



## The new and evolving pharmacotherapy of schizophrenia

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Following the introduction of the first antipsychotic agents in the early 1960s, the pharmacotherapy of schizophrenia essentially stagnated for a long time. Many new compounds have been introduced over the past few years, however, that have changed treatment considerably. These additional therapeutic options have provided grounds for heightened optimism for improved clinical outcomes among patients with schizophrenia. Important differences between these compounds are emerging so that drug choice needs to be tailored for individual patients.

Much literature already has appeared on these new, atypical antipsychotics, and additional findings are being reported at a rapid pace. Despite the burgeoning literature, however, much remains to be learned to use them optimally. A good deal of this literature needs to be interpreted with caution, owing to a plethora of methodologic shortcomings in many of the published studies. This article evaluates critically the evidence for efficacy of the new atypical antipsychotics by selecting only published randomized clinical trials (RCTs) and meta-analyses. Risperidone, olanzapine, quetiapine, ziprasidone, sertindole, and amisulpride are included. The role of each drug during key stages in the course of the illness (acute treatment, maintenance, first episode, and refractory) and differential effects on specific symptom domains is assessed. Although this article focuses purely on efficacy (the adverse effects of these agents are discussed in a separate article), it is necessary in selecting a drug to consider many other aspects.

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## Treatment of acute symptoms

### *Atypical antipsychotics versus placebo*

Despite ethical and scientific concerns associated with these trials, it still is generally accepted that efficacy of a new compound needs to be established against placebo [1].

#### *Risperidone*

Two RCTs compared risperidone, 2, 6, 10, or 16 mg/d; haloperidol, 20 mg/d; or placebo over 8 weeks in the treatment of schizophrenia (Table 1). The first trial investigated 135 inpatients with chronic schizophrenia. Doses of 6 to 16 mg/d were superior to placebo in overall and positive symptom improvement, whereas only risperidone, 6 mg/d, was significantly better than placebo on negative symptom improvement [2]. The second study comprised 388 subjects with schizophrenia. Compared with placebo, significant improvements were found for risperidone, 6 and 16 mg/d, for overall clinical improvement and negative symptoms and for risperidone, 6, 10, and 16 mg/d, for positive symptoms [3].

#### *Olanzapine*

Two studies comparing olanzapine with placebo for 6 weeks in acute schizophrenia reported significant advantages for olanzapine in overall symptom improvement and improvement in positive and negative symptoms [4,5]. The first study involved 152 subjects who received fixed doses of either olanzapine, 1 or 10 mg/d, or placebo. The significant differences all were between the olanzapine, 10 mg/d, group versus placebo, with the olanzapine, 1 mg/d, subjects showing no differences from the placebo group [4]. The second study involved 335 subjects who received olanzapine,  $5 \pm 2.5$  mg/d,  $10 \pm 2.5$  mg/d, or  $15 \pm 2.5$  mg/d, or placebo. Advantages were for the medium-dose and high-dose ranges of olanzapine for overall and positive symptoms and for the low-dose and high-dose ranges for negative symptoms [5].

#### *Quetiapine*

In a multicenter RCT, 286 hospitalized subjects with chronic or subchronic schizophrenia received 6 weeks of treatment with high-dose quetiapine (750 mg/d), low-dose quetiapine (250 mg/d), or placebo. High withdrawal rates were recorded in all three treatment groups (42%, 57%, and 59%), primarily because of treatment failure. High-dose quetiapine was significantly better than placebo in reducing Brief Psychiatric Rating Scale (BPRS) total, BPRS positive, and Clinical Global Impression (CGI) scores. Reduction of negative symptoms was less consistent; quetiapine was significantly better than placebo for Scale for the Assessment of Negative Symptoms (SANS), but not on the Positive and Negative Syndrome Scale (PANSS) negative subscale [6]. A multiple fixed dose study of quetiapine (75, 150,

Table 1  
Acute randomized controlled trials of atypical antipsychotics versus placebo

Reference	n	Duration	Dose (mg/d)	Outcome versus placebo		
				Overall	Positive symptoms	Negative symptoms
<i>Risperidone</i>						
2	135	8 wk	2, 6, 10, and 16	6–16 mg superior	6–16 mg superior	6 mg superior
3	388	8 wk	2, 6, 10, and 16	6–16 mg superior	6–16 mg superior	6 and 16 mg superior
<i>Olanzapine</i>						
4	152	6 wk	1 and 10	10 mg superior	10 mg superior	10 mg superior
5	335	6 wk	5 ± 2.5, 10 ± 2.5, and 15 ± 2.5	Medium and high dose superior	Medium and high dose superior	Low and high dose superior
<i>Quetiapine</i>						
6	286	6 wk	250 and 750	750 mg superior	750 mg superior	750 mg superior on SANS, not PANSS negative subscale
7	361	6 wk	75, 150, 300, 600, and 750	150–750 mg superior	150–750 mg superior	300 mg superior
<i>Ziprasidone</i>						
8	139	4 wk	40 and 120	120 mg superior	No differences	No differences
9	302	6 wk	80 and 120	Both doses superior	Both doses superior	Both doses superior
<i>Sertindole</i>						
10	205	40 days	4, 8, 12, and 20	20 mg superior	No differences	No differences
11	497	8 wk	12, 20, and 24	All doses superior	20 and 24 mg superior	20 mg superior
<i>Amisulpride</i>						
12	27	6 wk	50–100	No differences	No differences	Superior
13	104	6 wk	100 and 300	Not assessed	Not assessed	Both doses superior
14	243	12 wk	50 and 100	Not assessed	Not assessed	Both doses superior

300, 600, and 750 mg/d), haloperidol (12 mg/d), and placebo conducted in 361 subjects over 6 weeks reported significant differences between the four highest doses of quetiapine and placebo for BPRS total, BPRS positive symptoms, and CGI Severity of Illness scores and between quetiapine, 300 mg/d, and placebo for SANS summary score [7].

### *Ziprasidone*

A RCT was conducted in 139 subjects with acute exacerbation of schizophrenia comparing ziprasidone, 40 or 120 mg/d, and placebo for 28 days. Ziprasidone, 120 mg/d, was significantly more effective than placebo in improving the BPRS total, CGI-S, BPRS depression cluster, and BPRS anergia cluster scores and had significantly more responders (>30% BPRS reduction) than placebo [8]. In another study, 302 subjects were randomized to either ziprasidone, 80 or 160 mg/d, or placebo for 6 weeks. Both doses of ziprasidone were significantly more effective than placebo in reducing PANSS total, BPRS total, BPRS core items, CGI-S, and PANSS negative subscale scores. Ziprasidone, 160 mg/d, significantly improved depressive symptoms in subjects with higher baseline depression compared with placebo [9].

### *Sertindole*

A 40-day RCT in 205 previously treatment-responsive, hospitalized patients with schizophrenia compared sertindole, 4, 8, 12, and 20 mg/d, with placebo. A dose-related improvement was observed for PANSS total, BPRS, and CGI scores, with significant differences being recorded between sertindole, 20 mg/d, and placebo [10]. A further study compared sertindole, 12, 20, and 24 mg/d, with haloperidol, 4, 8, and 16 mg/d, and placebo in 497 hospitalized patients with schizophrenia over 8 weeks. All doses were significantly more effective than placebo. For treating negative symptoms, only sertindole, 20 mg/d, was superior to placebo [11].

### *Amisulpride*

*Low-dose.* Three RCTs were conducted to assess efficacy of low-dose amisulpride (50–300 mg/d) versus placebo in treating negative symptoms in subjects with predominantly negative symptoms over 6 to 12 weeks [12–14]. Amisulpride was consistently better than placebo in these studies, and the effect on negative symptoms was apparently unrelated to any changes in positive symptoms [14].

*High-dose.* No controlled studies were found comparing high-dose amisulpride with placebo. However, Fixed doses of amisulpride (400, 800, and 1200 mg/d) and haloperidol, 16 mg/d, were compared with a subtherapeutic dose of amisulpride (100 mg/d) for 4 weeks in 319 subjects with acute exacerbation of schizophrenia. The greatest improvement, in terms of BPRS total reductions, occurred in the two groups taking amisulpride, 400 mg or 800 mg/d [15].

*Atypical antipsychotics versus haloperidol**Risperidone*

A dose-finding study comparing risperidone, 2, 6, 10, or 16 mg/d; haloperidol, 20 mg/d; or placebo over 8 weeks in 135 inpatients with chronic schizophrenia found that risperidone, 6 mg/d, was significantly superior to haloperidol on the total PANSS, General Psychopathology, and BPRS scales (Table 2) [2]. A similar study in 388 subjects found risperidone, 6 mg/d and 16 mg/d, groups to have significantly more responders (defined as >20% reduction in total PANSS scores), although no other efficacy differences were found between risperidone and haloperidol [3]. A small (n = 35)

Table 2

Acute randomized controlled trials of atypical antipsychotics versus conventional antipsychotics

Reference	n	Duration	Dose (mg/d)	Outcome versus conventional agent		
				Overall	Positive symptoms	Negative symptoms
<i>Risperidone</i>						
2	135	8 wk	2, 6, 10, and 16	6 mg superior	Equal	Equal
3	388	8 wk	2, 6, 10, and 16	Equal	Equal	Equal
17	1362	8 wk	1, 4, 8, 12, and 16	Equal	Equal	Equal
29	98	6 wk	Mean 8	Equal	Equal	Equal
<i>Olanzapine</i>						
5	335	6 wk	5 ± 2.5, 10 ± 2.5, and 15 ± 2.5	Equal	Equal	15 ± 2.5 mg superior
21	431	6 wk	5 ± 2.5, 10 ± 2.5, and 15 ± 2.5	Equal	Equal	Equal
22	1996	6 wk	5–20	Superior	Superior	Superior
23	182	8 wk	5–15	Equal	Equal	Superior
<i>Quetiapine</i>						
7	361	6 wk	75, 150, 300, 600, and 750	Equal	Equal	Equal
24	448	6 wk	Mean 455	Equal	Equal	Equal
30	201	6 wk	Mean 407	Equal	Equal	Equal
<i>Ziprasidone</i>						
25	90	4 wk	4, 10, 40, and 160	160 mg equal	160 mg equal	160 mg equal
<i>Sertindole</i>						
11	497	8 wk	12, 20, and 24	Equal	Equal	Equal
<i>Amisulpride</i>						
26	41	6 wk		Equal	Equal	Equal
15	319	4 wk	100, 400, 800, and 1200	400 and 800 mg equal	400 and 800 mg equal	400 and 800 mg equal
27	191	6 wk	800	Equal	Equal	Superior
28	199	4 m	400–1200	Equal	Equal	Superior
31	132	6 wk	1000	Equal	Superior	Equal

RCT compared risperidone with haloperidol over 8 weeks and reported no differences in outcome [16]. A large multinational study compared risperidone, 1, 4, 8, 12, and 16 mg/d, with haloperidol, 10 mg/d, over 8 weeks in 1362 patients. The optimal risperidone doses were 4 and 8 mg/d, but no significant efficacy advantages over haloperidol were reported [17]. A later subanalysis of patients from Germany, Austria, and Switzerland reported significant advantages for risperidone over haloperidol, however, according to PANSS total and subscale scores [18]. Further post-hoc subanalyses reported that patients receiving risperidone, 4 mg/d, improved more rapidly than patients receiving haloperidol [19], and patients hospitalized for more than 60 days (median, 351 days) who received risperidone, 4 mg/d, improved significantly more than patients treated with haloperidol [20].

### *Olanzapine*

Three large RCTs compared olanzapine with haloperidol [5,21,22]. In these studies, olanzapine showed several efficacy advantages over haloperidol. In the first study ( $n = 335$ ), olanzapine,  $15 \pm 2.5$  mg/d, was significantly better than haloperidol,  $15 \pm 5$  mg/d, in reducing negative symptoms after 6 weeks [5]. In the second study ( $n = 431$ ), olanzapine,  $15 \pm 2.5$  mg/d, over 6 weeks was equal to haloperidol,  $15 \pm 5$  mg/d, on all efficacy measures [21]. In a study with a large sample ( $n = 1996$ ), olanzapine, 5 to 20 mg/d (mean, 13.2 mg/d) was significantly better than haloperidol, 5 to 20 mg/d (mean, 11.8 mg/d), over 6 weeks in reducing overall psychopathology [21], positive symptoms [21], negative symptoms [5,22], and depressive symptoms [22]. A RCT compared olanzapine with haloperidol over 8 weeks in a sample of 182 Asian patients with chronic schizophrenia. Olanzapine was found to be as effective as haloperidol in treating overall symptoms and significantly superior in treating negative symptoms [23].

### *Quetiapine*

In the multiple fixed dose study of quetiapine (75, 150, 300, 600, and 750 mg/d) versus haloperidol (12 mg/d) and placebo conducted in 361 subjects over 6 weeks [7], differences between quetiapine and haloperidol were not significant for any of the efficacy measures. Another RCT compared flexible doses of quetiapine (mean, 455 mg/d) and haloperidol (mean, 8 mg/d) over 6 weeks in 448 hospitalized patients with acute exacerbation of schizophrenia. Quetiapine and haloperidol reduced symptoms, with equal efficacy [24].

### *Ziprasidone*

A total of 90 patients with schizophrenia or schizoaffective disorder participated in a dose-finding study comparing ziprasidone, 4, 10, 40, and 160 mg/d, and haloperidol, 15 mg/d, for 4 weeks. Ziprasidone, 160 mg/d, was found to be comparable with haloperidol in reducing overall psychopathology and positive symptoms and in overall response rate [25].

### *Sertindole*

In a study comparing sertindole, 12, 20, and 24 mg/d, with haloperidol, 4, 8, and 16 mg/d, and placebo in 497 hospitalized patients with schizophrenia over 8 weeks, sertindole and haloperidol were comparably effective [11].

### *Amisulpride*

In a RCT of 41 subjects with schizophrenia, flexible doses of amisulpride or haloperidol were given over 42 days. Both groups showed similar overall improvement, with amisulpride patients doing significantly better regarding depressive symptoms [26]. In a further study, fixed doses of amisulpride (100, 400, 800, and 1200 mg/d) and haloperidol (16 mg/d) were compared for 4 weeks in 319 subjects with acute exacerbations of schizophrenia. The greatest improvement, in terms of BPRS total reductions, occurred in the two groups taking amisulpride, 400 or 800 mg/d [15]. Amisulpride, 800 mg/d, also was compared with haloperidol, 20 mg/d, over 6 weeks in 191 patients with acute exacerbations of schizophrenia. Amisulpride was as effective as haloperidol for positive symptoms and significantly more effective against negative symptoms (PANSS negative subscale) [27]. In a flexible dose study, 199 subjects with schizophrenia or schizophreniform disorder received amisulpride, 400 to 1200 mg/d, or haloperidol, 10 to 30 mg/d, for 4 months. The drugs were equally effective in reducing BPRS total scores and PANSS positive scores, whereas PANSS negative score reduction was significantly greater with amisulpride, as was the percentage of CGI responders [28].

### *Atypical antipsychotics versus other conventional antipsychotics*

#### *Risperidone*

Flexible doses of risperidone (mean dose, 8 mg/d) and flupenthixol (mean dose, 38 mg/d) were compared over 6 weeks in 98 subjects with acute exacerbation of schizophrenia or schizophreniform disorder. Both groups displayed comparable efficacy, with the onset of action being significantly faster in the risperidone group [29].

#### *Quetiapine*

A 6-week RCT compared flexible doses of quetiapine (mean end point dose, 407 mg/d) and chlorpromazine (mean end point dose, 384 mg/d) in 201 hospitalized patients with acute exacerbation of schizophrenia. Both treatments were equally effective in treatment of positive and negative symptoms [30].

#### *Amisulpride*

Amisulpride, 1000 mg/d, was compared with flupenthixol, 25 mg/d, in 132 patients with acute exacerbation of schizophrenia over 6 weeks. Results were similar for both drugs except that amisulpride was significantly better in reducing positive symptoms [31].

*Head-to-head comparisons of atypical antipsychotics**Risperidone versus olanzapine*

Two multisite RCTs compared olanzapine with risperidone (Table 3). The first, sponsored by Eli-Lilly, evaluated 339 subjects over a 28-week period. Olanzapine (10–20 mg/d) and risperidone (4–12 mg/d) were found to be effective, with olanzapine showing superiority over risperidone in reducing negative symptoms, in overall response rate, and in maintenance of response at 28 weeks [32]. The second study, sponsored by Janssen-Cilag, investigated a sample of 377 subjects over 8 weeks. Olanzapine (5–20 mg/d; mean, 12.4 mg/d) and risperidone (2–6 mg/d; mean, 4.8 mg/d) were found to be effective. There were no differences in efficacy between the groups according to the last observation carried forward analysis, although the completers analysis reported significant advantages for risperidone in treating positive and anxiety/depression symptoms [33].

*Risperidone versus clozapine (nonrefractory sample)*

Risperidone, 4 mg/d (n = 20) and 8 mg/d (n = 19), and clozapine, 400 mg/d (n = 20), were compared over 28 days in a nonrefractory sample. No differences in efficacy were reported [34]. Other studies comparing risperidone and clozapine were in samples with various degrees of refractoriness and are summarized subsequently.

*Risperidone versus amisulpride*

Amisulpride (800 mg/d) was compared with risperidone (8 mg/d) over 8 weeks in a RCT of 228 patients with acute exacerbation of schizophrenia. The drugs showed equal efficacy [35].

In a meta-analysis of nine RCTs (five with clozapine, three with olanzapine, and one with amisulpride), olanzapine and risperidone seemed to be

Table 3  
Head-to-head randomized controlled trials of atypical antipsychotics in nonrefractory samples

Reference	n	Duration (wk)	Dose (mg/d)	Outcome versus conventional agent		
				Overall	Positive symptoms	Negative symptoms
<i>Risperidone vs olanzapine</i>						
32	339	28 wk	Ol 10–20 Ris 4–12	Equal	Equal	Olanzapine superior
33	377	8 wk	Ol 5–20 Ris 2–6	Equal	Equal	Equal
<i>Risperidone vs clozapine</i>						
34	59	4 wk	Ris 4 and 8 Clo 400	Equal	Equal	Equal
35	228	8 wk	Ris 8 Ami 800	Equal	Equal	Equal

Abbreviations: Ami, amisulpride; Clo, clozapine; Ol, olanzapine; Ris, risperidone.

broadly similar in terms of response rates, whereas olanzapine caused fewer people to leave the study early. Amisulpride seemed broadly similar to risperidone. High attrition rates, short-term follow-up, and doses of risperidone higher than those recommended in practice were some of the limitations highlighted by the authors [36].

#### *Acute intramuscular administration*

##### *Olanzapine*

The efficacy of intramuscular olanzapine has been compared with intramuscular haloperidol and intramuscular placebo in treating acute agitation in hospitalized patients with schizophrenia. Subjects received one to three injections of olanzapine, 10 mg; haloperidol, 7.5 mg; or placebo over a 24-hour period. Intramuscular olanzapine provided rapid, effective, and safe treatment for acute agitation, showing superiority over haloperidol at 15, 30, and 45 minutes after the first injection. Olanzapine and haloperidol reduced agitation significantly more than placebo at 2 and 24 hours after the first injection [37].

##### *Ziprasidone*

A RCT conducted in acutely agitated psychotic patients compared 2-mg with 10-mg intramuscular injections (up to four injections in 24 hours) of ziprasidone in 119 subjects. The 10-mg dose was significantly more effective 4 hours after the first injection [38]. In an identical trial design, 2-mg and 20-mg injections of ziprasidone were compared in a sample of 79 patients. The 20-mg dose substantially and significantly reduced symptoms of acute agitation [39].

### **Maintenance treatment**

Some empirical evidence is emerging to suggest that atypical antipsychotics may differ from conventional agents in altering the long-term course of schizophrenia.

##### *Risperidone*

A RCT compared relapse rates in 397 clinically stable adult outpatients with schizophrenia or schizoaffective disorder receiving flexible doses of risperidone or haloperidol for a minimum of 1 year. Risk of relapse at the end of the study was significantly lower for the risperidone group (34%) than for the haloperidol group (60%) [40]. By using the National Psychiatric Hospital Case Registry of Israel, rehospitalization status over 2 years was monitored for subjects discharged while taking risperidone ( $n = 268$ ) and olanzapine ( $n = 313$ ). Rehospitalization rates of risperidone and olanzapine subjects were similar, both being more effective than conventional antipsychotics [41].

### *Olanzapine*

The efficacy of standard-dose oral olanzapine (5–15 mg/d) was compared with placebo and with ineffective-dose olanzapine (1 mg/d) in maintenance therapy of 120 subjects with schizophrenia. The patients treated with standard-dose olanzapine experienced significantly lower relapse risk over 1 year compared with patients treated with placebo or ineffective-dose olanzapine [42]. Three RCTs compared olanzapine and haloperidol in maintenance treatment for schizophrenia and related psychoses [5,21,22]. All were double-blind extensions of acute studies. Data from these three studies were pooled, and results were reported separately [43]. Fewer subjects experienced relapse at 1 year with olanzapine (19.7%) than with haloperidol (28%). Olanzapine also has been compared with risperidone for prevention of relapse in a RCT conducted over 28 weeks. Survival analysis revealed that significantly more olanzapine patients maintained their response at end point [44].

### *Sertindole*

Long-term efficacy was assessed in 282 clinically stable treatment-responsive outpatients with schizophrenia treated 1 year with sertindole or haloperidol. Time to treatment failure was not significantly different between the groups, but sertindole patients remained free of hospitalization for exacerbation of schizophrenia and remained compliant significantly longer than did the haloperidol-treated patients [45].

### *Amisulpride*

A study involving schizophrenics with predominantly negative symptoms compared low-dose amisulpride (100 mg/d) and placebo over 6 months in 141 subjects. Significantly more amisulpride patients completed the study—dropout rates were 27% with amisulpride and 47% with placebo [46]. No blinded maintenance studies were found for quetiapine and ziprasidone.

## **Meta-analyses**

### *Risperidone*

A meta-analysis of 11 RCTs comparing risperidone with conventional antipsychotics concluded that short-term efficacy of risperidone is comparable to that of other antipsychotics. The risperidone patients showed slightly greater clinical improvement and lower overall dropout rate [47]. Another meta-analysis of six trials comparing risperidone with haloperidol in patients with chronic schizophrenia treated for at least 4 weeks in RCTs reported significantly higher response rates with risperidone and lower dropout rates [48]. A Cochrane review reported on 12 short-term studies and 2 long-term studies comparing risperidone with conventional antipsychotics, providing data on 3401 subjects. Risperidone increased the odds of

moderate clinical improvement but seemed to have little or no additional effect on the positive and negative symptoms of schizophrenia. When data from subjects on higher doses of haloperidol (>10 mg/d) were excluded, the advantage for risperidone was lost [49].

### *Olanzapine*

In a Cochrane review of 20 RCTs comparing olanzapine with placebo or any antipsychotic treatment in subjects with schizophrenia or schizophreniform psychosis, olanzapine seemed superior to placebo (but results were equivocal regarding negative symptoms) and equally as effective as typical antipsychotics. These authors pointed out that high attrition rates in the olanzapine and typical antipsychotic groups made it difficult to draw firm conclusions from these studies [50].

### *Quetiapine*

A Cochrane review including 11 RCTs comparing quetiapine with placebo and other antipsychotic agents reported as follows: Compared with placebo, data suggest that patients allocated to quetiapine were less likely to leave the study early, particularly for treatment failure. Psychotic symptoms showed significant improvement in the quetiapine group. Compared with conventional antipsychotics, the proportion of patients leaving the studies early was marginally, but significantly, less for the quetiapine group. Symptom reduction was significantly greater in the high-dose range of quetiapine. High dropout rates and short duration of studies were cited as factors limiting interpretation of these studies [51].

### *Ziprasidone*

A Cochrane review of available RCTs reported that in studies ranging from 1 week (intramuscular preparation) to more than 6 months, ziprasidone seemed more effective than placebo and as effective as haloperidol. The authors noted that data currently are limited and that well-planned, well-conducted, and well-reported long-term RCTs are needed [52].

### *Sertindole*

A Cochrane review included only two RCTs because data on two others were incomplete. The evidence suggested that sertindole was more effective than placebo. The authors expressed reservations about its use in clinical practice because of cardiac problems that were evident in the trials [53].

## **Treatment of specific symptom domains**

It has been suggested that the atypical antipsychotics may have a broader spectrum of efficacy than conventional agents. In addition to positive

symptoms, their effects on negative, cognitive, depressive, and excited symptoms have been investigated. It has been suggested that the atypical antipsychotics may differ from one another in their effects on these domains and aspects such as overall quality of life and hospitalization status [54].

### *Negative symptoms*

Contrary to popular belief, conventional antipsychotics are effective in treating negative symptoms [55], although the effect is modest at best. Atypical antipsychotics have been reported to ameliorate negative symptoms to various degrees when compared with high doses of conventional antipsychotics. Few trials have specifically examined primary negative symptoms, however, and it has been suggested that improvements may be related to decreases in positive symptoms, reduced sedation, or fewer extrapyramidal side effects [56].

#### *Risperidone*

A meta-analysis of the pooled results from six RCTs comparing risperidone with conventional antipsychotics (haloperidol, perphenazine, and zuclopenthixol) reported that risperidone at doses between 4 and 8 mg/d had a significantly higher negative symptom response rate (>20% reduction in PANSS negative subscale) [57].

#### *Olanzapine*

Three of four RCTs comparing olanzapine with conventional antipsychotics reported superior efficacy for olanzapine (see Table 2). A post-hoc analysis of a RCT comparing low-dose, medium-dose, and high-dose ranges of olanzapine with 10 to 20 mg of haloperidol and placebo for 52 weeks focused on negative symptom outcome. Significantly greater improvement was observed in negative symptoms for the high-dose olanzapine group compared with placebo and haloperidol. Path analysis suggested that this was a direct medication effect [58].

#### *Amisulpride*

Low-dose amisulpride improved negative symptoms compared with placebo in subjects with predominantly deficit symptoms (see Table 1). Also, two of four RCTs comparing higher dosage of amisulpride with conventional antipsychotics reported superiority for amisulpride in improving negative symptoms (see Table 2).

### *Cognitive symptoms*

#### *Risperidone*

Three studies, employing a similar design, investigated the effects of risperidone versus haloperidol on cognitive functions in treatment-resistant

schizophrenia. Risperidone treatment had a greater beneficial effect on verbal working memory [59], reaction time, and manual dexterity [60] and greater improvement in general verbal learning ability [61].

### *Olanzapine*

In a neuropsychologic study, 65 patients were randomly assigned in a double-blind design to olanzapine (5–20 mg/d), risperidone (4–10 mg/d), or haloperidol (5–20 mg/d) over 6, 30, and 54 weeks. Olanzapine patients showed significantly greater improvement in general cognitive function at 6, 30, and 54 weeks compared with haloperidol and risperidone [62].

### *Quetiapine*

A RCT compared neuropsychologic changes in 25 patients treated with either quetiapine or haloperidol. Quetiapine subjects showed improvement on cognitive skills, particularly verbal reasoning and fluency skills and immediate recall, with additional improvements on executive skills and visuomotor tracking [63].

### *Depressive symptoms*

#### *Risperidone*

In a retrospective analysis of pooled data from 6 RCTs, change scores on the PANSS anxious/depressive cluster were significantly greater for risperidone than for haloperidol or placebo [64].

#### *Olanzapine*

In a separate analysis of a previously discussed RCT [5] in which 335 subjects were treated for 6 weeks with three fixed dose ranges of olanzapine; haloperidol, 10 to 20 mg; or placebo, BPRS depression/anxiety depression cluster was significantly improved for two dose ranges of olanzapine ( $10 \pm 2.5$  mg/d and  $15 \pm 2.5$  mg/d), whereas haloperidol was not [65]. Another post-hoc analysis of the largest olanzapine pivotal study [22] reported that olanzapine therapy was associated with greater baseline to end point improvement in BPRS anxiety/depression symptom cluster compared with haloperidol [65]. A post-hoc evaluation of the respective effects of olanzapine and risperidone on the PANSS depression cluster in a 28-week prospective, double-blind, randomized study reported that olanzapine was associated with a significantly greater improvement in depressive symptoms. In the risperidone group, the patients with a greater degree of improvement in depressive symptoms had a significantly greater chance of psychotic relapse [66]. In the other head-to-head study comparing olanzapine and risperidone, no significant differences were found with a last observation carried forward analysis, although a completers analysis revealed an advantage for risperidone in reducing depressive/anxiety symptoms [33].

### *Quetiapine*

A post-hoc analysis of quetiapine versus haloperidol subjects with schizophrenia who displayed a partial response to treatment [67] found that quetiapine produced a greater reduction in depressive scores than haloperidol. Path analyses indicated that this was a direct effect on depressive symptoms [68].

### *Excitement or hostility*

#### *Risperidone*

The effect on PANSS hostility item scores was compared in 139 subjects who participated in a multicenter study comparing risperidone, haloperidol, and placebo. Risperidone had a greater selective effect on hostility than did haloperidol or placebo [69].

### *PANSS five factor domains*

In a post-hoc analysis combining two RCTs, 513 patients with chronic schizophrenia who received risperidone (2, 6, 10, and 16 mg/d), haloperidol (20 mg/d), or placebo over 8 weeks were compared in terms of the five symptom domains identified by a factor analysis of the PANSS items (positive, negative, cognitive, excited, and depression/anxiety). Factor score reduction was significantly greater for patients receiving risperidone, 6 to 16 mg/d, than for patients receiving haloperidol or placebo. Differences were greatest for negative symptoms, uncontrolled hostility or excitement, and anxiety or depression but also were significant for positive symptoms and disorganized thought [70].

## **Other measures of outcome**

### *Pharmacoeconomic studies*

#### *Olanzapine*

Clinical, quality-of-life, and resource usage data were prospectively collected from patients with schizophrenia who were participating in a multicenter, randomized, double-blind clinical trial comparing olanzapine, 5 to 20 mg/d (n = 551), with haloperidol, 5 to 20 mg/d (n = 266), for 6 weeks. Responders entered a 46-week maintenance phase. Olanzapine was more effective than haloperidol in producing a clinical response in the acute phase, but no significant differences in clinical improvement were observed in the maintenance phase. Olanzapine led to reductions in inpatient and outpatient costs that more than offset olanzapine's higher acquisition costs [71].

#### *Olanzapine versus risperidone*

A RCT compared clinical and economic outcomes in 150 subjects receiving either olanzapine (10–20 mg/d) or risperidone (4–12 mg/d) for 28 weeks.

Olanzapine patients were reported to be more likely to maintain response, translating into savings in costs of care for inpatient and outpatient services [72].

A review of the evidence from pharmacoeconomic studies reported that clozapine is a cost-effective treatment for refractory schizophrenia. Compared with conventional antipsychotics, risperidone and olanzapine seem to be cost-neutral to slightly cost-saving, whereas there are too few available data for quetiapine, ziprasidone, and sertindole [73].

### *Quality of life*

In a separate analysis of the study reported earlier [71], quality of life was assessed as an outcome measure by means of the Quality of Life Scale and SF-36 Health Survey. Compared with haloperidol, olanzapine treatment resulted in modestly better improvement in overall quality of life and on various subscale scores during the 6-week acute phase and during the extension phase [74]. Another separate analysis of a previously reported RCT comparing three dose ranges of olanzapine with haloperidol, 10 to 20 mg/d, and placebo examined quality-of-life outcome in responders who were entered into a 46-week extension. Advantages were reported for olanzapine-treated subjects [75].

### *First-episode schizophrenia*

#### *Risperidone*

An international RCT was conducted in 183 patients with a first episode of schizophrenia or schizophreniform disorder. Flexible doses of risperidone (mean end point dose, 6.1 mg/d) and haloperidol (mean end point dose, 5.6 mg/d) were given over 8 weeks. The two compounds showed similar efficacy, with response rates for risperidone and haloperidol being 63% and 56% [76].

#### *Olanzapine*

A post-hoc analysis of a subpopulation of first-episode patients from a larger RCT [22] reported a significantly greater reduction in the BPRS total and negative scores and the PANSS total and positive scores and a significantly higher response rate for the olanzapine subjects compared with the haloperidol subjects [77].

### *Refractory schizophrenia*

#### *Risperidone*

Risperidone (mean dose, 6.4 mg/d) was compared with clozapine (mean dose, 291.2 mg/d) over 8 weeks in 86 patients with chronic schizophrenia who were either resistant or intolerant to conventional antipsychotics (Table 4). Treatments were found to be essentially similar, with a more rapid onset of action reported for risperidone [78]. Although this trial provides

Table 4  
Randomized controlled trials of atypical antipsychotics in refractory schizophrenia

Reference	n	Sample description	Duration (wk)	Dose (mg/d)	Outcome versus conventional agent		
					Overall	Positive symptoms	Negative symptoms
<i>Risperidone vs clozapine</i>							
73	86	Resistant or intolerant	8	Ri mean 6.4 Cl mean 291	Equal	Equal	Equal
77	29	Partial response	6	Ri mean 5.9 Cl mean 403.6	Equal	Clozapine superior	Equal
78	273	Severe chronic schizophrenia	8	Ri 9 Cl 642	Clozapine superior	Clozapine superior	Clozapine superior
<i>Risperidone vs haloperidol</i>							
83	67	Severe resistance	8	Ri mean 7.5	Equal	Equal	Equal
<i>Olanzapine vs chlorpromazine</i>							
84	84	Severe resistance	8	Ol 25	Equal	Equal	Equal
<i>Clozapine, olanzapine, and risperidone vs haloperidol</i>							
Ref	157	Chronic schizophrenia with inadequate response	14	Mean doses: Cl 526.6 Ol 30.4 Ri 11.6	Clozapine and olanzapine superior	Equal	Clozapine, olanzapine and risperidone superior
<i>Quetiapine vs haloperidol</i>							
64	288	Partial responders	8	Qu 600	Equal	Equal	Equal

Abbreviations: Cl, clozapine; Ol, olanzapine; Qu, quetiapine; Ri, risperidone.

good evidence for the efficacy of risperidone in moderately refractory patients, certain concerns have been voiced. The study population was not well defined, the sample size was relatively small, clozapine dosing was relatively low, and the treatment period was possibly too brief [79–81]. The authors responded by pointing out that their sample corresponds with the criteria normally applied when considering patients for clozapine treatment and suggested that a less restrictive definition of treatment resistance may be more appropriate in clinical settings. In a RCT of 29 patients with partial response to conventional antipsychotics, risperidone was compared with clozapine over 6 weeks. End point dose was 5.9 mg/d for risperidone and 403.6 mg/d for clozapine. Clozapine was superior to risperidone for positive symptoms, whereas total symptoms, negative symptoms, and depression did not differ between groups [82]. A RCT compared increasing increments of risperidone and clozapine over 8 weeks in 273 subjects with severe chronic schizophrenia. The magnitude of improvement in mean BPRS and CGI scores was significantly greater in the clozapine group, as were most of the secondary efficacy measures [83].

A RCT investigated the effects of risperidone versus haloperidol in a severely refractory sample of subjects with schizophrenia. Patients were randomly assigned to an initial 4-week, fixed-dose phase of either risperidone, 6 mg/d, or haloperidol, 15 mg/d, followed by a further 4-week, flexible-dose phase. Risperidone was significantly better than haloperidol in reducing overall symptoms at 4 weeks but not at end point [84].

### *Olanzapine*

A prospective, randomized, double-blind study compared the efficacy of olanzapine versus chlorpromazine in treatment-resistant schizophrenia [85]. Criteria for resistance were similar to those of Kane and Honigfeld [86]. This was an 8-week, fixed-dose trial of either olanzapine, 25 mg/d, or chlorpromazine, 1200 mg/d, plus benztropine, 4 mg/d (both drugs were given at half-dose for the first week). No differences in efficacy were shown between the two drugs. Of patients, 7% in the olanzapine group and none in the chlorpromazine group met a priori criteria for clinical response. There were also no differences in dropout rates.

### *Quetiapine*

A RCT was conducted to assess the efficacy of quetiapine in 288 patients with schizophrenia who had been partially responsive to treatment. Patients who experienced persistent symptoms on conventional antipsychotics were subjected to 4 weeks of open treatment with fluphenazine, and patients showing partial or no response were randomized to quetiapine, 600 mg/d, and haloperidol, 20 mg/d, for 8 weeks. Treatments were equally effective in total PANSS symptom reduction, whereas quetiapine patients had a significantly greater response rate [67] and significantly greater reduction of depressive symptoms [68].

Clozapine, olanzapine, risperidone, and haloperidol were compared in a RCT comprising a sample of 157 inpatients with chronic schizophrenia who had not responded adequately to other antipsychotic medications. Trial duration was 14 weeks (8 weeks' fixed dose, followed by 6 weeks' flexible dose). Mean end point doses for clozapine, olanzapine, risperidone, and haloperidol were 526.6, 30.4, 11.6, and 25.7 mg/d. Compared with haloperidol, there were significant advantages for clozapine and olanzapine regarding overall improvement (PANSS total) and general psychopathology and for clozapine, risperidone, and olanzapine regarding negative symptoms [87].

A review and meta-analysis of 12 studies comparing typical and atypical antipsychotics in subjects with refractory schizophrenia reported that clozapine exhibits superiority over typical antipsychotics in terms of efficacy and safety. The magnitude of the advantage for clozapine was not consistently robust, however. Efficacy data for other atypical antipsychotics in the treatment of refractory schizophrenia were inconclusive [88].

## Summary

Based on the evidence presented here, the following tentative conclusions can be drawn. Atypical antipsychotics (except amisulpride) have shown superiority over placebo in acute schizophrenia. Compared with conventional antipsychotics, they are at least as effective. Generally, analyses employing conservative criteria (eg, Cochrane reviews) report few efficacy differences between atypical and conventional agents. There are now many well-controlled studies indicating modest advantages for the atypical antipsychotics, however, particularly in specific symptom domains. For the treatment of negative symptoms, olanzapine and to a lesser extent amisulpride seem most promising. Risperidone, olanzapine, and quetiapine display advantages in improving cognitive and depressive symptoms. There are indications that the atypical antipsychotics are associated with decreased likelihood of rehospitalization and improved quality of life. In head-to-head comparisons of atypical antipsychotics, none have shown consistent efficacy advantages. In severely refractory samples, no atypical antipsychotics have consistently been shown to be as effective as clozapine or superior to conventional agents. There are indications, however, that risperidone, olanzapine, and quetiapine have advantages over conventional agents in less severely refractory patients. Few maintenance RCTs have been published, and efficacy advantages for atypical antipsychotics in prospective RCTs in first-episode schizophrenia have not been reported.

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