* (Werry et al. 1991; McClellan and Werry 1992; Spencer et al. 1992). (For a review, see Campbell et al. 1991.) These studies also showed that the clinical picture of childhood-onset schizophrenia, with minor exceptions, is identical to adolescent- or adult-onset schizophrenia.

Our present sample is derived from an ongoing double-blind, placebo-controlled study of haloperidol in hospitalized children with schizophrenia. Subjects were admitted to the Bellevue Hospital Center's Children's Psychiatric Inpatient Unit between September 1989 and May 1991.

Sources of referral to the study included the Bellevue Hospital Center's Child and Adolescent Mental Hygiene Clinic, Pediatric Psychiatry Consultation Liaison Unit, and Pediatric Emergency Service, as well as child psychiatric services at several other hospitals and clinics in Manhattan and other New York City boroughs. A letter announcing the new project was sent to local hospitals and child mental health treatment facilities where psychotic children might present for evaluation and treatment. Referrals were screened by telephone and, as appropriate, in person, using *DSM–III–R* diagnostic criteria for schizophrenia and additional inclusion and exclusion criteria specific to this study: actively psychotic prepubertal males and females, ages 5–11 years; and absence of intercurrent systemic illness, seizure disorder, tardive dyskinesia, or mental retardation below the borderline range.

A total of 34 hospitalized children with the presumptive diagnosis of schizophrenia were interviewed for the study. Of these, 13 had psychotic features but did not meet *DSM–III–R* criteria for schizophrenia; 2 were diagnosed as having schizophrenia by the clinical staff, but their parents did not consent to their participation. Three entered the placebo baseline without proceeding to double-blind treatment, because the diagnosis of schizophrenia was uncertain or because of diminution of psychotic symptoms. In addition, four children were interviewed as outpatients, and one was screened as a psychiatric inpatient at another hospital. Our study sample thus consisted of 16 children, selected from the 34 considered and interviewed for the study, and represented 12 percent of all children ages 2–12 years (n = 131) hospitalized on our ward between September 1989 and May 1991. The sample included 12 males and 4 females, 5.5–11.75 years (mean = 8.86 years). The Hollingshead Two-Factor Index of Social Position (Hollingshead and Redlich 1958), which determines socioeconomic status (SES) from the occupation and education of the head of the household, indicated that the SES for the 16 children was as follows: 2 were from social class III, 3 were from IV, and 11 were from social class V.

Prior psychiatric diagnoses in 12 of the children were as follows: schizophrenia in 1; atypical psychosis in 3; atypical pervasive developmental disorder in 1; attention deficit hyperactivity disorder in 5; conduct disorder in 1; adjustment disorder with mixed disturbance of conduct and emotions in 1; pica in 1; and borderline personality disorder in 1. Of the four children without known prior psychiatric diagnoses, two had previous contact with mental health professionals in the context of foster care placement, and a third had been evaluated briefly for reported suicidal ideation.

In many children it was difficult to determine the age at onset of active schizophrenic symptoms. This difficulty may have been due in part to the chronicity of the children's nonspecific behavioral problems, the prior development of symptoms consistent with nonpsychotic psychiatric diagnoses, and the generally insidious onset of psychosis. In general, active psychotic symptoms, such as audi-

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tory hallucinations and delusions, are apparent and prompt hospitalization, while "negative" symptoms (Andreasen and Olsen 1982), such as blunted affect and withdrawal, are less likely to attract attention. For most of the children, the emergence of active schizophrenic symptoms or associated symptoms (such as aggression or suicidal ideation) precipitated hospitalization. Often admission was initiated because of bizarre or dangerous behavioral sequelae to command hallucinations or delusional beliefs.

Hallucinations. Every child reported prominent auditory hallucinations, characterized universally as voices and, in one case, as the squeaking of a rat. The children attributed the voices to a spectrum of entities, including family members or other people ("a baby," "little boys and little girls"); animals ("the rat," "an owl"); malevolent forces ("a spirit," "the demon," "the Devil," "a witch"); characters from current horror movies (Freddie Kruger, Chucky, Bloody Mary); and less specifically identified sources ("bad things," "the whispers").

The children's histories showed that the duration of auditory hallucinations ranged from 1 week for one subject to more than 1 year for four. For 10 children, the duration was judged to be from 1 month to 1 year. For the majority, auditory hallucinations were among the chief complaints prompting hospitalization. The child who reported the shortest duration, however, was a 7-year-old girl, known since age 5 to Bellevue Hospital Center's outpatient clinic, who had displayed a pattern of gradually worsening thought disorder, inappropriate affect, and behavioral disturbance over a period of several months. She reported new auditory hallucinations after a screening interview for the study and continued to manifest this symptom after hospitalization. Similarly, an 11-year-old boy described auditory hallucinations for the first time after he was hospitalized for aggressive behavior, with a provisional diagnosis of conduct disorder. In contrast to these two children, among the subset of the group known to have reported hallucinations for several years, hallucinations had either been disregarded or viewed as a chronic symptom not representing serious risk.

For the most part, auditory hallucinations were simple rather than complex in nature, consisting of brief phrases or sentences. The children frequently described hearing themselves cursed or threatened. Command auditory hallucinations were common and experienced by more than half of the group: "Kill her, kill her." "Kill somebody tomorrow morning, or else I'll kill you." "Don't listen to the staff." "Leave this place and go to California." In response to auditory commands, two children had burned themselves. One, who had applied rubbing alcohol to his abdomen and ignited himself with matches, required skin grafting and hospitalization in an intensive care burn unit. He did not, however, disclose that he was experiencing auditory commands until his psychiatric admission several months later.

Fewer children experienced a voice that maintained a running commentary on their behavior or thoughts, or two or more voices conversing. When these symptoms did occur, they again had simple rather than complex content. Commenting voices told one child when he "was being good or bad." Conversing voices were described both as talking to each other about the children or speaking in conversational cadence but with indistinguishable words: "I hear them conversating all the time." "It's like yelling."

Hallucinations in other sensory modalities included visual hallucinations, reported by 11 children, and tactile hallucinations, reported by 4. These other types of hallucinations did not occur in the absence of auditory hallucinations and commonly were related to the auditory hallucinations. For example, children reported seeing the entities from which voices emanated or to which they attributed the voices. The child who heard the squeaking rat also saw the rat and felt it brushing against his leg and spitting on him.

Overall the children were distressed and frightened by their hallucinations and expressed relief when this symptom remitted. One child had developed suicidal ideation, with the conviction that she could make the "conversating voices" stop by killing herself.

Delusions. Every child in this group of 16 also reported delusions, which tended to arise in connection with hallucinatory experiences. Delusions were characterized as persecutory and somatic. Children also reported delusions of control. Many said they were being menaced by the entities causing their auditory and visual hallucinations ("the whispers," "the ghosts"). Some maintained a conviction that talking about or disobeying their voices would cause them to retaliate, by harming either the child or someone he or she knew. Some children re-

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ported being controlled by an outside force (a movie projector, a "smoke creature") or inhabited by an entity. The youngest subject, a 5½-year-old boy, believed that a baby was inside his throat telling him to kill himself, and he reached down his throat to try to extract the baby.

The children's histories showed that the duration of delusions was shorter than that of hallucinations, ranging from at least 1 week to 1 year. As described by these children, the majority of delusions, like their hallucinations, were simple rather than complex. A few of the older children, however, reported some degree of elaboration. The 9-year-old boy who believed that he was being controlled by a movie projector had acted on that conviction by leaving his family's apartment at night to search for the projector in a nearby park. After admission, he expressed beliefs that a microphone had been placed in his jacket, that he was being monitored through the hospital air ventilators, and that his food was being poisoned. A floridly psychotic 11-year-old boy, with several months' history of ideas of reference and paranoid ideation, became convinced that his foster mother's daughter would murder him; he barricaded himself in a room and later became assaultive. On admission he displayed a series of delusions: that swallowing his saliva would give him AIDS (hence his carrying and spitting into a paper cup and becoming dehydrated, with a blood urea nitrogen of 36); that he was being harassed by the squeaking, spitting rat described above, which was also trying to infect him with AIDS; that dead rats were in his orange juice; and that staff members, some inhabited by enemies, were withholding important information from him.

Other Symptoms. Some degree of thought disorder was noted in 13 children, who variously displayed tangentiality, illogicality, and loosening of associations. Only two floridly psychotic subjects, however, displayed sustained periods of incoherence, which was observed in the hospital during baseline. Thirteen children displayed some degree of affective disturbance, although with a range of severity. Several showed blunted rather than flat affect and a lesser degree of inappropriate affect than would be considered "grossly inappropriate" (*DSM–III–R*, p. 194). Overall, the clinical picture of this group of 16 children with schizophrenia supports the observation that childhood-onset schizophrenia has the same manifestations as adolescent- and adult-onset schizophrenia and is the same as reported in earlier studies (see table 1).

As noted above, eligibility for entry into our study requires the diagnosis of schizophrenia by *DSM–III–R* criteria, with severity of illness necessitating inpatient hospitalization and warranting pharmacotherapy. With these criteria, the most commonly reported active schizophrenic symptoms were auditory hallucinations and delusions, which were experienced by all 16 subjects. Associated visual hallucinations occurred in 11 (69%), and tactile hallucinations occurred in 4 (25%). Thought disorder was shown by 13 (81%), as was inappropriate affect.

Previous studies of children with schizophrenia also have reported auditory hallucinations as common. In a sample of 33 children with late-onset psychosis, ages 7–13 years, 81.8 percent reported auditory hallucinations (Kolvin 1971*a*, 1971*b*; Kolvin et al. 1971*a*, 1971*b*, 1971*c*, 1971*d*, 1971*e*). In two studies using *DSM–III* criteria for schizophrenic disorder, auditory hallucinations were reported by 79.2 percent of 24 children, ages 6.7–11 (Green et al. 1984); in 16 other children, ages 5.7–12.6, the rate

Table 1. Comparison of schizophrenic symptoms shown by subjects in three studies

	Green et al. 1984	Werry et al. 1991	Current study
n	24	30	16
Age range	6.7–11.11	7–17	5.5–11.75
Diagnosis	*DSM–III*	*DSM–III–R*	*DSM–III–R*
Hallucinations, %	NR	57	100
Auditory	79.2	53	100
Visual	37.0	13	69
Tactile	8.3	13	25
Delusions, %	54.2	47	100
Inappropriate/flat affect, %	NR	57	81
Thought disorder, %	100	NR	81
Incoherence	NR	13	17

Note.—NR = not reported; *DSM–III* and *DSM–III–R* = *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980, 1987).

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was 93.8 percent (Green and Padron-Gayol 1986). Using *DSM–III* criteria, Russell et al. (1989) found that 28 of 35 children (80%), ages 4.75–13.25 years, also showed auditory hallucinations. In New Zealand, a followup study evaluating 59 child and adolescent psychotic patients by *DSM–III–R* criteria (Werry et al. 1991) revealed auditory hallucinations in 53 percent of 30 schizophrenia patients, ages 7–17 years. The current study replicates the finding by others that, in the absence of auditory hallucinations, other types of hallucinations are rare or nonexistent.

Delusions were common in the subjects of these previous studies, but they occurred more frequently in the current study. Previously reported rates of delusions have been as follows: 57.6 percent (Kolvin 1971*a*; Kolvin et al. 1971*c*); 54.2 percent (Green et al. 1984); 43.8 percent (Green and Padron-Gayol 1986); 63 percent (Russell et al. 1989); and 47 percent (Werry et al. 1991).

Many of our patients also have demonstrated some degree of thought disorder. Previously reported frequencies of thought disorder have been 60 percent (Kolvin 1971*a*; Kolvin et al. 1971*c*), 100 percent (Green et al. 1984), and 40 percent (Russell et al. 1989). More precise quantification of the degree of thought disorder shown by children with schizophrenia is a future study goal for our group.

Werry et al. (1991) define early-onset schizophrenia as beginning before age 18, and they differentiate between "very early-onset" schizophrenia, beginning before age 13, and "adolescent" schizophrenia, beginning between ages 13–17. In their followup study of 59 psychotic patients (mean age at onset = 13.9 years), 10 subjects fell in the very early-onset category—7 showed onset at age 12, and 3 at ages 7–11. Werry et al. describe eight probable characteristics that differentiate early-onset, and particularly very early-onset, schizophrenia patients from adult schizophrenia patients. These features include male predominance, insidious onset, increased neurodevelopmental abnormalities, "odd" premorbid personality, increased family history of schizophrenia, less differentiated symptomatology, greater resistance to antipsychotic medication, and poorer outcome. They note that, except for the greater male predominance, most of these features require confirmation.

By definition, all 16 children described in our study fall in the category of very early-onset schizophrenia. The current sample is predominantly male and shows insidious onset. Two sisters in our group of 16 are the only first-degree relatives diagnosed with schizophrenia, although 5 of 15 families (33.3%) had a positive history for schizophrenia.

Pharmacotherapy

If response to treatment is a confirmation of diagnosis, then, at least in the context of treatment on a short-term inpatient basis, our patients' positive response to haloperidol validates the diagnosis of schizophrenia. Our study supports the fact that young children not only can meet diagnostic criteria for adults with schizophrenia, but they can also benefit from a class of medication that is effective in adults.

The study design and methodology of our ongoing 10-week crossover study have been more fully described elsewhere (Spencer et al. 1992). In brief, after a 2-week placebo baseline period, subjects who continue to show active schizophrenic symptoms are assigned randomly to one of two 8-week treatment sequences: haloperidol for 4 weeks followed by placebo for 4 weeks, or placebo for 4 weeks followed by haloperidol for 4 weeks. Dosage, which is regulated individually, begins with 0.5 mg/d and is increased to a maximum of 10 mg/d, given in three daily doses. Baseline symptomatology and treatment response are rated on a battery of scales completed by child psychiatrists, nurses, and teachers in a variety of settings (Spencer et al. 1992). Rating instruments include the Children's Psychiatric Rating Scale (CPRS; National Institute of Mental Health 1985) and Clinical Global Impressions (CGI; Guy 1976), and the Brief Psychiatric Rating Scale for Children (BPRS–C; Overall and Pfefferbaum 1982), among others. Ratings are conducted twice during placebo baseline and after each 4-week double-blind treatment. At the end of the study, the clinical and research staff meet jointly to attain a Global Clinical Judgments consensus rating (GCJ; Campbell et al. 1984), which compares the child's response during each double-blind period to baseline.

All 16 subjects improved on haloperidol and continued receiving haloperidol after the study. Optimal dose was determined clinically as the dose at which the child showed greatest remission of symptoms in the absence of, or with minimal, untoward effects. On the basis of GCJ ratings, comparing treatment response to baseline, 12 children on haloperidol showed marked improvement, 3 showed moderate improvement,

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and 1 showed mild improvement. On placebo, compared with baseline, 3 subjects were unchanged or worse, 11 showed mild improvement, and 1 showed moderate improvement.

For the 16 subjects in this ongoing study, the mean optimal dose for haloperidol was 1.92 mg/d, or 0.057 mg/kg/d (range = 0.5–3.5 mg/d, or 0.02–0.12 mg/kg/d). For 11 of 16 subjects, the optimal dose was 0.04–0.06 mg/kg/d. Of note, one subject who showed marked improvement on 1.5 mg/d (0.04 mg/kg/d) had been judged a nonresponder to haloperidol on doses up to 10 mg/d in another hospital. Two of the three children who required higher than mean doses for optimal response were sisters.

Results of preliminary analyses for 12 subjects have been reported elsewhere (Spencer et al. 1992). Significant haloperidol treatment effects were found for CGI Severity of Illness, CGI Global Improvement, BPRS–C Total Pathology, and for four of eight selected CPRS items pertinent to schizophrenia (item 57, ideas of reference; item 58, persecutory; item 59, other thinking disorders; and item 61, hallucinations). Haloperidol was not superior to placebo for the other four CPRS items (item 17, suspicious affect; item 19, blunted affect; item 60, delusions; and item 62, peculiar fantasies) in this small sample. Ours is the first double-blind, placebo-controlled clinical trial of a neuroleptic in children with schizophrenia (Spencer et al. 1992). Another study at the National Institute of Mental Health involves haloperidol and clozapine (Gordon et al. 1994). As shown in table 2, only three published double-blind, placebo-controlled studies involve children or adolescents who have schizophrenia. A marked increase in onset of schizophrenia occurs after puberty—Loranger (1984) reported a cumulative percentage of 39 between ages 15 and 19 for 100 males. But only three published studies involved psychoactive agents in adolescents (Pool et al. 1976; Realmuto et al. 1984; Siefen and Remschmidt 1986), and only one of these was double blind and placebo controlled (Pool et al. 1976). Perhaps because schizophrenia is so rare in children under age 12, knowledge is even more limited about the efficacy and safety of psychoactive drugs in the youngest population of schizophrenia patients. For reviews, see Campbell and Spencer 1988; Campbell et al. 1993.

Review and analysis of the literature on pharmacotherapy made it clear that certain issues had to be addressed. These issues are as follows: (1) diagnosis and diagnostic criteria for this age group of schizophrenia patients; (2) duration of illness; (3) sample size, design, and methodology employed; and (4) dosage of psychoactive agents. Furthermore, response to haloperidol and its relationship to chronologic age, IQ, and severity and duration of illness are presented.

Diagnosis and Diagnostic Criteria. Type of schizophrenia or chronicity, certainly in adult schizophrenia patients, may or will influence response to an antipsychotic agent or the response to a specific type of antipsychotic agent. Children with different disorders may respond in different ways to antipsychotic agents. It is conceivable that children who suffer from schizophreniform disorder or brief reactive psychosis may respond more favorably to pharmacotherapy than children who meet all the criteria for schizophrenia. In reviewing the pertinent literature from the late 1950s on, with a few exceptions, it is difficult to know whether the children have schizophrenia, autism, schizoid personality disorder, or schizotypal personality disorder. As shown in table 2, only four studies specify the diagnosis so that the criteria and symptoms are identifiable. Pool et al.'s study (1976) involves adolescents with acute schizophrenia or chronic schizophrenia with acute exacerbation; Realmuto et al.'s report (1984) involves adolescents with chronic schizophrenia. Siefen and Remschmidt (1986) use the International Classification of Diseases (ICD-9; World Health Organization 1978) criteria, and their sample of 21 adolescents includes a variety (5 types) of schizophrenic disorders. However, the majority, 15 out of 21 patients, were diagnosed with schizophrenia, paranoid type. Two of the 21 patients were schizoaffective, 2 were other (295.8), 1 was disorganized type, and 1 was catatonic type. *DSM–III–R* criteria and the Diagnostic Interview for Children and Adolescents–Revised (DICA–R; Reich and Welner 1990) were used for children under 12 (Spencer et al. 1992).

Duration of Illness. Certainly duration of illness, one of the variables differentiating schizophrenia from schizophreniform disorder, may influence response to treatment. Furthermore, chronic schizophrenia (> 2 years according to *DSM–III–R*) may respond differently to a psychoactive agent than does schizophrenia of only 6 months' duration, the minimum duration for *DSM–III–R* diagnosis. *DSM–III–R* requires "Continuous signs of the disturbance for at least six months. The six-month

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Table 2. Clinical drug trials in children and adolescents with schizophrenia

Author(s)	*n*	CA[1]	Diagnosis	Drug(s)	Daily dose, mg (mg/kg)	Response
Double-blind and placebo-controlled studies						
Pool et al. (1976)	75	13–18	Acute schizophrenia or exacerbation	Loxapine Haloperidol	25–200, M = 87.5 2–16, M = 9.8	Both drugs superior to placebo
Naruse et al. (1982)	4 (of 87)	3–16	Psychosis (mainly child schizophrenia)	Haloperidol Pimozide	0.75–3.00 1.0–4.0	
Spencer et al. (1992)	16	5.50–11.75 (M = 8.89)	Schizophrenia (*DSM–III–R*)	Haloperidol	0.5–3.5, M = 1.77 (0.02–0.12, M = 0.058)	Haloperidol superior to placebo
Open/retrospective studies						
Debray et al. (1972)	2 (of 187)	20 months[2] –17 years	"Infantile defect schizophrenia"	Pimozide	2.0–6.0, M = 3	1 failed to respond; the other improved
Pangalila-Ratulangi (1973)	8 (of 10)	9–14	Schizophrenia or schizophrenia-like symptomatology	Pimozide	1.0–2.0	7 improved on drug
Realmuto et al. (1984)	21	11.75–18.75 (M = 15.08–16.08)	Chronic schizophrenia (*DSM–III*)	Thiothixene Thioridazine	4.8–42.6, M = 16.2 (0.3) 91–228, M = 178 (3.3)	Drugs comparable in efficacy; half of sample improved
Siefen and Remschmidt (1986)	21	12 subjects < 18 years (M = 18.1)	Schizophrenia, paranoid type, *n* = 15 (of 21) (*ICD–9*)	Clozapine	254–700, M = 352	Marked improvement or remission in 11

Note.—M = mean; *DSM–III* and *DSM–III–R* = *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 1980, 1987); ICD-9 = International Classification of Diseases (World Health Organization 1978).

[1]CA = Chronological age in years.

[2]Age range for a subsample of 11 psychotic children and not only for the 2 with schizophrenia

period must include an active phase (of at least one week, or less if symptoms have been successfully treated) during which there were psychotic symptoms characteristic of Schizophrenia..., with or without a prodromal or residual phase..." (American Psychiatric Association 1987, p. 194).

Siefen and Remschmidt (1986) studied adolescents with schizophrenia (mean age = 18.1) in whom the mean time period between the onset of first symptoms and current treatment was 18.6 months. Evidence suggests that chronic adolescents with schizophrenia respond differently to a low-potency neuroleptic than to a high-potency neuroleptic (Realmuto et al. 1984) and that the magnitude of response is smaller than in those with acute schizophrenia (Pool et al. 1976). Pimozide is a neuroleptic that has been shown to be effective in reducing negative symptoms in chronic as well as acute schizophrenia (for review, see Campbell et al. 1990).

Sample Size, Design, and Methodology. We found only eight reports in the published literature that can be considered clinical trials relevant to children and adolescents with schizophrenia. Three studies involve adolescents (Pool et al. 1976; Realmuto et al. 1984; Siefen and Remschmidt 1986), and

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only one deals exclusively with children under age 12 (Spencer et al. 1992). In addition to a case report (Meyers et al. 1980), three reports included at least a subgroup of schizophrenia patients or a few such patients (Debray et al. 1972; Pangalila-Ratulangi 1973; Naruse et al. 1982). No conclusions can be made about these last three reports, given the small number of schizophrenia subjects and the diagnostically heterogeneous samples, as shown in table 2. Of the eight studies, only three are double blind and placebo controlled with randomized assignment to treatment (Pool et al. 1976; Naruse et al. 1982; Spencer et al. 1992). Siefen and Remschmidt's (1986) report is an open study of clozapine, that does not use a design. Various data were collected and ratings were done on a 67-item symptom scale with 5 steps: never existed, no change/worse, slightly improved, markedly improved, and ceased. Failure to respond to other neuroleptics was among the inclusion criteria.

There are a few earlier reports, but they are all flawed: they consist of small samples of diagnostically heterogeneous patients (schizophrenia and autism subjects are mixed), diagnostic criteria are ill defined, or no controls were employed (for review, see Campbell 1978). These samples are heterogeneous not only diagnostically, but also in terms of chronologic age (range = 6–22). The drugs and doses employed were as follows: trifluoperazine, 13–20 mg/d; fluphenazine, 0.75–16 mg/d; haloperidol, 0.75–16 mg/d; thiothixene, 6–30 mg/d; and pimozide, 1–2 mg/d (see Campbell 1978 and table 2).

Dosage. The fourth issue to be addressed in analyzing the literature on pharmacotherapy is the therapeutic dosage or minimum effective dosage. Failure to recognize excess dose sometimes is thought of as failure to respond to the neuroleptic. Behavioral toxicity is often overlooked in children (Campbell et al. 1985). Frequently, excessively high doses are employed without beneficial effects, or adverse effects outweigh the beneficial effects. Haloperidol was administered to the majority of patients in the published reports. As shown in table 2, the dose range is wide: 0.5–16.0 mg/d. In our clinical experience with children who have schizophrenia (Campbell, personal communication 1994), and on the basis of the study by Spencer et al. (1992), conservative doses of haloperidol (0.02–0.12 mg/kg/d) are more effective and freer of side effects than are higher doses. Still, there are individual differences, and the ranges of minimal effective doses are wide. Dose may influence or determine the effect of the drug on cognition and performance (for review, see Werry and Aman 1975; Aman 1978). The effect of neuroleptics on cognition also may be a function of diagnosis. In children with autism, administration of haloperidol was associated with no change in learning (Anderson et al. 1989), facilitation of learning (Campbell 1978; Anderson et al. 1984), or increase in IQ (Shell et al. 1987). However, in conduct-disordered children performance was adversely affected (Platt et al. 1984). The data from our systematic studies of haloperidol in three diagnostic categories of children (autism, conduct disorder, and schizophrenia) suggest that diagnosis may influence the presence or absence of side effects at therapeutic doses. In short-term studies of children with autism, we were able to titrate the dosage so that the children were free of side effects (Campbell et al. 1978; Anderson et al. 1984, 1989), whereas in children with conduct disorder (Campbell et al. 1984) and schizophrenia (Spencer et al. 1992), marked improvement was associated with side effects. Furthermore, diagnosis may influence or determine the level of dosage. As tables 3 and 4 show, of the three diagnostic groups we studied, aggressive children with con-

Table 3. Daily dosage of haloperidol in mg in three diagnostic groups of children

Authors	*n*	mg/d	Mean	mg/kg/d	Mean
Conduct disorder					
Campbell et al. (1982)	5	4–16	9.2	0.12–0.76	—
Campbell et al. (1984)	20	1–6	2.95	0.04–0.21	0.096
Schizophrenia					
Spencer et al. (1992)	16	0.5–3.5	1.92	0.02–0.12	0.057
Autism					
Campbell (1978)	20	0.5–4.0[1]	1.65	—	—
Anderson et al. (1984)	40	1–3	1.11	0.019–0.217	0.05
Anderson et al. (1989)	45	0.25–4.00	0.844	0.016–0.184	0.047

[1]0.5 for 9 subjects.

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Table 4. Haloperidol daily dosage

	mg/d	Mean	mg/kg/d	Mean
Conduct disorder (Campbell et al. 1984)	1.0–6.0	2.95	0.04–0.21	0.096
Schizophrenia (Spencer et al. 1992)	0.5–3.5	1.92	0.02–0.12	0.057
Autism (Anderson et al. (1989)	0.25–4.0	0.844	0.016–0.184	0.047

duct disorder require the highest dose of haloperidol, followed by children with schizophrenia; children who have autism require the least.

Responders Versus Nonresponders. At the present time, 16 children have completed our ongoing study of haloperidol (4 in addition to the 12 reported in Spencer et al. 1992). As shown in table 5, 12 showed marked improvement and 4 showed mild or moderate improvement on haloperidol, as rated on the GCJ consensus rating. Clinical response to haloperidol seemed to be related to age, IQ, and duration of illness, as shown in table 6. The four children with schizophrenia who showed only mild to moderate improvement on haloperidol were younger, had lower IQs and earlier onset of psychosis, and were diagnosed as having schizophrenia at a younger age (see table 6). Age was also positively related to improvement in a large sample of children with autism (n = 125) and was the only factor predicting improvement on haloperidol (Locascio et al. 1991).

Of the symptoms shown by our sample of 16 children with schizophrenia, as rated on the CPRS, the reduction of persecutory ideation, which included persecutory delusions, was most significant ($p < 0.01$, one-tailed), followed by decreases in hallucinations, ideas of reference, and other thinking disorders ($p < 0.05$, one-tailed). Other thinking disorders (item 59 on the CPRS) include irrelevant speech, incoherent speech, or loose associations. Delusions, peculiar fantasies, and blunted affect did not change significantly, although there was a trend for delusions to decrease ($p = 0.07$, one-tailed). The 12 children who improved markedly had more severe symptoms at baseline than the 4 who improved only mildly (table 7). The only excep-

Table 5. Response to haloperidol of 16 children with schizophrenia, rated on four measures, mean

	Global Clinical Judgments consensus ratings								
	Mild/Moderate, n = 4			Marked, n = 12			Total sample, n = 16		
	Baseline	Placebo[1]	Haloperidol	Baseline	Placebo	Haloperidol	Baseline	Placebo[2]	Haloperidol
BPRS–C total pathology score[3]	45.56	41.11	43.80	53.82	40.92	33.50	51.75	47.26	36.10
CGI severity of illness[4]	5.24	4.11	4.25	5.34	4.00	2.79	5.32	4.34	3.10
CGI global improvement[5]	3.45	2.22	2.25	3.35	2.26	1.26	3.37	2.58	1.51

Note.—Global Clinical Judgments Scale (Campbell et al. 1984).

[1] n = 3 for the placebo condition.

[2] n = 15 for the placebo condition.

[3] BPRS–C = Brief Psychiatric Rating Scale for Children (Overall and Pfefferbaum 1982); total pathology score = sum of scores on 21 items; also see Overall and Gorham 1962.

[4] CGI = Clinical Global Impressions (Guy 1976); severity of illness item is an 8-point rating scale: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.

[5] CGI = Clinical Global Impressions (Guy 1976); global improvement item is an 8-point scale: 0 = not assessed; 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

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Table 6. Haloperidol response, as rated on the Global Clinical Judgments consensus ratings and demographic variables in 16 children with schizophrenia, mean (range)

	Global Clinical Judgments consensus ratings		
	Mild/Moderate *n* = 4	Marked *n* = 12	Total sample *n* = 16
Chronological Age (CA)	7.56 (6.83–8.08)	9.29 (5.50–11.75)	8.86 (5.50–11.75)
Full Scale IQ[1]	73.25 (65–83)	81.25 (60–123)	80.93 (60–123)
Verbal IQ[1]	75 (62–88)	82.92 (66–114)	80.93 (62–114)
Performance IQ[1]	74 (60–81)	83.25 (55–114)	80.94 (55–128)
CA at onset of behavioral problems	4.5 (3–5)	5 (1.5–9.0)	4.88 (1.5–9.0)
CA at onset of schizophrenia	5.88 (5–7)	8.34 (5–10.5)	7.7 (5–10.5)
CA at time diagnosis of schizophrenia was made[2]	7 (6–8)	8.92 (5–11)	8.44 (5–11)

Note—Global Clinical Judgments Scale (Campbell et al 1984).

[1]IQ = Intelligence quotient on Wechsler Intelligence Scale for Children–Revised (Wechsler 1974) or Wechsler Preschool and Primary Scale of Intelligence (Wechsler 1967).

[2]At the time when the child was accepted to the present study

Table 7. Haloperidol response, as rated on the Global Clinical Judgments consensus ratings and 8 selected CPRS items in 16 children with schizophrenia, mean

	Global Clinical Judgments consensus ratings								
CPRS[1] items	Mild/Moderate, *n* = 4			Marked, *n* = 12			Total sample, *n* = 16		
	Baseline	Placebo[2]	Haloperidol	Baseline	Placebo	Haloperidol	Baseline	Placebo[3]	Haloperidol
Suspicious affect	1.12	1.00	1.25	2.47	1.65	1.17	2.14	1.58	1.19
Blunted affect	1.65	1.33	1.25	2.83	2.53	1.58	2.54	2.29	1.50
Ideas of reference	1.44	1.33	1.00	2.62	2.28	1.36	2.33	2.09	1.27
Persecutory	2.04	1.22	1.00	3.99	3.54	1.58	3.50	3.08	1.43
Other thinking disorders	5.01	2.00	3.75	2.79	1.86	1.83	3.34	1.73	2.31
Delusions	3.88	3.67	3.92	4.28	3.31	2.11	4.17	3.36	2.56
Hallucinations	4.04	3.56	2.83	4.61	2.93	1.36	4.47	3.06	1.73
Peculiar fantasies	3.08	2.00	3.92	4.18	2.86	2.36	3.90	2.74	2.75

Note.—Global Clinical Judgments Scale (Campbell et al. 1984).

[1]CPRS = Children's Psychiatric Rating Scale (National Institute of Mental Health 1985); each item is an 8-point scale: 0 = not assessed; 1 = not present, 2 = very mild; 3 = mild; 4 = moderate; 5 = moderately severe; 6 = severe; 7 = extremely severe

[2]n = 3 for the placebo condition.

[3]*n* = 15 for the placebo condition.

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tion was item 59, other thinking disorders, which was higher for the four children who improved mildly or moderately and also was the highest mean on baseline of all the means. On the whole, the four children who showed less improvement were more impoverished and displayed less florid symptoms.

In summary, though the amount of data is modest, and much more research is required, there is some evidence that in young children with schizophrenia haloperidol is an effective psychoactive agent when administered on a short-term basis under inpatient conditions. Under these conditions haloperidol is also a safe drug, although side effects, mainly sedation, may be seen at optimal doses.

Conclusions

Our study in progress (Spencer et al. 1992) has replicated previous findings that children under age 12 can be diagnosed with schizophrenia using *DSM–III* (Green et al. 1984; Green and Padron-Gayol, 1986; Watkins et al. 1988; Russell et al. 1989) or *DSM–III–R* (Werry et al. 1991) criteria. Our study also shows that children with schizophrenia display the same symptoms as adult schizophrenia patients. The preliminary results of our ongoing double-blind, placebo-controlled study of haloperidol are promising; ours is the first study of this type in children (Spencer et al. 1992). Haloperidol has been superior to placebo in reducing several symptoms, including hallucinations and persecutory ideation, and all 16 children have continued receiving haloperidol upon discharge from the study. These results must be replicated in larger samples of patients. Longitudinal followup of these children will be pursued to assess their response to long-term haloperidol and to monitor their diagnostic and phenomenologic status as they enter adolescence and young adulthood.

References

Aman, M.G. Drugs, learning and the psychotherapies. In: Werry, J.S., ed. *Psychopharmacology. The Use of Behavior Modifying Drugs in Children.* New York, NY: Brunner/Mazel, 1978. pp. 79–108.

American Psychiatric Association. *DSM–III: Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington, DC: The Association, 1980.

American Psychiatric Association. *DSM–III–R: Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed., revised. Washington, DC: The Association, 1987.

Anderson, L.T.; Campbell, M.; Adams, P.; Small, A.M.; Perry, R.; and Shell, J. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *Journal of Autism and Developmental Disorders,* 19:227–239, 1989.

Anderson, L.T.; Campbell, M.; Grega, D.M.; Perry, R.; Small, A.M.; and Green, W.H. Haloperidol in the treatment of infantile autism: Effects on learning and behavioral symptoms. *American Journal of Psychiatry,* 141:1195–1202, 1984.

Andreasen, N.C., and Olsen, S. Negative *v* positive schizophrenia: Definition and validation. *Archives of General Psychiatry,* 39:789–794, 1982.

Beitchman, J.H. Childhood schizophrenia. A review and comparison with adult-onset schizophrenia. *Psychiatric Clinics of North America,* 8:793–814, 1985.

Campbell, M. The use of drug treatment in infantile autism and childhood schizophrenia. In: Lipton, M.A.; DiMascio, A.; and Killam, K.F., eds. *Psychopharmacology: A Generation of Progress.* New York, NY: Raven Press, 1978. pp. 1451–1461.

Campbell, M.; Anderson, L.T.; and Small, A.M. Pharmacotherapy in autism. A summary of research at Bellevue/New York University. *Brain Dysfunction,* 3:299–307, 1990.

Campbell, M.; Cohen, I.L.; and Small, A.M. Drugs in aggressive behavior. *Journal of the American Academy of Child Psychiatry,* 21:107–117, 1982.

Campbell, M.; Gonzalez, N.M.; Ernst, M.; Silva, R.R.; and Werry, J.S. Antipsychotics (neuroleptics). In: Werry, J.S., and Aman, M.G., eds. *Practitioner's Guide to Psychoactive Drugs for Children and Adolescents.* New York, NY: Plenum Press, 1993. pp. 269–296.

Campbell, M.; Green, W.H.; and Deutsch, S.I. *Child and Adolescent Psychopharmacology.* Beverly Hills, CA: Sage Publications, 1985.

Campbell, M.; Small, A.M.; Green, W.H.; Jennings, S.J.; Perry, R.; Bennett, W.G.; and Anderson, L.T. Behavioral efficacy of haloperidol and lithium carbonate: A comparison in hospitalized aggressive children with conduct disorder. *Archives of General Psychiatry,* 41:650–656, 1984.

Campbell, M., and Spencer, E.K. Psychopharmacology in child and adolescent psychiatry: A review of the past five years. *Journal of the American Academy of Child and Adolescent Psychiatry,* 27:269–279, 1988.

Downloaded from https://academic.oup.com/schizophreniabulletin/article/20/4/713/1933469 by guest on 18 April 2024

Campbell, M.; Spencer, E.K.; Kowalik, S.C.; and Erlenmeyer-Kimling, L. Schizophrenic and psychotic disorders in childhood and adolescence. In: Wiener, J.M., ed. *Textbook of Child and Adolescent Psychiatry*. Washington, DC: American Psychiatric Press, 1991. pp. 223–239.

Debray, P.; Messerschmitt, P.; Lonchap, D.; and Herbault, M. The use of pimozide in child psychiatry. *Nouvelle Presse Medicale*, 43(1):2917–2918, 1972.

Gordon, C.T.; Frazier, J.A.; McKenna, K.; Giedd, J.; Zametkin, A.; Zahn, T.; Hommer, D.; Hong, W.; Kaysen, D.; Albus, K.E.; and Rapoport, J.L. Childhood-onset schizophrenia: An NIMH study in progress. Schizophrenia Bulletin, 20(4):697–712, 1994.

Green, W.H.; Campbell, M.; Hardesty, A.S.; Grega, D.M.; Padron-Gayol, M.; Shell, J.; and Erlenmeyer-Kimling, L. A comparison of schizophrenic and autistic children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 23:399–409, 1984.

Green, W.H., and Padron-Gayol, M. Schizophrenic disorder in childhood: Its relationship to *DSM–III* criteria. In: Shagass, C.; Josiassen, R.C.; Bridger, W.H.; Weiss, K.J.; Stoff, D.; and Simpson, G.M., eds. New York, NY: Elsevier Science Publishers, 1986. pp. 1484–1486.

Guy, W. *ECDEU Assessment Manual for Psychopharmacology*, revised. DHEW Pub. No. (ADM)76-338. Rockville, MD: National Institute of Mental Health, 1976.

Hollingshead, A.B., and Redlich, F.C. *Social Class and Mental Illness*. New York, NY: John Wiley & Sons, 1958.

Kanner, L. Problems of nosology and psychodynamics of early infantile autism. *American Journal of Orthopsychiatry*, 19:416–426, 1949.

Karno, M., and Norquist, G.S. Schizophrenia: Epidemiology. In: Kaplan, H.I., and Sadock, B.J., eds. *Comprehensive Textbook of Psychiatry/V*. Vol. I. Baltimore, MD: Williams & Wilkins Company, 1989. pp. 699–704.

Kolvin, I. Psychoses in childhood—A comparative study. In: Rutter, M., ed. *Infantile Autism. Concepts, Characteristics and Treatment*. London, England: Churchill Livingstone, 1971*a*. pp. 7–26.

Kolvin, I. Studies in the childhood psychoses: I. Diagnostic criteria and classification. *British Journal of Psychiatry*, 118:381–384, 1971*b*.

Kolvin, I.; Garside, R.F.; and Kidd, J.S.H. Studies in the childhood psychoses: IV. Parental personality and attitude and childhood psychoses. *British Journal of Psychiatry*, 118:403–406, 1971*a*.

Kolvin, I.; Humphrey, M.; and McNay, A. Studies in the childhood psychoses: VI. Cognitive factors in childhood psychoses. *British Journal of Psychiatry*, 118:415–419, 1971*b*.

Kolvin, I.; Ounsted, C.; Humphrey, M.; and McNay, A. Studies in the childhood psychoses: II. The phenomenology of childhood psychoses. *British Journal of Psychiatry*, 118:385–395, 1971*c*.

Kolvin, I.; Ounsted, C.; Richardson, L.M.; and Garside, R.F. Studies in the childhood psychoses: III. The family and social background in childhood psychoses. *British Journal of Psychiatry*, 118:396–402, 1971*d*.

Kolvin, I.; Ounsted, C.; and Roth, M. Studies in the childhood psychoses: V. Cerebral dysfunction and childhood psychoses. *British Journal of Psychiatry*, 118:407–414, 1971*e*.

Kydd, R.R., and Werry, J.S. Schizophrenia in children under 16 years. *Journal of Autism and Developmental Disorders*, 12:343–357, 1982.

Locascio, J.J.; Malone, R.P.; Small, A.M.; Kafantaris, V.; Ernst, M.; Lynch, N.S.; Overall, J.E.; and Campbell, M. Factors related to haloperidol response and dyskinesias in autistic children. *Psychopharmacology Bulletin*, 27(2):119–126, 1991.

Loranger, A.W. Sex differences in age at onset of schizophrenia. *Archives of General Psychiatry*, 41:157–161, 1984.

McClellan, J.M., and Werry, J.S. Schizophrenia. *Psychiatric Clinics of North America*, 15(1):131–148, 1992.

Meyers, B.; Tune, L.E.; and Coyle, J.T. Clinical response and serum neuroleptic levels in childhood schizophrenia. *American Journal of Psychiatry*, 137:483–484, 1980.

Naruse, H.; Nagahata, M.; Nakane, Y.; Shirahashi, K.; Takesada, M.; and Yamazaki, K. A multi-center double-blind trial of pimozide (Orap), haloperidol and placebo in children with behavioral disorders, using a crossover design. *Acta Paedopsychiatrica*, 48:173–184, 1982.

National Institute of Mental Health. Special feature: Rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacology Bulletin*, 21(4):765–770, 1985.

Overall, J.E., and Gorham, D.R. The Brief Psychiatric Rating Scale. *Psychological Reports*, 10:799–812, 1962.

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Overall, J.E., and Pfefferbaum, B. The Brief Psychiatric Rating Scale for Children. *Psychopharmacology Bulletin,* 18(2):10–16, 1982.

Pangalila-Ratulangi, E.A. Pilot evaluation of Orap (pimozide R6238) in child psychiatry. *Psychiatria Neurologia Neurochirurgia,* 76:17–27, 1973.

Platt, J.; Campbell, M.; Green, W.H.; and Grega, D.M. Cognitive effects of lithium carbonate and haloperidol in treatment-resistant aggressive children. *Archives of General Psychiatry,* 41:657–662, 1984.

Pool, D.; Bloom, W.; Wielke, D.H.; Roniger, J.J.; and Gallant, D.M. A controlled evaluation of loxitane in seventy-five adolescent schizophrenic patients. *Current Therapeutic Research,* 19:99–104, 1976.

Realmuto, G.M.; Erickson, W.D.; Yellin, A.M.; Hopwood, J.H.; and Greenberg, L.M. Clinical comparison of thiothixene and thioridazine in schizophrenic adolescents. *American Journal of Psychiatry,* 141:440–442, 1984.

Reich, W., and Welner, Z. *Diagnostic Interview for Children and Adolescents–Revised.* St. Louis, MO: Washington University Press, 1990.

Russell, A.T.; Bott, L.; and Sammons, C. The phenomenology of schizophrenia occurring in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry,* 28:399–407, 1989.

Rutter, M. Childhood schizophrenia reconsidered. *Journal of Autism and Childhood Schizophrenia,* 2:315–337, 1972.

Shell, J.; Spencer, E.K.; Curren, E.L.; Perry, R.; Die Trill, M.; Campbell, M.; Lynch, N.; and Polonsky, B. Long-term haloperidol administration and intellectual functioning in autistic children. In: Greenhill, L., ed. *Scientific Proceedings of the Annual Meeting.* Vol. III. Washington, DC: American Academy of Child and Adolescent Psychiatry, 1987. p. 49

Siefen, G., and Remschmidt, H. Behandlungsergebnisse mit Clozapin bei schizophrenen Jugendlichen. *Zeitschrift für Kinder- und Jugendpsychiatrie,* 14:245–257, 1986.

Spencer, E.K.; Kafantaris, V.; Padron-Gayol, M.; Rosenberg, C.; and Campbell, M. Haloperidol in schizophrenic children: Early findings from a study in progress. *Psychopharmacology Bulletin,* 28(2):183–186, 1992.

Watkins, J.M.; Asarnow, R.F.; and Tanguay, P.E. Symptom development in childhood onset schizophrenia. *Journal of Child Psychology and Psychiatry,* 29:865–878, 1988.

Wechsler, D. *Wechsler Preschool and Primary Scale of Intelligence.* New York, NY: Psychological Corporation, 1967.

Wechsler, D. *Wechsler Intelligence Scale for Children–Revised.* New York, NY: Psychological Corporation, 1974.

Werry, J.S., and Aman, M.G. Methylphenidate and haloperidol in children. *Archives of General Psychiatry,* 32:790–795, 1975.

Werry, J.S.; McClellan, J.M.; and Chard, L. Childhood and adolescent schizophrenic, bipolar and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry,* 30:457–465, 1991.

World Health Organization. *Mental Disorders: Glossary and Guide to Their Classification in Accordance With the Ninth Revision of the International Classification of Diseases.* Geneva, Switzerland: The Organization, 1978.

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