The Efficacy and Safety of Conventional and Atypical Antipsychotics in First-Episode Schizophrenia: A Review of the Literature

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Abstract

Objective: To review the evidence for the short- and long-term efficacy and safety of conventional and atypical agents in patients with first-episode schizophrenia, and to highlight strategies to improve medication adherence in this patient group. **Methods:** Studies published or in press between January 1975 and December 2006 that evaluated the efficacy and safety of conventional and atypical antipsychotic agents in first-episode schizophrenia were identified from a literature search using MEDLINE and reviewed. In addition, issues of adherence to medication were reviewed. **Results:** Seventeen studies were identified that met criteria for inclusion in the review. Results from short-term studies indicate that both atypical and conventional agents produced substantial and significant reductions in symptom severity and psychopathology. However, the long-term studies found advantages for atypical antipsychotics over conventional agents, including faster treatment responses, fewer relapses, more time spent in remission, and better retention of patients in treatment. In general, conventional antipsychotics were associated with more extrapyramidal symptoms, while patients receiving atypical agents experienced greater weight gain and prolactin elevation. Studies that compared dosages suggest that lower doses are as or more effective than higher doses in first-episode patients. Adherence remains a critical problem in the first episode. Long-acting antipsychotic agents that ensure continuous drug delivery and the provision of appropriate psychosocial therapy have the potential to address this problem. Initial data reviewed here suggest that long-acting risperidone, the first atypical antipsychotic available in a long-acting formulation, could be a valuable addition to the armamentarium of pharmacologic treatment strategies for long-term treatment of first-episode schizophrenia. **Conclusion:** Atypical antipsychotic agents offer advantages in the long-term management of first-episode schizophrenia. A long-acting atypical antipsychotic may provide a novel strategy for patients with first-episode schizophrenia.

Key Words: First-Episode Schizophrenia, Antipsychotic Medications, Outcomes

Introduction

Since the early 1990s, there has been a growing interest in the treatment of the early phases of psychosis (1). The first episode of schizophrenia can be defined both conceptually and clinically. Conceptually, it is defined according to the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association by both the characteristic symptoms of schizophrenia (positive and negative symptoms) and their duration (at least six months) (2). In clinical practice, however, patients rarely present for treatment at the precise point in time when they meet these two formal criteria. A clinical definition of a first-episode schizophrenia patient, therefore, is broader and includes patients who do not meet the duration criterion set out in the *Manual*. Patients may also have suffered symptoms for months or even years before presenting for diagnosis. Indeed, in many studies of first-episode patients, the duration of untreated psychotic symptoms is over one year (3). Researchers and clinicians often assess antipsychotic medication exposure to determine whether a patient is in a first or later episode of their illness, with a number of studies arbitrarily setting this criterion for first-episode schizophrenia at twelve weeks or less of medication exposure (3). As a result, first-episode

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patients are not always drug-naive. Taking all these criteria into consideration, a useful operational definition of first-episode schizophrenia is a patient who has characteristic symptoms of schizophrenia, regardless of whether these symptoms have been present for six months, and who has not yet received more than three months of treatment with antipsychotic medication.

A growing body of evidence suggests that intervention with appropriate antipsychotic medications during the early stages of schizophrenia may have a beneficial effect on functioning and improve the long-term course of the disease (4-9). Indeed, several studies of patients in the first episode of their illness have demonstrated higher relative rates of therapeutic response and symptom remission compared to patients with multiple prior episodes (10-14). However, although the majority of patients recover from their psychotic symptoms following their first episode of illness (15), they are subsequently at a high risk for a relapse and, ultimately, for persistent morbidity in the form of residual positive or negative symptoms, neurocognitive impairment, and deficits in social and vocational functioning (16, 17).

The management of early schizophrenia illness, therefore, remains a challenging task for psychiatrists. The treatment of these patients is further complicated by the fact that first-episode patients appear to be more sensitive to the pharmacologic effects of antipsychotic drugs than older chronic patients in that they exhibit more frequent extrapyramidal and other side effects and require lower drug doses (12, 18). Moreover, first-episode patients are highly likely to abuse drugs and alcohol, are more likely to have depression and suicidal ideation, and are often lacking "disease insight," all of which may negatively impact on medication adherence (3, 19-21). Although medication non-adherence is a problem with any long-term treatment, it is especially problematic in patients early in their course of schizophrenia and is considered to be a key factor associated with relapse. Robinson and colleagues found that the risk of relapse in patients with early disease was almost five times greater when not taking antipsychotic medications (3). Successive relapses can increase refractoriness to future treatment (22) and have been associated with biologic changes in brain morphology (23). Furthermore, with each occurring relapse the likelihood that patients will return to their baseline level of functioning decreases (22). For this reason, the choice of an antipsychotic agent that offers both effectiveness and good tolerability in first-episode schizophrenia is essential if better treatment adherence is to be attained.

Until the past decade, the conventional antipsychotic agents, which were introduced in the 1950s, were the mainstay of treatment for patients with schizophrenia, including those early in the course of illness. However, the recent availability of the second-generation or so-called "atypical" antipsychotic agents has further sparked research in the early phases of schizophrenia. While both conventional and atypical agents offer similar efficacy for amelioration of positive symptoms in first-episode patients, atypical agents may provide better tolerability, especially with regards to extrapyramidal symptoms (EPS) and tardive dyskinesia (24). However, weight gain, sedation, and an apparently adverse impact on lipid and glucose metabolism have been linked to treatment with some currently available atypical antipsychotic agents (25-28), which are important considerations relating to both the short- and long-term treatment of patients with schizophrenia. Unfortunately, comparisons between the conventional and atypical antipsychotic agents have been almost entirely conducted in studies of chronically ill patients, whose symptoms may have been partially resistant to treatment. Although the first treatment intervention for patients with recent onset of schizophrenia is a critical therapeutic opportunity that may potentially influence the course and outcome of what is often a lifelong illness (29), the comparative efficacy and safety of conventional and atypical antipsychotic agents has not been extensively examined in first-episode patients.

The aim of this review is to investigate current treatment options for first-episode patients with schizophrenia as currently presented in the literature, and to review the evidence for both the short- and long-term efficacy and safety of conventional and atypical agents in patients with first-episode schizophrenia. In addition, a number of strategies to improve patient adherence and help prevent relapse in patients with first-episode schizophrenia will be highlighted.

Methods

This review evaluates the literature published between January 1975 and December 2006 that studied the efficacy and safety of conventional and atypical antipsychotic agents for the treatment of first-episode patients, as identified from an electronic literature research of English-language articles using MEDLINE. The primary search parameters were "first-episode" or "early-episode" and "schizophrenia" or "psychosis" and "antipsychotic." Only publications in peer-reviewed journals that reported results based on original data from clinical trials were included. No formal assessment of the quality of the trials or of the definitions of "first episode" was undertaken. General review papers and meta-analyses were excluded from this analysis.

Results

Altogether, seventeen studies were identified that evaluated the short-term and/or long-term (≥6 months) comparative efficacy and safety of conventional and atypical antipsychotic agents in the treatment of first-episode psychosis either given orally or via intramuscular injections. Findings of studies that evaluated both short- and long-term efficacy are represented in both sections.

Short-Term Studies in Patients with First-Episode Schizophrenia

Eleven short-term studies examined the efficacy and safety of oral conventional (haloperidol and chlorpromazine) and atypical antipsychotic agents (clozapine, risperidone, and olanzapine) in first-episode schizophrenia patients. A further study examined the clinical efficacy of intramuscular injections of the conventional agent fluphenazine enanthate.

Oral Antipsychotic Agents—Randomized Trials

Nine short-term, randomized, controlled clinical studies evaluated the efficacy and safety of oral antipsychotic agents in the treatment of first-episode schizophrenia. The results of these studies are presented in Table 1. A further two non-randomized studies were also identified.

Emsley and colleagues conducted a six-week, international, multi-center, double-blind study in 183 patients with a first psychotic episode who were treated with flexible doses of risperidone or haloperidol (mean daily doses = 6.1 and 5.6 mg, respectively). The authors report that the severity of psychotic symptoms (Positive and Negative Syndrome Scale [PANSS] total scores) improved clinically compared to baseline in both the risperidone and haloperidol groups (p=0.001, 63% and 56% of patients, respectively), with no differences between the treatment arms. The severity of EPS (Extrapyramidal Symptom Rating Scale [ESRS] scores) was significantly lower in patients receiving risperidone than haloperidol (30). Furthermore, a post hoc analysis revealed that the severity of EPS and the use of anti-parkinsonian medications were significantly lower in patients receiving low doses (≤ maximum 6 mg/day) than high doses (maximum >6 mg/day) of risperidone or haloperidol (30).

Sanger and colleagues evaluated the comparative efficacy and safety of olanzapine and haloperidol (mean modal dose = 11.6 and 10.8 mg, respectively) in a subpopulation of first-episode patients (n=83) drawn from a larger multi-center, international, double-blind, six-week acute trial (31). Compared to haloperidol, olanzapine demonstrated a statistically significantly greater reduction in the Brief Psychiatric Rating Scale (BPRS) total (primary efficacy outcome) and negative scores as well as PANSS total and positive scores from baseline to endpoint. Olanzapine-treated patients were twice as likely to achieve a clinical response (defined as a 40% or greater improvement from baseline in BPRS total score) than haloperidol-treated patients. Olanzapine-treated patients further showed statistically significant improvements in the Simpson Angus Scale and the Barnes Akathisia Scale scores, while haloperidol-treated patients worsened on both measures (31).

Two studies compared fixed doses of risperidone (32, 33). Lane and colleagues reported the findings of a double-blind pilot study in 20 drug-naive and newly hospitalized first-episode schizophrenia patients (32). Results indicated that both doses (3 and 6 mg/day) had comparable efficacy over six weeks with at least 20% symptom improvement (64% and 67%, respectively). The 3 mg/day group "tended" to have fewer EPS and other adverse events. However, the authors recognize that the small study size limits interpretation of findings (32). Merlo and colleagues compared 2 and 4 mg/day in an eight-week, double-blind trial to assess clinical psychopathology and fine motor functions in first-episode, acutely psychotic, neuroleptic-naive patients (33). Both doses significantly reduced positive ($p<0.0001$) and negative ($p<0.01$) symptoms at week eight, but there were no differences between the two groups in these parameters. There were no significant dose differences in motor side effects using the Barnes Akathisia Scale and the Simpson Angus Scale, but computerized fine motor assessment showed significantly less motor dysfunction in the 2 mg/day group (33).

Lieberman and colleagues compared the acute effectiveness of haloperidol (mean modal dose 4.4 mg) with that of olanzapine (mean modal dose 9.1 mg) in patients with first-episode psychosis in a randomized, double-blind trial (n=263) (34). Both antipsychotic agents were associated with substantial and comparable baseline-to-endpoint reductions in symptom severity, which did not differ significantly in last-observation-carried-forward analyses. Olanzapine-treated patients experienced a lower rate of treatment-emergent parkinsonism and akathisia, but had significantly more weight gain compared with the haloperidol-treated patients (34). Overall, significantly more olanzapine-treated patients than haloperidol-treated patients completed the twelve-week study (67% versus 54%) (34).

A second study by Lieberman and colleagues compared the efficacy and safety of chlorpromazine and clozapine (median dose 600 mg and 400 mg/day, respectively) in treatment-naive patients experiencing their first episode of schizophrenia (35). Results from the twelve-week analysis of this fifty-two week trial indicate that clozapine was superior to chlorpromazine on some measures of symptom severity: the Scale for the Assessment of Negative Symptoms (SANS p=0.01) and the Global Assessment of Functioning (GAF p=0.006) but not others; BPRS total score (p=0.33) and Clinical Global Impressions (CGI p=0.13). The long-term results of this study are presented later in this review.

Schooler and colleagues compared risperidone with haloperidol treatment (mean modal = 3.3 and 2.9 mg/day, respectively) in a randomized and double-blind trial (36). There was no significant difference between the groups in improvement on the PANSS total score or CGI at three months; more than three-quarters of both groups showed clinical improvement (decrease of more than 20% in total PANSS score) (Table 1). However, significantly more weight gain was observed in the risperidone group early in treatment (36). The long-term results of this study are presented later in this review.

Oosthuisen and colleagues compared the efficacy and

Table 1 Overview of short-term, randomized, controlled, clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents

Study details	Treatment groups	Efficacy	Adverse events
Oral antipsychotics			
Emsley et al 1999 (30) • 6-week, double-blind, multi-center, comparative study in patients with a first psychotic episode • Patients aged 15–45 years	• Starting dose=2 mg/day, with flexible dosing (2–8 mg/day) thereafter in 2 mg/day increments • Risperidone (n=99): mean daily dose 6.1 mg • Haloperidol (n=84): mean daily dose 5.6 mg	• 80% of risperidone-treated patients and 69% of haloperidol-treated patients completed the study • Percentage of patients clinically improved (≥50% reduction in PANSS total scores): o Risperidone: 63% o Haloperidol: 56% o Difference between groups, p=0.19 • Percentage of patients "not ill" or "with mild symptoms" at endpoint: o Risperidone: 67% o Haloperidol: 63% o Difference between groups, p=0.59 • Percentage of patients "much" or "very much improved:" o Risperidone: 71% o Haloperidol: 70% o Difference between groups, p=0.817	• Percentage of patients reporting AEs: o Risperidone: 78% o Haloperidol: 90% o Difference between groups, p<0.05 • Percentage of patients withdrawing due to AEs: o Risperidone: 8% o Haloperidol: 26% o Difference between groups, p=0.02 • Percentage of patients requiring anti-parkinsonian medication: o Risperidone: 50% o Haloperidol: 75% o Difference between groups, p<0.001 • Percentage of patients with non-extrapyramidal AEs: o Risperidone: 59% o Haloperidol: 62%
Sanger et al 1999 (31) • A subpopulation of first-episode patients from a prospective, multi-center, double-blind, 6-week acute study • Length of current psychotic episode ≤5 years • Patients aged ≤45 years at onset of first psychotic symptoms	• Starting dose=5 mg/day, with flexible dosing thereafter (5–20 mg/day) in 5 mg increments/7 days • Olanzapine (n=59): mean modal dose 11.6 mg/day • Haloperidol (n=24): mean modal dose 10.8 mg/day	• 73% of olanzapine-treated patients and 38% of haloperidol-treated patients completed the study • Percentage of patients discontinuing treatment due to lack of efficacy: o Olanzapine: 13.6% o Haloperidol: 33.3% o Difference between groups, p=0.06 • Mean (±SD) improvement in total PANSS scores at endpoint: o Olanzapine: –27.5±20.5 o Haloperidol: –16.3±18.1 o Difference between groups, p=0.02 • Percentage of patients with clinical response (40% or greater) improvement in BPRS total score from baseline: o Olanzapine: 67.2% o Haloperidol: 29.2% o Difference between groups, p=0.003 • Percentage of patients with a reduction in BPRS total score of at least 20%: o Olanzapine: 82.2% o Haloperidol: 58.3% o Difference between groups, p=0.03	• Percentage of patients withdrawing due to AEs: o Olanzapine: 2% o Haloperidol: 17% • Mean (±SD) change from baseline to endpoint in SAS total score: o Olanzapine: –0.5±3.3 o Haloperidol: 4.5±7.4 o Difference between groups, p<0.001 • Mean (±SD) change from baseline to endpoint on BARS: o Olanzapine: –0.1±0.8 o Haloperidol: 0.5±1.2 o Difference between groups, p=0.005 • Percentage of patients with treatment-emergent parkinsonian (total score of 3 or more on SAS): o Olanzapine: 18.8% o Haloperidol: 52.6% o Difference between groups, p=0.01 • Percentage of patients with treatment-emergent akathisia (total score of 2 or more on BARS): o Olanzapine: 11.3% o Haloperidol: 38.1% o Difference between groups, p=0.02 • Percentage of patients receiving anticholinergics: o Olanzapine: 13.6% o Haloperidol: 41.7% o Difference between groups, p=0.008

Table 1 Overview of short-term, randomized, controlled, clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents *(Continued)*

Study details	Treatment groups	Efficacy	Adverse events
			• Mean increase in body weight: o Olanzapine: 4.1 kg o Haloperidol: 0.5 kg o Difference between groups, p<0.001 • Prolactin levels were 4.5 times higher in the haloperidol group at endpoint, p<0.001
Lane et al 2001 (32) • 6-week, pilot, double-blind, fixed-dose study in antipsychotic-naive patients with first-episode schizophrenia • Patients aged 18–45 years	• Risperidone 3 or 6 mg/day (n=24) after titration over the first week	• 83% of patients completed the study • Percentage of patients achieving response (≥20% reduction on PANSS). No statistics stated. • On Day 14: o Risperidone 3 mg: 27.3% o Risperidone 6 mg: 50.6% • On Day 28: o Risperidone 3 mg: 72.7% o Risperidone 6 mg: 50.0% • On Day 42: o Risperidone 3 mg: 63.6% o Risperidone 6 mg: 66.7% • Median time to first response was 28 days for both groups	• The 3 mg/day group had fewer EPS and other side effects • Number of patients receiving benztropine at endpoint: o Risperidone 3 mg: 3 patients o Risperidone 6 mg: 6 patients • Number of patients receiving lorazepam at endpoint: o Risperidone 3 mg: 5 patients o Risperidone 6 mg: 4 patients
Merlo et al 2002 (33) • 8-week, double-blind, fixed-dose study in acutely psychotic, neuroleptic-naive patients • Patients aged 16–40 years	• Risperidone 2 mg/day (n=23) • Risperidone 4 mg/day (n=26)	• 79.6% of patients completed study • Mean (±SD) improvement in total BPRS scores at endpoint: o Risperidone 2 mg: –32.3±15.1 o Risperidone 4 mg: –38.4±16.9 o No statistical difference between groups • Probability of remission at endpoint: o Risperidone 2 mg: 69.6% o Risperidone 4 mg: 76.9% o Difference between groups, p=0.20 • Probability of improvement at endpoint: o Risperidone 2 mg: 65.2% o Risperidone 4 mg: 80.8% o Difference between groups, p=0.23 • Less motor dysfunction in the 2 mg group than the 4 mg group as assessed by: o Line Tracking Test, p=0.015 o Tapping Test, p=0.004	• No serious AEs reported • Patients with score of 3 or more ("strong") on SAS: o Risperidone 2 mg: 2 patients o Risperidone 4 mg: 3 patients • Patients with score of 2 or more ("moderate") on BARS: o Risperidone 2 mg: 2 patients o Risperidone 4 mg: 4 patients • 30–50% of patients had mild-to-moderate degrees of side effects for: concentration difficulties, asthenia/increased fatigue, sleepiness/sedation, failing memory, depression, tension, increased sleep duration, emotional indifference, weight gain, diminished sexual desire
Lieberman et al 2003 (34) • A 12-week, randomized, double-blind trial in patients with first-episode psychosis • Patients aged 16–40 years	• First 6 weeks initial dose titration range: o 5–10 mg = olanzapine o 2–6 mg = haloperidol	• 67% of olanzapine-treated patients and 54% of haloperidol-treated patients completed the study	• Percentage of patients withdrawing due to AEs: o Olanzapine: 3.1% o Haloperidol: 6.8%

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Table 1 Overview of short-term, randomized, controlled, clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents *(Continued)*

Study details	Treatment groups	Efficacy	Adverse events
• Mean duration of illness was 62.5 weeks	• Second 6 weeks dose titration range: o 5–20 mg = olanzapine o 2–20 mg = haloperidol • Olanzapine (n=131): mean modal dose 9.1 mg/day • Haloperidol (n=132): mean modal dose 4.4 mg/day	• Mean (±SD) improvement in PANSS total scores: o Olanzapine: 75.90±18.07 at baseline to 55.85±16.52 at endpoint o Haloperidol: 75.56±14.90 at baseline to 59.33±19.41 at endpoint o Difference between groups, p=0.58 • Percentage of patients responding to treatment at endpoint: o Olanzapine: 55% o Haloperidol: 46% o Difference between groups, p=0.19 • Median time-to-response: o Olanzapine: 7.9 weeks o Haloperidol: 8.4 weeks o Difference between groups, NS	• Patients receiving concomitant medications: o Olanzapine: anticholinergics (17%), benzodiazepines (63%), propranolol (2%) o Haloperidol: anticholinergics (52%), benzodiazepines (74%), propranolol (18%) • Incidence of treatment-emergent parkinsonism (change in SAS from ≤3 at baseline to >3 post-baseline): o Olanzapine: 26.1% o Haloperidol: 54.8% o Difference between groups, p<0.001 • Incidence of treatment-emergent akathisia (change in BARS from <2 at baseline to ≥2 post baseline): o Olanzapine: 11.9% o Haloperidol: 51.2% o Difference between groups, p<0.001 • Mean increases in prolactin: o Olanzapine: 1.2 ng/ml o Haloperidol: 6.9 ng/ml o Difference between groups, p<0.0001 • Proportion of patients with a >7% increase in body weight: o Olanzapine: 61.5% o Haloperidol: 22.7% o Difference between groups, p<0.001
Lieberman et al 2003 (35) • 12-week, interim analysis from a 52-week, flexible-dose, randomized, double-blind study in antipsychotic-naive first-episode schizophrenia • Patients aged 16–40 years • Duration of symptoms ≤5 years	• Medication doses were increased using a standardized regimen over the first 28 days • Chlorpromazine (n=83): median dose 600 mg/day • Clozapine (n=81): median dose 400 mg/day	• 90% of chlorpromazine-treated patients and 89% of clozapine-treated patients completed 12 months of treatment • Improvement in BPRS total scores from baseline to week 12 (p=0.33 between groups): o Chlorpromazine: 44.4 at baseline to 23.6 at week 12 o Clozapine: 43.4 at baseline to 22.2 at week 12 • Improvement in SANS total scores from baseline to week 12: o Chlorpromazine: 16.6 at baseline to 11.4 at week 12 o Clozapine: 14.8 at baseline to 6.9 at week 12 o Difference between groups, p<0.01 • Improvement in CGI-S scores from baseline to week 12: o Chlorpromazine: 5.6 at baseline to 2.4 at week 12	• Mean SAS total score at week 12: o Chlorpromazine: 1.41 o Clozapine: 0.41 o Difference between groups, p<0.01 • Mean parkinsonian score at week 12: o Chlorpromazine: 0.90 o Clozapine: 0.38 o Difference between groups, p<0.01

Table 1 Overview of short-term, randomized, controlled, clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents *(Continued)*

Study details	Treatment groups	Efficacy	Adverse events
		o Clozapine: 5.6 at baseline to 2.1 at week 12 o Difference between groups, p=0.13 • Improvement in GAF from baseline to week 12: o Chlorpromazine: 35.4 at baseline to 67.7 at week 12 o Clozapine: 36.2 at baseline to 72.8 at week 12	
Schooler et al 2005 (36) • 3-month interim analysis from a double-blind, randomized, controlled, flexible-dose study in first-episode psychosis • Patients aged 16–45 years • <12 weeks exposure to antipsychotics	• Initial dose=1 mg/day, increased to 2 mg/day on day 4 and by 1 mg/day/ 7 days (up to 4 mg/day) • Risperidone (n=278): mean modal dose 3.3 mg/day • Haloperidol (n=277): mean modal dose 2.9 mg/day	• Patients with clinical improvement (>20% decrease in total PANSS score): o Risperidone: 73.6% o Haloperidol: 76.2% o Difference between groups, p=0.48	• Mean increase in body weight: o Risperidone: 4.6 kg o Haloperidol: 3.5 kg o Difference between groups, p=0.03
Oosthuizen et al 2004 (37) • 6-week, randomized, controlled study in first-episode psychosis • Patients aged 16–55 years • ≤4 weeks exposure to antipsychotics	• Haloperidol 2 mg (n=20) • Haloperidol 8 mg (n=20) (increased in 2 mg/day increments every two days from initial dose of 2 mg/day)	• 73% of patients completed the study • Mean (±SD) improvement in total PANSS scores from baseline to endpoint: o Haloperidol 2 mg: 100.1±19.3 at baseline to 72.3±29.8 at endpoint o Haloperidol 8 mg: 95.7±13.0 at baseline to 76.1±32.6 at endpoint o Difference between groups, p=0.70 • Mean CGI-S ratings at endpoint: o Haloperidol 2 mg: 3.47±1.71 o Haloperidol 8 mg: 3.35±1.70 o Difference between groups, p=0.82 • Mean depressive symptoms, as assessed by the Calgary Depression Rating Scale, at endpoint: o Haloperidol 2 mg: 0.6±1.35 o Haloperidol 8 mg: 1.2±2.97 o Difference between groups, p=0.42	• Ratings on the parkinsonism subsection of the ESRS from baseline to endpoint: o Haloperidol 2 mg: 1.9±3.1 at baseline to 7.3±8.7 at endpoint o Haloperidol 8 mg: 0.7±1.5 at baseline to 18.6±18.2 at endpoint o Difference between groups, p=0.019 • Number of patients developing dystonic reactions (ESRS Dystonia subscale): o Haloperidol 2 mg: 2 patients o Haloperidol 8 mg: 6 patients o Difference between groups, p=0.13 • Number of patients developing akathisia: o Haloperidol 2 mg: 3 patients o Haloperidol 8 mg: 8 patients o Difference between groups, p=0.16 • Mean (±SD) increases in prolactin: o Haloperidol 2 mg: 14.1±10.1 ng/ml at baseline to 15.5±8.4 ng/ml at endpoint o Haloperidol 8 mg: 14.1±9.5 ng/ml at baseline to 51.4 ± 34.8 ng/ml at endpoint o Difference between groups, p=0.16
Robinson et al 2006 (38) • 4-month interim analysis from a 3-year, randomized, comparative trial in patients with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder • Mean age 23.3 years • 78% of patients were antipsychotic naive	• Initial doses=2.5 mg olanzapine and 1 mg risperidone • Thereafter, slow dose titration possible every three weeks until patient improved (maximum dose 20 mg olanzapine and 6 mg risperidone)	• 71% of patients completed 4 months of study participation • Percentage of patients achieving a response (absence of delusions, hallucinations or significant thought disorder): o Olanzapine: 43.7% o Risperidone: 54.3%	• Cumulative rate of parkinsonism: o Olanzapine: 8.9% o Risperidone: 16.0% • EPS severity scores: o Olanzapine: 1.2 o Risperidone: 1.4 o Difference between groups, p<0.07

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Table 1 Overview of short-term, randomized, controlled, clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents *(Continued)*

Study details	Treatment groups	Efficacy	Adverse events
	• Olanzapine (n=56): mean modal daily dose 11.8 mg • Risperidone (n=56): mean modal daily dose 3.9 mg	o Difference between groups, p<0.35 • Mean time to response: o Olanzapine: 10.9 weeks o Risperidone: 10.4 weeks • Percentage of patients meeting response criteria who had a subsequent rating not meeting the response criteria: o Olanzapine: 40.9% o Risperidone: 18.9% o Difference between groups, p<0.08 • Mean length of time that patients maintained their responder status: o Olanzapine: 6.6 weeks o Risperidone: 9.5 weeks	• Percent weight gain from baseline to four months: o Olanzapine: 17.3% o Risperidone: 11.3% o Difference between groups, p<0.01 • Increase in BMI: o Olanzapine: 24.3 at baseline versus 28.2 at month 4 o Risperidone: 23.9 at baseline versus 26.7 at month 4
Long-acting antipsychotics			
Goldstein et al 1978 (41) • 6-week, fixed-dose, controlled trial in acute young patients with schizophrenia	• Fluphenazine enanthate 25 or 6.25 mg/2 weeks with or without crisis-orientated family therapy (n=104)	• 10 patients deteriorated clinically and had to be rehospitalized or their medication altered • Percentage of patients relapsing: o High dose therapy group: 0% o High dose, no family therapy group: 10% o Low dose therapy group: 9% o Low dose, no family therapy group: 24%	• AEs were not recorded

Abbreviations: AE=adverse event; BARS=Barnes Akathisia Rating Scale; BMI=Body Mass Index; BPRS=Brief Psychiatric Rating Scale; CGI-S=Clinical Global Impression-Severity scale; EPS=Extrapyramidal Symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAF=Global Assessment of Function; NS=not significant; PANSS=Positive and Negative Syndrome Scale; SANS=Scale for the Assessment of Negative Symptoms; SAS=Simpson Angus Extrapyramidal Symptom Scale

tolerability of low (2 mg/day) and high (8 mg/day) doses of haloperidol in forty patients with first-episode psychosis (37). Both treatments were equally effective in reducing the PANSS total and subscale scores, although there were no significant differences between the groups. However, the low dose of haloperidol was better tolerated with fewer EPS, less frequent use of anti-cholinergic medication, and smaller elevations in prolactin levels (37).

Finally, Robinson and colleagues compared olanzapine with risperidone (mean modal doses=11.8 and 3.9 mg/day, respectively) in a randomized, open-label study with masked assessments in patients with first-episode schizophrenia, schizophreniform, or schizoaffective disorder (n=112) (38). The four-month data are derived from an ongoing study assessing first-episode patients over three years. Cumulative response rates by four months were similar with olanzapine and risperidone. However, approximately twice as many patients who responded to olanzapine compared with risperidone later had ratings no longer meeting substantial improvement criteria, although the difference was not statistically significant (p<0.08). There were no significant differences between medications in analyses with the SANS global measures for affective flattening, alogia, avolition-apathy, and asociality-anhedonia. Measures of parkinsonism and akathisia did not differ significantly between the two treatments. However, olanzapine-treated patients experienced more weight gain (38).

Short-Term Trials—Non-Randomized

Two short-term, non-randomized studies were also identified that examined the efficacy and safety of oral conventional and atypical antipsychotic agents (39, 40).

Kopala and colleagues prospectively assessed extrapy-

ramidal signs or symptoms and clinical symptoms in twenty-two first-episode schizophrenia patients admitted to hospital before antipsychotic treatment, and during and after treatment with risperidone (mean dose 4.7 mg/day) (39). Among those who received a higher dose of risperidone (5–8 mg), 32% of the patients developed mild drug-induced akathisia or parkinsonian rigidity, which diminished following dosage reduction. No clinically significant EPS were observed in patients receiving 2–4 mg of risperidone. Superior clinical outcome was seen in the 2–4 mg group compared with the 5–8 mg group for all three symptom clusters of the PANSS. In the lower-dose group, 91% of patients achieved a 20% or greater reduction in total PANSS scores compared with 27% for the higher dose group (39). Since dose was clinically titrated, dosage comparisons must be viewed with caution.

Bobes and colleagues conducted a prospective, comparative, non-randomized, observational study in the treatment of 158 first-episode schizophrenia patients in acute psychiatric inpatient wards to compare olanzapine (mean modal dose 15.8 mg/day) with conventional antipsychotic agents; haloperidol was received by 88% (mean modal dose = 15.3 mg/day) (40). Olanzapine was significantly superior to conventional antipsychotics in lowering both the total BPRS score (p=0.003), as well as each one of the following BPRS subscales: positive symptoms (p=0.0019), negative symptoms (p<0.0001), depression (p=0.018), and agitation (p=0.007). Olanzapine was also significantly more effective than the conventional agents in reducing overall severity of illness (CGI p=0.013) (40). Clinical response (defined by a decrease of at least 40% in the BPRS total score plus a CGI scale score of mild or better) was 76.7% in the olanzapine group compared to 54.4% in the conventional antipsychotic group (p=0.003). New EPS emerged, or previously existing ones worsened more frequently with conventional antipsychotics than with olanzapine (55.1% versus 13.5%, p<0.001) (40). Lastly, a higher percentage of patients had at least one adverse effect in the conventional antipsychotic group compared to the olanzapine group (60.9% versus 19.1%, p<0.001) (40).

Long-Acting Antipsychotic Agents

One randomized controlled study by Goldstein and his colleagues was identified, which examined the short-term clinical efficacy of two doses of fluphenazine enanthate in 104 acute, young patients with schizophrenia (mean age 23.4 years) (41). Results from the six-week, controlled treatment period in which patients were randomly assigned to one of two dose levels of fluphenazine enanthate (25 or 6.25 mg/2 weeks) in the presence or absence of family therapy, found that relapses were lowest in patients who received both high-dose and family therapy (0%) and greatest (24%) in the low dose, no family therapy group (41). The study included a six-month, long-term component.

Long-Term Studies in Patients with First-Episode Schizophrenia

Six long-term studies were identified that examined the efficacy and safety of oral conventional (haloperidol and chlorpromazine) and atypical antipsychotic agents (clozapine, risperidone, and olanzapine) in first-episode schizophrenia patients. Two further studies examined the clinical efficacy of the long-acting conventional agent, fluphenazine enanthate, and the long-acting atypical agent, risperidone microspheres.

Oral Antipsychotic Agents—Randomized Trials

Three long-term, randomized, controlled clinical trials were identified that evaluated the efficacy and safety of oral antipsychotic agents. The results of these studies are presented in Table 2. A further three non-randomized studies were also identified.

Lieberman and colleagues examined the long-term (52-week) outcome of treatment-naive, first-episode patients comparing chlorpromazine and clozapine described above (35). The primary efficacy measures were time to first remission and the proportion of time remaining in remission. Remission was defined as a 50% reduction in total BPRS scores from baseline with no score greater than mild on the five BPRS psychosis items (unusual thought content, suspiciousness, hallucinations, conceptual disorganization, mannerisms and posturing) and a CGI-severity score of mild or less. At fifty-two weeks the number of patients achieving remission was similar between the two groups (Table 2). However, when adjusting for gender, baseline total BPRS, duration of untreated psychosis, and the age of onset of psychosis, both the rate of remission (Cox regression model, 95% CI=1.18, 2.44, p=0.005) and the odds for being in remission (logistic regression model, odds ratio=1.73 [1.20, 2.50, p=0.003]) during the trial were almost doubled for the clozapine group in comparison with the chlorpromazine group (35). As described previously, clozapine had been superior to chlorpromazine in the improvement of some symptoms at twelve weeks. However, by week fifty-two many of the symptom differences between the two treatment groups were no longer statistically significant. This analysis only included patients who completed the study. The authors reported a further exploratory analysis that compares the BPRS scores of those patients who dropped out of the study compared with those who remained on treatment. Those patients treated with chlorpromazine who left the study had significantly higher BPRS scores (26.0±7.5) at discharge than those patients treated with chlorpromazine who remained in the study or those patients treated with clozapine. As such, the dropout of patients with more severe symptoms from the chlorpromazine group may have contributed to the lack of persistent difference between the two groups. Generally, clozapine produced fewer side effects than chlorpromazine, particularly EPS. There was no significant difference between treatments in weight change or glucose metabolism (35).

Table 2 Overview of long-term (≥6 months) randomized, controlled clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents

Study details	Treatment groups	Efficacy	Adverse events
Oral antipsychotics			
Lieberman et al 2003 (35) • 52-week, flexible-dose, randomized, double-blind study in antipsychotic-naive first-episode schizophrenia • Patients aged 16–40 years • Duration of symptoms ≤5 years	• Medication doses were increased using a standardized regimen over the first 28 days • Chlorpromazine (n=83): median dose 600 mg/day • Clozapine (n=81): median dose 400 mg/day	• 76% of chlorpromazine-treated patients and 85% of clozapine-treated patients completed the study • Percentage of patients achieving remission: o Chlorpromazine: 79% o Clozapine: 81% • Median time-to-first remission: o Chlorpromazine: 12 weeks o Clozapine: 8 weeks o Difference between groups, p=0.02 • Improvement in BPRS total scores from baseline to endpoint: o Chlorpromazine: 44.4 at baseline to 22.1 at endpoint o Clozapine: 43.3 at baseline to 22.3 at endpoint • Improvement in SANS total scores from baseline to endpoint: o Chlorpromazine: 16.6 at baseline to 9.5 at endpoint o Clozapine: 14.8 at baseline to 7.5 at endpoint • Improvement in CGI-S scores from baseline to endpoint: o Chlorpromazine: 5.6 at baseline to 2.0 at endpoint o Clozapine: 5.6 at baseline to 2.2 at endpoint • Improvement in GAF from baseline to week 12: o Chlorpromazine: 35.4 at baseline to 71.4 at endpoint o Clozapine: 36.2 at baseline to 72.4 at endpoint	• Withdrawals due to AEs: o Chlorpromazine: 6 patients o Clozapine: 2 patients • Mean SAS total score at endpoint: o Chlorpromazine: 0.44 o Clozapine: 0.28 o Difference between groups, p=0.40 • Mean parkinsonian score at endpoint: o Chlorpromazine: 0.33 o Clozapine: 0.18 o Difference between groups, p=0.32 • Change in mean body weight from baseline to follow up (131 weeks after starting medication for chlorpromazine and 137.5 weeks after starting medication for clozapine): o Chlorpromazine: +8.5 kg o Clozapine: +9.9 kg o Difference between groups, p=0.30
Schooler et al 2005 (36) • A long-term, double-blind, randomized, controlled, flexible-dose study in first-episode psychosis • Patients aged 16–45 years • <12 weeks exposure to antipsychotics • Median treatment length was 206 days	• Initial dose =1 mg/day, increased to 2 mg/day on Day 4 and by 1 mg/day/7 days (up to 4 mg/day) • Risperidone (n=278): mean modal dose 3.3 mg/day • Haloperidol (n=277): mean modal dose 2.9 mg/day	• 42.1% of risperidone-treated patients and 36.5% of haloperidol-treated patients discontinued the study • Median time to clinical improvement (based on those patients who met the predefined clinical improvements criterion): o Risperidone: 26 days o Haloperidol: 22 days o Difference between treatment groups, p=0.22 • Mean (±SE) improvement in PANSS total scores at endpoint: o Risperidone: –21.0±14.6 o Haloperidol: –20.6±1.43 o Difference between treatment groups, p=0.49	• Withdrawals due to AEs: o Risperidone: 5.4% o Haloperidol: 6.1% o Difference between treatment groups, p=0.71 • Percentage of patients with persistent dyskinesia: o Risperidone: 1.8% o Haloperidol: 3.3% o Difference between groups, p=0.28 • Use of concomitant medications for EPS: o Risperidone: anticholinergics (41.7%), benzodiazepines (54.7%), beta-blocking agents (5.0%) o Haloperidol: anticholinergics (49.5%), benzodiazepines (61.7%), beta-blocking agents (10.5%)

Table 2 Overview of long-term (≥6 months) randomized, controlled clinical studies in patients with first-episode schizophrenia or young patients with schizophrenia receiving conventional or atypical antipsychotic agents *(Continued)*

Study details	Treatment groups	Efficacy	Adverse events
		• Percentage of patients relapsing among those who achieved clinical improvement: o Risperidone: 42.1% o Haloperidol: 54.7% • Median time to relapse: o Risperidone: median 466 days o Haloperidol: median 205 days o Difference between treatment groups, p=0.008	• Change in mean body weight at endpoint: o Risperidone: +7.5 kg o Haloperidol: +6.5 kg o Difference between groups, p=0.26 • Percentage of patients with abnormal prolactin levels: o Risperidone: 73.8% o Haloperidol: 49.8% • Number of patients with prolactin-related AEs: o Risperidone: 14 patients o Haloperidol: 1 patient
Green et al 2006 (42) • 2-year, randomized, double-blind, international study in first-episode psychosis • Patients aged 16–40 years • <16 weeks cumulative exposure to antipsychotics • Duration of symptoms ≤5 years	• Olanzapine: 5–20 mg/day (n=131); mean modal dose 10.20 mg/day • Haloperidol: 2–20 mg/day (n=132); mean modal dose 4.82 mg/day	• 23.4% of olanzapine-treated patients and 12.1% of haloperidol-treated patients remained on treatment at 2 years • Mean time in the study: o Olanzapine: 322.09 days o Haloperidol: 230.38 days o Difference between groups, p<0.0263 • Percentage of patients achieving response (no rating of >3 on items P1, P2, P3, P5 and P6 on the PANSS and a CGI severity score ≤3): o Olanzapine: 67.2% o Haloperidol: 59.9% • Percentage of patients achieving remission (patients meeting the response criteria for at least 4 consecutive weeks): o Olanzapine: 57.3% o Haloperidol: 43.9% • Difference between groups, p<0.036	• Percentage of patients withdrawing due to AEs: o Olanzapine: 7% o Haloperidol: 16.4% o Difference between groups, p<0.0378 • Symptoms of parkinsonism (SAS): o Olanzapine: 2.28 o Haloperidol: 4.57 o Difference between groups, p<0.001 • Symptoms of akathisia (BARS): o Olanzapine: 0.98 o Haloperidol: 2.83 o Difference between groups, p<0.0001 • Percentage of patients receiving anti-cholinergic medications: o Olanzapine: 20% o Haloperidol: 47% o Difference between groups, p<0.0001 • Percentage of patients with a >7% increase in weight gain: o Olanzapine: 72% o Haloperidol: 42% o Difference between groups, p<0.0001 • Percentage of patients with at least one abnormal prolactin level: o Olanzapine: 49.6% o Haloperidol: 67.4% o Difference between groups, p<0.00040
Long-acting antipsychotics			
Goldstein et al 1978 (41) • 6-month follow up of a 6-week, fixed-dose, controlled trial in acute young patients with schizophrenia	• Fluphenazine enanthate 25 mg (high dose) or 6.25 mg (low dose), with or without crisis-orientated family therapy (n=104) o n=25, high dose and therapy o n=28, high dose and no therapy o n=27, low dose and therapy o n=24, low dose and no therapy	• Number of patients relapsing: o High dose, therapy group: 0 patients o High dose, no family therapy group: 2 patients o Low dose, therapy group: 3 patients o Low dose, no family therapy group: 3 patients	• AEs were not recorded

Abbreviations: AE=adverse event; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CGI-S=Clinical Global Impression-Severity scale; EPS=Extrapyramidal Symptoms; GAF=Global Assessment of Function; PANSS=Positive and Negative Syndrome Scale; SANS=Scale for the Assessment of Negative Symptoms; SAS=Simpson Angus Extrapyramidal Symptom Scale

Schooler and colleagues conducted a double-blind, randomized, flexible-dose study that compared the long-term effectiveness of risperidone versus haloperidol in 555 first-episode psychosis patients for a minimum of one year of treatment and a maximum treatment of over four years (36). At study endpoint, slightly more than three-quarters of the patients in each group met the pre-defined clinical improvement criterion (decrease of more than 20% on total PANSS score). Both treatments showed clinical improvement according to PANSS scores and CGI ratings (p=0.47 and p=0.56, for between treatment group comparison, respectively), with no significant differences between the risperidone and the haloperidol groups. Among those who met clinical improvement, time to relapse was significantly longer in the risperidone than the haloperidol group—risperidone median 446 days, haloperidol median 205 days (p=0.008, between groups). There were significantly more extrapyramidal signs and symptoms in the haloperidol group compared with the risperidone group and this was significant for emergent dyskinesia (p=0.05), total EPS (p=0.04), parkinsonism and parkinsonism/dystonia (p=0.05, for each symptom), and akathisia (p=0.0001). Patients treated with haloperidol also had higher adjunctive medication use. Greater prolactin elevation was observed in the risperidone group (36). There was less weight gain with haloperidol initially, but no significant differences between the groups at endpoint (36).

Green and colleagues, following the same study group assessed by Lieberman et al after twelve weeks of treatment (34), assessed the two-year differential clinical response of patients in their first episode of psychosis to treatment with olanzapine and haloperidol (mean modal dose=10.2 and 4.82 mg, respectively) (42). Both olanzapine and haloperidol treatment were associated with substantial and comparable reduction in symptom severity (the primary outcome measure) (42). The percentage of patients classified as treatment responders (defined as no rating of >3 [mild] on positive symptom items of the PANSS and a CGI severity score ≤3 [mildly ill]) were not significantly different in patients treated with olanzapine as compared to those treated with haloperidol. However, the treatment groups differed on two secondary efficacy measures. Patients treated with olanzapine were twice as likely to remain on medication as those treated with haloperidol (p<0.0085). Moreover, the percentage of patients achieving remission, defined as meeting response criteria for at least four consecutive weeks, was greater in patients treated with olanzapine as compared to those treated with haloperidol (p<0.036). EPS were greater in those treated with haloperidol; weight gain, cholesterol level, and liver function values were greater in olanzapine-treated patients (42).

Long-Term Trials—Non-Randomized

An additional three non-randomized studies were also identified that examined the efficacy and safety of oral conventional and atypical antipsychotic agents in first-episode patients (43-45). Malla and colleagues compared two matched samples of patients with first-episode schizophrenia who had been treated with either a conventional antipsychotic agent (haloperidol, oral flupenthixol, zuclopenthixol decanoate, trifluoperazine, and flupenthixol decanoate) or risperidone on a number of outcome dimensions for a period of approximately two years (43). The mean daily antipsychotic dose was relatively low for both groups (conventional antipsychotic group mean±SD chlorpromazine equivalent = 228.7±161.8 mg; risperidone-treated group mean±SD dose = 2.5±1.5 mg of risperidone). Compared with the conventional antipsychotic group, risperidone-treated patients demonstrated a statistically significantly shorter duration of first hospitalization (11 vs. 28.5 days, p<0.01), total percentage of time spent in hospital (p<0.002), number of hospital admissions per year (p<0.001), and utilization of inpatient beds during the course of treatment (p<0.001) (43). A higher proportion of patients in the conventional group compared with the risperidone group (21% vs. 5.3%) showed at least mild evidence of parkinsonism, but there were no statistically significant differences in rated parkinsonism. There were no statistically significant differences in the use of antidepressant, anti-anxiety, or mood-stabilizing drugs, or in changes in living circumstances or employment (43).

Montes and colleagues compared olanzapine, risperidone, and conventional antipsychotics in 182 patients with first-episode schizophrenia drawn from a larger, naturalistic study who were evaluated after six months of treatment (44). Most patients in the conventional antipsychotic group received haloperidol (67.6%). The mean doses used throughout the study were as follows: olanzapine 13.5 mg/day, risperidone 5.4 mg/day, and haloperidol 12.4 mg/day. Similar improvements on the CGI-S and GAF were observed in the three treatment groups at the end of the study period (44). Patients' subjective attitudes towards medication was significantly better after six months treatment with olanzapine compared with those patients treated with conventional antipsychotic agents (p<0.05). Patients treated with risperidone also showed an improvement in attitudes, but the difference was not statistically significant (44). Treatment-emergent EPS were significantly lower in olanzapine-treated patients (17.8%) than in the risperidone (46.6%) and the conventional antipsychotic (62.2%) groups. Weight gain was the only adverse event that had a greater incidence in the olanzapine-treated group (44).

Malla and colleagues subsequently compared risperidone (median dose 2.5 mg/day) and olanzapine (median dose 10 mg/day) in eighty-four drug-naive, first-episode patients who were treated for at least one year (45). Patients in both groups showed substantial improvement, and there were no significant differences in the magnitude of change in reality distortion, disorganization, and psychomotor poverty symptoms (45). Similarly, there were no differences between groups on change in the level of EPS. However, a greater proportion of patients on risperidone (four versus

one on olanzapine) required prescription of anti-cholinergic medication. Both groups demonstrated similar levels of improvement in aspects of cognition. However, patients in the risperidone group showed a greater trend for improvement on processing speed and Trail Making Test-B (a test of executive function) (45).

Long-Acting Injectable Antipsychotic Agents

Two long-term studies were identified that examined the efficacy of long-acting agents. Results from a six-month follow-up by Goldstein and colleagues of the six-week randomized, controlled trial of two dose levels of fluphenazine enanthate (25 or 6.25 mg/2 weeks; n=104), described in the previous section examining short-term studies, found that relapses were lowest in patients who received both higher dose and family therapy (0%) and greatest (48%) in the low dose, no family therapy group (41). There had been a significant effect of family treatment on BPRS symptoms at six weeks that was sustained at six months only for patients in the higher drug dose group (41).

Parellada and colleagues assessed 382 patients with schizophrenia and schizoaffective disorder early in the course of illness, less than three years, who received long-acting risperidone for up to six months. Doses of 25 mg, 37.5 mg or 50 mg every two weeks were administered to patients who required a treatment change from either atypical antipsychotics (70%) or depot neuroleptics (24%) (46). At the end of the six-month treatment period, 45% of patients were treated with the lowest dose (25 mg), with 27% and 28% treated with the higher (37.5 mg and 50 mg) doses. The total PANSS and subscales scores improved significantly ($p \leq 0.0001$). At baseline, 156 (41%) patients were hospitalized. The majority (81%) were discharged at endpoint and only 18 patients (5%) were newly hospitalized during the study (46). Adverse events were reported by 69% of patients. The most frequently reported treatment-emergent adverse events were "psychiatric disorders" and "central" and "peripheral nervous system disorders," with insomnia (7%) and exacerbation of disease (6%) being the most common. Twenty-one patients (6%) discontinued the study prematurely due to adverse events. Body mass index increased by 0.6 kg/m^2 from baseline to endpoint ($p \leq 0.001$) (46).

Discussion

Early and appropriate treatment with antipsychotic agents in patients with first-episode schizophrenia is critical for both initial treatment and subsequent prevention of relapse. Definitive comparisons of antipsychotic medication to placebo confirm the long-term need for antipsychotic medication in this population as in later episode schizophrenia patients (47, 48). Given that antipsychotic medication is indicated in this population, two key questions need to be addressed. Which antipsychotic medication should first-episode patients receive? How can non-adherence to medication be addressed? Due to the difficulty of conducting first-episode studies, there have been very few randomized and controlled comparisons of atypical and conventional antipsychotic drugs and there are still no peer-reviewed published trials of quetiapine, aripiprazole, or ziprasidone. However, results from the studies reviewed here provide valuable information on both early treatment response and relapse of patients with first-episode psychosis, and the comparative efficacy and safety of clozapine, olanzapine, and risperidone to older antipsychotics. Data for the comparative efficacy among the newer medications are extremely sparse. We identified only one study that included more than one atypical antipsychotic (38).

Results from the short-term studies indicate that both atypical medications and conventional agents studied produce significant reductions in symptom severity and psychopathology, and that there were no significant differences between conventional and atypical medications or between risperidone and olanzapine (the only available comparison among the newer medications) (30, 31, 34-36, 38, 40). There are substantial differences in adverse events. Patients receiving conventional agents had significantly more EPS-related adverse events and required more anti-cholinergic medication (30, 31, 34) even at relatively low doses. Patients receiving atypical agents, especially olanzapine, experienced greater weight gain (31, 34, 36). Greater prolactin elevation was seen with risperidone (36). There are also short-term data that inform dosing of both risperidone and haloperidol (30, 32, 33, 37, 39). These data are consistent with clinical experience in finding that low doses of risperidone and haloperidol, and possibly other antipsychotic agents, may be best for many first-episode patients, who appear to be more sensitive to both the therapeutic and adverse effects of antipsychotic medications. In an early study that investigated dosing with haloperidol using a neuroleptic threshold strategy, McEvoy and colleagues found that first-episode patients had a significantly lower neuroleptic threshold than patients who had had extensive exposure to antipsychotic medication (18).

Results from the long-term studies reviewed here show quite different results from those seen in short-term trials. In the longer term, olanzapine and risperidone have advantages over conventional agents, most dramatically in significantly extending the length of time until relapse (35, 36, 42). Consistent with results of the short-term studies, there were significantly more EPS and medication for EPS in the conventional group, and greater weight gain (olanzapine) and prolactin elevation (risperidone) in the atypical group over the long term (35, 36, 42).

Two long-term studies examined the probability of first-episode patients achieving remission (35, 42). Lieberman and colleagues found no differences in overall remission between clozapine and chlorpromazine, but the time to remission was significantly shorter in the clozapine group (35). Green and colleagues found a higher remission rate with olanzapine than haloperidol (42). Criteria in both of

these studies focused on remission of positive symptoms. More recently, criteria for remission that include both positive and negative symptoms have been proposed by the Remission in Schizophrenia Working Group (49). The consensus definition of remission was defined as a symptom level of mild or less simultaneously in core positive and negative symptoms that is sustained for a minimum duration of six months (49). While these criteria are based on core symptom reduction, they appear to correlate with other outcome and quality of life measures (50). Indeed, results from a recent study by Wunderink and colleagues that examined the predictive validity of the remission criteria in first-episode patients responding to antipsychotic agents, reported that patients who achieved remission demonstrated a significantly better outcome during follow-up on all PANSS subscale scores (positive, negative, and general symptom subscales) and a significantly higher level of social functioning than patients who did not fulfill the consensus criteria (51). Recovery represents a goal beyond remission and a recent study by Robinson and colleagues has assessed this important goal, defined by both symptomatic and functional outcomes, for patients with a first episode of schizophrenia (52). Overall, recovery was low (14%), but symptomatic remission after five years was relatively high (47%) and comparable to the rates found by Green and colleagues (42). In the Robinson study, all patients received conventional antipsychotic agents and this remission rate sits squarely between the olanzapine and haloperidol remission rates reported by Green et al (42).

Based on short-term trials, choice of antipsychotic treatment should weigh which adverse effects the clinician and patient wish to avoid since all the medications studied appear to offer comparable efficacy. As has often been observed, first-episode patients respond well to lower doses of medication than patients with more established illness. Long-term trials provided information that may be more helpful in guiding a clinical choice. In longer-term clinical trials that compared both olanzapine and risperidone to haloperidol, relapse free time was extended by more than one hundred days (36, 42). For first-episode patients this time can buy the opportunity to return to work or school and to pursue interrupted developmental life tasks.

Although the introduction of the atypical agents may improve outcomes in schizophrenia, their clinical potential for all patients is limited by patients' non-adherence to medication—whether conventional or atypical (53). This represents a particularly acute problem for first-episode patients. Robinson and colleagues found that the strongest predictor of relapse in this population was discontinuation of antipsychotic medication (3). First-episode patients' understanding of the need for long-term treatment to prevent recurrence is often influenced by their experience of a good short-term response to treatment. For experienced clinicians this signals the need for continuing medication. For the patient and family it may be viewed as an indication that this illness, like an acute infection, is behind them and that treatment should be discontinued. Thus, the development of strategies for engaging first-episode patients in long-term medication treatment is critical.

The study by Goldstein and colleagues suggests that a combination of a moderate dose of a long-acting injectable antipsychotic and family therapy significantly reduced relapse during the initial six-month period following a brief initial hospitalization (41). Long-acting antipsychotic agents were developed in the 1960s as a novel method of drug delivery aimed at enhancing treatment adherence in patients with schizophrenia. Their advantages are that they may be convenient for patients and families who no longer have the burden of remembering to take medication on a daily basis. From a clinician's perspective, a critical advantage is that non-adherence is identified as soon as an injection has been missed so that efforts can be undertaken to deal effectively with the problem before the consequences of medication discontinuation appear (53). An additional benefit of long-acting therapy may be the regular contact between patients and treatment teams, which provides additional psychosocial support. Long-acting antipsychotic agents also have several pharmacologic advantages over their oral counterparts. Administration of a long-acting agent avoids the variability associated with absorption and first-pass metabolism, and usually results in a better correlation between the administered dose and the plasma levels achieved (54, 55). Once steady-state is achieved, plasma levels remain relatively stable, avoiding the daily peaks and troughs that occur with oral agents (54, 55). Long-acting antipsychotics also facilitate the use of the lowest effective dose principle, thereby reducing the frequency of adverse events, including akathisia, dysphoria, and antipsychotic-induced deficit syndrome (56, 57). However, until recently, all long-acting antipsychotics were formulations of conventional agents, which meant that clinicians wishing to use a newer agent were unable to consider a long-acting formulation.

Risperidone is the first atypical antipsychotic to become available in a long-acting injectable formulation. This review identified only one study that examined the efficacy and safety of long-acting risperidone in patients in the early phases of schizophrenia and schizoaffective disorders (46). Direct initiation of long-acting risperidone, without an oral risperidone run-in period, was both effective and well accepted in patients. Improvements in symptom control and reductions in movement disorders led to high levels of patient satisfaction and improved patient functioning (46). Although further studies are required, the development of long-acting risperidone, which combines the benefits of an atypical agent (long-term efficacy and tolerability) with those of a long-acting formulation (improved and assured bioavailability and medication delivery), may represent an effective treatment option for patients in the early phases of psychosis. The critical issue will be the development of strategies to engage first-episode patients in a treatment strategy that involves injections. A recent motivational inter-

viewing approach called GAIN (Goal setting, Action, Initiation, Nurturing motivation) was developed for use with patients with a well-established schizophrenia diagnosis (58). Adaptation of this approach for use with first-episode patients could provide the kind of support that clinicians and patients need to allow acceptance of not only long-term treatment but long-term injections.

There are several limitations to this review. It analyzes clinical trials encompassing a wide range of different designs, patient numbers, and follow-up periods. In addition, patients included had different durations of treated or untreated psychosis and were treated with a variety of different concomitant medications. Moreover, wide variations in the definition of "relapse," and in many instances absence of this measurement, and the lack of a clinically meaningful definition of symptom remission at the time of these studies, which would have allowed for a more accurate assessment of the degree and duration of symptom control, has made it difficult to compare the efficacy of different treatment regimens. However, despite these factors, the evidence presented here reports a clear long-term advantage in efficacy for the use of atypical agents over conventional agents in first-episode schizophrenia.

The most recent published guidelines currently recommended atypical antipsychotics as first-line therapy for first-episode patients (59, 60), although treatment recommendations for the use of long-acting atypical agents in first-episode schizophrenia are not available. Two recent and important publications that provide new information regarding the effectiveness of conventional and atypical antipsychotic agents specifically excluded first-episode patients (61, 62).

Conclusion

Early initiation of effective interventions is essential for preventing relapse and achieving long-term positive clinical outcomes in first-episode patients. Results from the studies presented here consistently demonstrated that atypical antipsychotic medications have substantial long-term advantages over conventional agents indicated by fewer relapses, more effective symptom control, and a lower incidence of movement disorders, although some atypical agents were associated with a higher incidence of weight gain or prolactin elevation. However, the clinical advantages of the atypical agents have often been limited by patients' partial compliance with therapy. As such, the development of a long-acting atypical antipsychotic agent may have the potential to advance the management of first-episode patients.

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