

Are There Any Differences in the Efficacy among Second Generation Antipsychotics in the Treatment of Schizophrenia and Related Disorders?

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Background. The goal of this review is to summarize the results of head to head efficacy studies that compare second generation antipsychotics in the treatment of schizophrenia and related disorders.

Methods. A literature search through the Medline database and Google was conducted. Articles published up to September 2005 were included. Abstracts from conference papers and posters were not included.

Results. Randomized controlled trial data on possible differences in efficacy among atypical antipsychotics are limited. Moreover, the comparison is difficult, as studies differ in outcome measures. The results indicate that first-line second-generation antipsychotics (amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone and zotepine) show comparable efficacy.

Conclusion. Possible new studies should focus on long-term effects, including cost-effectiveness, quality of life, social functioning and service utilization.

Keywords Atypical antipsychotics, Schizophrenia, Efficacy

INTRODUCTION

Second generation antipsychotics (SGAs) offer advantages over first generation drugs in the treatment of schizophrenia and related disorders (1,2). While the different profiles of side effects of these drugs have been reviewed extensively (3–6), this overview deals with possible differences in efficacy. This particular issue has not been sufficiently addressed in psychiatric literature yet.

The most relevant information on possible differences in efficacy is obtained from head to head comparison studies. From the clinical point of view it is practical to describe short- and middle-term trials separately from long-term

trials. The goals of treatment during acute, stabilization and stable phases differ (7). Short-term trials are up to 8 weeks long and they are designed to assess acute phase treatment outcome. The intermediate length trials (9–24 weeks) are designed to assess treatment outcomes of stabilization phase. Long-term trials are those that cover a period longer than 24 weeks and assess the efficacy for the stable phase treatment. We described double-blind trials and open-label trials separately. The distinction between those two types of studies reflects methodological superiority of double-blind trials and thus greater clinical relevance of results concluded from those trials.

For better transparency, first-line SGAs head to head trials are described separately (Tables 1 and 2) from those that included clozapine (Table 3). First-line SGAs—amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone

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Table 1 First-line SGAs Head to Head Double-blind Trials: List Made According to the Length of the Study

Author	Medication	Study period	Number of subjects	Daily mg mean dose (SD)	Results and outcome measures	Comments
Potkin et al., 2003	aripiprazole versus risperidone versus placebo	4-week	arip 101 risp 99 placebo 103	arip 20 arip 30 risp 6	arip=risp in PANSS	Fixed dose
Simpson et al., 2004 Harvey et al., 2004	ziprasidone versus olanzapine	6-week	zipra 136 ola 133	zipra 129.9 (27.3) ola 11.3 (2.8)	zipra=ola in BPRS and CGI zipra=ola in cognitive enhancement	
Peuskens et al., 1999	amisulpride versus risperidone	8-week	ami 115 risp 113	ami 800 risp 8	ami=risp in PANSS	Fixed dose
Conley and Mahmoud, 2001	risperidone versus olanzapine	8-week	risp 188 ola 189	risp 4.8 (1.2) ola 12.4 (4.6)	ola=risp in PANSS, risp>ola in anxiety/depression subscale PANSS	
Addington et al. 2004	ziprasidone versus risperidone	8-week	zipra 149 risp 147	zipra 114.2 risp 7.4	zipra=risp in PANSS, BPRS, CGI	Maximal dose: Zipra 160 Risp 10
Van Bruggen et al., 2003	olanzapine versus risperidone	6–10 week	ola 18 risp 26	risp 4.4 (1.5) ola 15.6 (4.0)	ola=risp in PANSS	Recent onset schizophrenia
Martin et al., 2002; Mortimer, 2004	amisulpride versus olanzapine	2-month	ami 189	ami 489 (132)	ami=ola in BPRS	
Sechter et al., 2002	amisulpride versus risperidone	6-month	ola 188 ami 152	ola 12 (3) ami 683 (204)	ami=ola in BPRS ami=risp in PANSS, BPRS, BMRS	
Tran et al., 1997	olanzapine versus risperidone	6-month	risp 158	risp 6.92 (2.14)		
Tran et al., 1997	olanzapine versus risperidone	28-week	ola 172 risp 167	ola 17.2 (3.6) risp 7.2 (2.7)	ola>risp in SANS, ola>risp in number of patients responding	
Edgell et al., 2000	olanzapine versus risperidone	28-week	ola 75 risp 75	ola 17.7 (3.4) risp 7.9 (3.2)	ola=risp in PANSS, ola>risp in number of patients more likely to maintain response	
Feldman et al., 2003	olanzapine versus risperidone	28-week	ola 20 risp 19	ola 18.8 (3.1) risp 8.9 (2.3)	ola=risp in PANSS positive subscale, ola>risp in PANSS negative subscale	Chronic psychosis in older patients
Gureje et al., 2003	olanzapine versus risperidone	30-week	ola 32 risp 33	ola 17.2 (2.8) risp 6.6 (1.6)	ola=risp in PANSS	
Purdon et al., 2000	olanzapine versus risperidone	54-week	ola 80 risp 65	ola 11.0 (4.6) risp 6.0 (1.8)	ola>risp in amount of change in the general cognitive index from baseline	
Lieberman et al., 2005	olanzapine versus quetiapine versus risperidone versus ziprasidone versus perhenazine	18 months	ola 336 perphe 261 quet 337 risp 341 zipra 185	ola 20.1 perphe 20.8 quet 543.4 risp 3.9 zipra 112.8	ola>quet and risp in time to the discontinuation for any cause	

and zotepine—can be used as first choice treatment. Clozapine, on the other hand, is not first choice treatment because of side-effect profile. As it is reserved for treatment-resistant population, the patients in the studies with clozapine might have different clinical characteristics from the non-resistant patients, which could make comparisons difficult to interpret. However, in identified studies with clozapine, not all participants met

criteria for treatment-resistance. Therefore for clozapine we use the term second-line SGA.

Comparisons between clinical trials have obvious limitations. Clinical trials are designed and statistically powered to answer specific clinical questions, and are often carried out in selected patient populations, which may not necessarily reflect routine clinical practice. Most trials are powered to address

Table 2 First-line SGAs Head to Head Open Trials: List Made According to the Length of the Study

Authors	Medication	Study period	Number of subjects	Daily mg mean dose (SD)	Results and Outcome measures	Comments
Ho et al., 1999	olanzapine versus risperidone	4-week 6-month	ola 21 risp 21	ola 13.8 (7.6) risp 4.5 (2.3)	4 weeks: ola=risp in BPRS, GAS, SANS, SAPS6 months: risp>ola in the sum of delusions and hallucinations global ratings in SAPS	
Gothelf et al., 2003	olanzapine versus risperidone versus haloperidol	8-week	ola 19 risp 17 halop 7	ola 12.9 (3.1) risp 3.3 (1.1) halop 8.3 (3.8)	ola=risp in PANSS	adolescents
Briken et al., 2002	zotepine versus olanzapine versus risperidone	Acute phase (not specified)	ola 25 zot 24 rispe 20	ola 11.88 (5.94) zot 152.27 (76.20) risp 3.88 (1.45)	zot>ola in grandiosity subscale PANSS zot>risp in hostility subscale PANSS	
Dinakar et al., 2002	olanzapine versus risperidone	3-month	ola 32 risp 47	ola 20.2 (5.06) risp 6.3 (2.1)	ola=risp in BPRS	Treatment refractory schizophrenia, patients hospitalized for more than 5 years in a state mental hospitals
Mullen et al., 2001	quetiapine versus risperidone	4- month	quet 553 risp 175	quet 253.9 risp 4.4	quet=risp in PANSS Quet > risp in HAM-D	
Dossenbach et al., 2004	olanzapine versus risperidone versus quetiapine	6-month	ola 3222 risp 1116 quet 189 halop 256	ola 10.9 (4.8) risp 4.0 (2.1) quet 339.5 (188.9) halop 12.2 (9.3)	ola>quet in CGI-S adapted	
Garcia-Cabeza et al., 2001	olanzapine versus risperidone	6-month	ola 2128 risp 417	ola 13.6 risp 5.4	ola>risp Drug Attitude Inventory (DAI-10)	subjective response to treatment
Ascher-Svanum et al., 2004	olanzapine versus risperidone	3-year	ola 159 risp 112	ola 14.5 risp 4.5	ola>risp: lower hospitalization rate, fewer hospitalization days	Median doses ola 14.3 risp 4.3
Soholm et al., 2002	olanzapine versus risperidone	3.1 ± 0.2 years	ola 45 risp 10	ola 5–40 risp 4–8	ola=risp in number of responders/non-responders	Median peak daily doses (mg) Risp 6 Ola 20

only a primary outcome measure, such as the change from baseline in the overall Positive and Negative Symptoms Scale (PANSS) score (8). The identified outcome measures in selected trials were: general psychopathology, cognitive performance, hostility, subjective response to treatment, treatment compliance, depressive symptoms and suicidal behavior.

We summarize the results of head to head studies that compare second generation antipsychotics in the treatment of schizophrenia and related disorders. We focus on the efficacy in the acute and stabilization phase of treatment (short and intermediate length trials), and stable phase of treatment (long-term trials, more than 6 months). First-line SGAs head to head trials are described separately from those that included clozapine.

METHODS

We used routine search strategies through the Medline database and Google. Articles published up to September 2005 were included. We summarized articles released in peer-reviewed journals exclusively. We did not include abstracts from conference papers and posters.

It should be clearly stated that in some cases acute phase and long-term treatment trials published separately are two different reports on the same study cohort. For the sake of simplicity we considered them in accordance with their separate publication refraining from further comparison of the study groups enrolled in those trials.

Table 3 Second-line, Second-generation: Clozapine versus Other SGAs Head to Head Double-blind and Open Trials: List Made According to the Length of the Study

Authors	Medication	Study period	Number of subjects	Daily mg mean dose (SD)	Results and Outcome measures	Comments
Breier et al., 1999	clozapine versus risperidone	6-week	cloz 14 risp 15	cloz 403.6 (79.6) risp 5.9 (1.6)	risp=cloz in BPRS totalcloz>risp in BPRS positive	
Bondolfi et al., 1998	clozapine versus risperidone	8-week	cloz 43 risp 43	cloz 291.2 (150–400) risp 6.4 (3–10)	risp=cloz in PANSS, CGI	Inpatients with chronic schizophrenia
Wahlbeck et al., 2000	clozapine versus risperidone	10-week	cloz 10 risp 9	cloz 385 (219) risp 8.0 (2.1)	risp=cloz in PANSS	
Azorin et al., 2001	clozapine versus risperidone	12-week	cloz 138 risp 135	cloz 642 (212) risp 9 (4)	cloz>risp in PANSS Calgary depression scale, Psychotic depression scale, Psychotic anxiety scale	
Citrome et al., 2001,	clozapine versus olanzapine versus risperidone versus haloperidol	14-week	cloz 40 ola 39 risp 41 halop 37	cloz 526.6 (140.3) ola 30.4 (6.6) risp 11.6 (3.2) halop 25.7 (5.7)	cloz>risp in hostility item PANSS	
Bilder et al., 2002	clozapine versus olanzapine versus risperidone versus haloperidol	14-week	cloz 24 ola 26 risp 26 halop 25	cloz 498 (184) ola 30.0 (5.8) risp 11.3 (3.3) halop 26.8 (4.5)	risp>clo in memory	Global neurocognitive function
Tollefson et al., 2001	clozapine versus olanzapine	18-week	cloz 90 ola 90	cloz 303.6 (108.7) ola 20.5 (2.8)	ola=cloz in PANSS	
Bitter et al., 2004	clozapine versus olanzapine	18-week	cloz 72 ola 75	cloz 216.2 (107.9) ola 17.2 (4.8)	ola=cloz in PANSS, CGI	
Meltzer et al., 2003	clozapine versus olanzapine	24 months	cloz 490 ola 490	cloz 274.2 (155) ola 16.6 (6.4)	cloz>ola in occurrence of a significant suicide attempt and Clinical Global Impression of Suicide Severity	Open trial

RESULTS

Acute and Stabilization Phase Treatment: First-line Second-generation Antipsychotics

Double-blind Trials

Olanzapine versus Risperidone. We identified two trials with a total of 421 participants comparing the clinical efficacy of olanzapine and risperidone in acute and stabilization phase.

The short-term efficacy was published by Conley and Mahmoud (9). It was a multicentric (41 sites in the United States), randomized, double-blind parallel-group, 8-week prospective study of 377 subjects with schizophrenia or schizoaffective disorder. The patients were randomly assigned to receive 2–6 mg/day of risperidone (mean modal dose = 4.8 mg/day) or 5–20 mg/day of olanzapine (mean modal dose = 12.4 mg/day). The two study groups were similar at baseline

except the olanzapine group was slightly younger than the risperidone group (mean age years 38.9 and 41.0 respectively, $p=0.04$). Total PANSS scores and scores on the five Positive and Negative Syndrome Scale factors were improved in both groups at week 8 (subjects who completed the study) and endpoint (all subjects, including dropouts). Comparison of individual factors showed no significant differences at endpoint. However, among those who completed 8 weeks of the study (observed cases) improvements on Positive and Negative Syndrome Scale factors for positive symptoms and anxiety/depression were greater with risperidone than olanzapine ($p < 0.05$). Nevertheless, statistical differences in subscale items in absence of differences in overall scale should be interpreted in an exploratory sense only.

Another short-term trial was published by van Bruggen et al. (10). Forty-four actively symptomatic young patients with recent onset schizophrenia randomly received olanzapine 15 mg (median dose) or risperidone 4 mg (median dose). Eighteen

patients (mean age=21.0 years) were randomized to olanzapine, 26 patients (mean age=20.6) to risperidone. Symptom response and side-effects were measured during a 6–10 week treatment study. No major differences were observed between the two treatment groups. Symptoms as measured by PANSS improved significantly in both groups. Using five symptom dimensions, both drugs were effective in treating positive symptoms and agitation/excitement symptoms and neither olanzapine nor risperidone influenced disorganization and depressive symptoms. The data indicate that the differences between olanzapine and risperidone in symptom response are small. In spite of the relatively low power, the study suggests no significant differences in treatment effects of olanzapine and risperidone.

Amisulpride versus Olanzapine. We identified two studies describing clinical efficacy of amisulpride (N=189) and olanzapine (N=188) during acute and stabilization phase. Martin et al. (11) described short-term results at two months and Mortimer et al. (12) reported on the second study analyses six-month results in the same study population.

Three hundred and seventy seven patients with predominantly positive symptomatology were treated for six months with either amisulpride (N=189, 200–800 mg/day) or olanzapine (N=188, 5–20 mg/day). Short-term results were analyzed after two months of treatment. Psychotic symptoms, as measured by BPRS score, improved with both treatments, amisulpride being equivalent to olanzapine. All BPRS factor scores as well as depressive symptoms improved to a similar extent with both treatments. Amisulpride and olanzapine showed equivalent efficacy at two months in the treatment of acute psychotic exacerbations of schizophrenia (11). After six months the improvement of BPRS score was 32.7% in the amisulpride group and 33.0% in the olanzapine group; thus the efficacy of amisulpride is equal to that of olanzapine. All other secondary efficacy outcome variables evolved to a similar extent in both groups. The authors concluded that the efficacy of amisulpride is not inferior to that of olanzapine in the treatment of acute schizophrenia (12).

Amisulpride versus Risperidone. Amisulpride was compared with risperidone in patients with acute exacerbations of schizophrenia. Double-blind 8-week study reported by Peuskens et al. (13) involved 228 patients assigned either to amisulpride 800 mg (N=115) or risperidone 8 mg (N=113) for eight weeks. Both treatments produced a marked improvement in schizophrenic symptomatology. Amisulpride and risperidone were equally effective against positive symptoms on the PANSS positive syndrome subscale.

Aripiprazole versus Risperidone versus Placebo. In a four-week double-blind study published by Potkin et al. (14), 404 patients were randomized to 20 mg/day (N=101) or 30 mg/day (N=101) of aripiprazole, placebo (N=103), or 6 mg/day of risperidone (N=99). Aripiprazole (20 and 30 mg/day) and risperidone (6 mg/day) were significantly better than placebo on all efficacy measures ($p < 0.001$). Separation from placebo occurred at week 1 for PANSS total and positive scores with

aripiprazole and risperidone, and for PANSS negative scores with aripiprazole. There were no significant differences in PANSS scores between aripiprazole and risperidone.

Ziprasidone versus Olanzapine. We identified two published studies comparing acute phase treatment with olanzapine (N=133) versus ziprasidone (N=136). The first one deals with efficacy (15), the other analyzes the relative cognitive enhancing effects (16).

Simpson et al. (15) reported about a six-week, multicenter, double-blind, parallel-design, flexible-dose trial. Patients with schizophrenia or schizoaffective disorder were randomly assigned to receive ziprasidone (N=136) or olanzapine (N=133). The overall mean daily doses were 129.9 mg/day for ziprasidone and 11.3 mg/day for olanzapine. Both antipsychotics were efficacious in improving symptoms and global illness severity. The two treatment groups did not differ significantly in primary or secondary efficacy measures at endpoint or in by-visit analysis. During six weeks of treatment, ziprasidone and olanzapine demonstrated comparable antipsychotic efficacy.

The goal of the other study published by Harvey et al. (16) was to compare the relative cognitive enhancing effects of ziprasidone (N=136) and olanzapine (N=133) in the above described population. Cognitive testing measuring attention (Continuous performance test, Trail-making test), motor speed, memory (verbal memory: the Rey auditory verbal learning test), executive functioning (Wisconsin card-sorting test, Trail-making test, part B), and verbal skills (verbal fluency examination) were performed on all patients at baseline and endpoint. Treatment with either ziprasidone or olanzapine was associated with statistically significant improvements from baseline in attention, memory, working memory, motor speed and executive functions. Treatment with olanzapine was also associated with a statistically significant improvement in verbal fluency. No statistically significant differences between these medications were found in the magnitude of improvement from baseline in any of the cognitive measures (other than verbal fluency in an exploratory analysis). The observed changes were not associated with changes in clinical symptoms measured using the PANSS or changes in movement disorders. During six weeks of treatment, ziprasidone and olanzapine demonstrated substantial and comparable cognitive-enhancing effects relative to previous treatment. These effects were noted in all aspects of cognitive functioning previously proven to predict functional outcome in schizophrenia. No overall differences were detected between the medications in terms of the extent of cognitive enhancement.

Ziprasidone versus Risperidone. Addington et al. (17) compared ziprasidone (40 to 80 mg b.i.d.) (N=149) and risperidone (3 to 5 mg b.i.d.) (N=147) for eight weeks in patients with acute exacerbation of schizophrenia or schizoaffective disorder. Equivalence was demonstrated in PANSS total scores, CGI/S scores, PANSS negative subscale scores, BPRS total and core item scores and PANSS total and CGI-I responder rates.

Open Trials

Olanzapine versus Risperidone. Ho et al. (18) compared the clinical efficacy of olanzapine (N=21, mean daily dose 13.8 ± 7.6 mg) and risperidone (N=21, mean daily dose 4.5 ± 2.3 mg) in a non-randomized six-month open-label study. No differential effects were observed in BPRS, GAS, SANS/SAPS scores. At six-month follow-up, 13 subjects in the olanzapine and 13 subjects in the risperidone-treatment group were compared. Risperidone was more effective than olanzapine in reducing psychotic symptoms characterized as the sum of the of the delusions and hallucinations global ratings in SAPS ($p=0.03$).

Garcia-Cabeza et al. (19) measured subjective response to treatment in a six-month prospective naturalistic study using the 10-item version of Drug Attitude Inventory (DAI-10). The final DAI-10 score is the grand total of the positive and negative points. A positive total score means a positive subjective response. A total number of 2128 patients (overall mean daily dose 13 mg) treated with olanzapine and 417 subjects treated with risperidone (mean dose 5.4 mg/day) participated in the study. Olanzapine-treated patients had significantly higher DAI-10 scores ($p < 0.001$) and significantly better treatment compliance compared to risperidone.

Olanzapine versus Risperidone versus Quetiapine versus Haloperidol. Dossenbach et al. (20) evaluated the effectiveness of olanzapine (N=3222, mean daily dose 10.9 mg), risperidone (N=1116, mean daily dose 4.0 mg), quetiapine (N=189, mean daily dose 339.5 mg) and haloperidol (N=256, mean daily dose 12.2 mg) in outpatients with schizophrenia in a naturalistic, prospective observational study. To ensure that the study reflects the naturalistic setting within each country, choice of antipsychotic and dose prescribed was at the psychiatrist's discretion. The primary outcome measure was the Clinical Global Impressions-Severity of Illness Rating Scale (CGI-S). The CGI-S was adapted to include four additional symptom domains (positive, negative, depressive, and cognitive symptoms), each rated from 1 to 7 (1-normal, 7- severely ill). At six months, olanzapine resulted in significantly greater improvement in overall, positive, negative, depressive and cognitive symptoms compared with quetiapine, risperidone or haloperidol ($p < 0.001$). Improvements in overall, negative, and cognitive symptoms were significantly higher for risperidone compared with haloperidol ($p < 0.001$), whereas improvements across all symptoms were comparable for quetiapine and haloperidol.

Olanzapine versus Risperidone. The efficacy of olanzapine (N=32) and risperidone (N=47) among patients with treatment refractory schizophrenia who had been hospitalized for more than five years and who were not suitable candidates for a clozapine trial was retrospectively analysed by Dinakar et al. (21). The mean dose of olanzapine was 20.2 mg/day, risperidone 6.3 mg/day. After the three-month study period the patients in both groups showed significant improvements in scores on the 18-item BPRS. There were no significant differences between olanzapine and risperidone. Forty-four percent in the

olanzapine group and 43% in the risperidone group were discharged to supervised residencies on the basis of their clinical improvement.

Olanzapine versus Risperidone versus Haloperidol. The goal of the study published by Gothelf et al. (22) was to evaluate and compare the drug response and side effects in adolescents with schizophrenia treated with olanzapine, risperidone, and haloperidol. Forty-three patients were treated with olanzapine (N=19), risperidone (N=17), and haloperidol (N=7) for eight weeks in a nonrandomized open clinical trial. Significant improvement evaluated with PANSS was observed by week 4 for all medications. Olanzapine, risperidone and haloperidol appeared to be equally effective for the treatment of schizophrenia in adolescent inpatients

Quetiapine versus Risperidone. In a multicenter four-month, open-label, randomized clinical trial published by Mullen et al. (23) 728 patients were randomized, 553 to quetiapine and 175 to risperidone. Doses were adjusted to maximize efficacy and to minimize adverse events; mean prescribed doses were 253.9 mg/day for quetiapine and 4.4 mg/day for risperidone. There were no significant between-group differences on the Positive and Negative Symptom Scale (PANSS) between both medications. At end-point, quetiapine-treated patients had significantly lower Hamilton Rating Scale for Depression (HAM-D) scores ($p=0.028$). The results of this study suggest that quetiapine is as effective as risperidone for the treatment of psychotic symptoms and is more effective for depressive symptoms.

Zotepine versus Olanzapine versus Risperidone. The study by Briken et al. (24) compared olanzapine (mean dose 11.88 mg/day), zotepine (mean dose 152.27 mg/day) and risperidone (mean 3.88 mg/day) with regard to hostility in 69 patients with schizophrenia or schizoaffective disorder. The data were collected in an open-label, randomized, acute-phase trial. Patients treated with zotepine showed a significantly more improvement on hostility and hostile excitement syndrome than those who received risperidone and more reduction of grandiosity than those receiving olanzapine.

Second-line Second-generation Antipsychotics: Clozapine

Double-blind Trials

Clozapine versus Risperidone. We identified four trials comparing clozapine with risperidone with a total of 407 participants. The first one was published by Bondolfi et al. (25). It was a controlled double-blind, multicenter eight-week study with 86 treatment-resistant chronic schizophrenic patients, who did not respond to or did not tolerate conventional neuroleptics. The patients were randomly assigned to receive risperidone (mean dose 6.4 mg /day) or clozapine (mean dose 291.2 mg/day). Both risperidone and clozapine significantly reduced the severity of psychotic symptoms (PANSS, CGI) with no significant between-group differences. At the endpoint, 67% of

the risperidone group and 65% of the clozapine group were clinically improved (reduction of 20% or more in total PANSS). Risperidone was well tolerated and as effective as medium doses of clozapine in patients with chronic schizophrenia who had been resistant to or intolerant of conventional neuroleptics (25).

The second study was published by Breier et al. (26). A double-blind, parallel-group comparison of the effects of clozapine (mean dose 403.6 mg/day) and risperidone (mean dose 5.9 mg/day) was investigated in a six-week trial in 29 chronic schizophrenic patients who met a priori criteria for partial response to traditional neuroleptic agent fluphenazine. Clozapine was superior to risperidone for positive symptoms, but there were no significant differences between the two drugs in measures of negative symptoms, BPRS total scores and depression scores. The clozapine patients, but not risperidone patients, demonstrated significant reductions from the fluphenazine baseline in positive symptoms, total symptoms, and depression (26).

The third trial was published by Wahlbeck et al. (27). A parallel-group comparison of the effects of clozapine and risperidone was investigated in a 10-week trial in 19 treatment-resistant patients. Patients were randomly assigned to clozapine or risperidone and treatment outcomes were assessed blindly. Five clozapine patients and six risperidone patients achieved clinical improvement defined as a 20% decrease in the PANSS total score. No significant differences between the groups were detected at baseline or at endpoint in terms of positive or negative symptoms, disease severity, global or social functioning scores. The patients' opinion of the drugs did not differ between groups (27).

The fourth trial was published by Azorin (28). This prospective, double-blind, randomized multicenter, parallel-group, 12-week study compared the efficacy and safety of therapeutic doses of clozapine and risperidone in 273 patients with severe chronic schizophrenia and poor previous treatment response. The magnitude of improvement in the mean BPRS and CGI scores from baseline to the end of the study was significantly greater in the clozapine group than in the risperidone group. Statistically significant differences in favor of clozapine were also seen for most of the secondary measures of efficacy (PANSS, Calgary Depression Scale and Psychotic Anxiety Scale). Clozapine showed superior efficacy over risperidone in this patient population (28).

Clozapine versus Olanzapine. We identified two trials comparing clozapine with olanzapine with a total of 252 participants. The first one was published by Tollefson et al (29). The study was designed to demonstrate the "noninferiority" of olanzapine compared to clozapine after 18 weeks of double-blind treatment in 180 neuroleptic-resistant patients. Patients were randomly assigned to treatment with olanzapine 15–25 mg/day (mean dose 20.5) or clozapine 200–600 mg/day (mean dose 303.6). Using the last observation carried forward (LOCF) approach, the authors showed that mean changes from baseline to end-point in PANSS total score were similar and

both agents were comparably effective, i.e., demonstrated "noninferiority" of olanzapine when compared to clozapine.

The second study was published by Bitter et al. (30). The efficacy and safety of olanzapine (5–25 mg/day) was compared to clozapine (100–500 mg/day) in an 18-week, randomized, double blind, parallel study on 147 schizophrenic patients who failed to respond adequately to antipsychotic medication or who experienced intolerable adverse effects associated with the medication. At the endpoint no statistically significant differences were found between olanzapine and clozapine in any measure of efficacy (PANSS, CGI). Likewise, the response rates were not significantly different between olanzapine-treated (57.9%) and clozapine-treated patients (60.8%). Olanzapine exerted similar efficacy to clozapine in patients who failed to respond to previous treatment (treatment resistance) or to tolerate side effects (treatment intolerance).

Clozapine versus Olanzapine versus Risperidone versus Haloperidol. In a double-blind trial by Citrome et al. (31) 157 inpatients with a history of suboptimal treatment response were randomly assigned to treatments with clozapine (mean dose 526.6 mg/day) olanzapine (mean dose 30.4 mg/day), risperidone (mean dose 11.6 mg/day), or haloperidol (25.7 mg/day) for 14 weeks (an 8-week titration and fixed-dose period followed by a six-week variable-dose period). Specific anti-aggressive effects of clozapine were compared with those of olanzapine, risperidone and haloperidol. Patients differed in their treatment response as measured by the hostility item of the PANSS. The scores of patients taking clozapine indicated significantly greater improvement than those of patients taking haloperidol or risperidone. Clozapine was not shown to be superior to olanzapine. The effect on hostility appeared to be independent on the antipsychotic effect of clozapine measured by other PANSS items that reflect delusional thinking, a formal thought disorder, or hallucinations. Hostility was also independent of sedation as measured by the NOSIE. Neither risperidone nor olanzapine showed superiority to haloperidol. Clozapine has a relative advantage over other antipsychotics as a specific antihostility agent.

Clozapine versus Olanzapine versus Risperidone versus Haloperidol. The effect of clozapine (mean dose 452 mg/d), olanzapine (mean dose 20.2 mg/d), risperidone (mean dose 8.3 mg/d) and haloperidol (19.6 mg/d) was examined by Bilder et al. (32) using 16 measures of neurocognitive functioning in a double-blind, 14-week trial involving 101 patients. Global neurocognitive function improved both with olanzapine and risperidone treatments, and these improvements were superior to those seen with haloperidol. Patients treated with olanzapine showed an improvement in general and attention domains but not more than observed with other treatments. Patients treated with risperidone improved in memory significantly more than patients on clozapine or haloperidol. Clozapine yielded improvement in motor function, but not more than in other groups. The average effect sizes for change were in the "small to medium" range. More than half of the patients treated with olanzapine and risperidone experienced "clinically significant"

improvement, i.e., changes in the score of at least 0.5 SD from baseline). These findings did not appear to be secondary to changes in symptoms, side effects, or blood levels of medications. Cognitive deficits in patients with a history of suboptimal response to conventional treatments may improve on newer antipsychotic drugs. There may be differences between SGAs in their patterns of cognitive effects.

Stable-phase Treatment: First-line Second-generation Antipsychotics

Double-blind Trials

Olanzapine versus Risperidone. Tran et al. (33) studied the efficacy and safety characteristics of olanzapine versus risperidone in a 28-week prospective study conducted with 339 patients who met the DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder. The mean modal drug dose was 17.2 ± 3.6 mg/day for the olanzapine group (N=172) and 7.2 ± 2.7 mg/day for the risperidone treatment group (N=167) respectively. Both treatment groups showed significant ($p < 0.001$) improvement in PANSS, BPRS, CGI-S scores. In this study, olanzapine demonstrated a significantly greater efficacy ($p=0.02$) in negative symptoms according to SANS summary score. A significantly greater proportion of olanzapine-treated patients achieved a response of at least 40% improvement in PANSS total score than risperidone-treated patients (olanzapine 36.8% vs. risperidone 26.7%, $p = 0.049$).

Edgell et al. (34) assessed the efficacy of olanzapine (N = 75) compared with risperidone (N= 75) in a 28-week double-blind prospective study. The mean modal dosages were 17.7 ± 3.4 mg/day for the olanzapine and 7.9 ± 3.2 mg/day for the risperidone treatment group. No significant treatment group differences were found in the proportion of patients demonstrating a response based on PANSS total scores. However, olanzapine-treated patients were more likely to maintain a response compared with the risperidone-treated subjects ($p = 0.048$) (34).

The study of Feldman et al. (35) compared the efficacy of olanzapine and risperidone in controlling negative and positive symptoms of chronic psychosis in older patients. In the double-blind, 28-week study, patients with schizophrenia aged 50 to 65 years were randomly assigned to receive risperidone (4–12 mg/day, N = 19) or olanzapine (10–20 mg/day, N = 20). At 8 weeks and 28 weeks, the magnitude of change in PANSS positive subscale scores did not differ between the treatment groups. However, by week 8, olanzapine had reduced PANSS negative subscale scores significantly more than risperidone ($p = 0.032$). By week 28, olanzapine continued to maintain significantly greater reduction in baseline-to-endpoint PANSS negative subscale scores ($p=0.032$).

Gureje et al. (36) conducted a double-blind, parallel, 30-week study compared the efficacy of olanzapine (N=32, 10–20 mg/day, mean modal dose 17.2) versus risperidone (N=33, 4–8 mg/day, mean modal dose 6.6) in 65 patients who met the

DSM-IV criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder. The olanzapine treatment group showed significantly greater improvement than the risperidone treatment group in PANSS total ($p=0.038$), PANSS general psychopathology ($p=0.016$), and BPRS total scores ($p=0.012$) at endpoint. There were no significant between-group differences in improvement in PANSS positive and negative, or CGI-S scores. After 30 weeks, more olanzapine-treated patients achieved a response of at least 20% improvement in PANSS total score than risperidone-treated patients ($p=0.01$).

The efficacy of novel antipsychotic medications in the treatment of cognitive impairment in early phase schizophrenia was assessed in a 54 week double-blind study by Purdon et al. (37). A battery of tests to assess motor skills, attention span, verbal fluency and reasoning, nonverbal fluency and construction, executive skills and immediate recall was administered at baseline and after 6, 30, and 54 weeks of treatment. Patients were randomly assigned to olanzapine (N=80, 5–20 mg/day, mean 11.00) or risperidone (N=65, 4–10 mg/day, mean 6.00). The primary outcome measure was a general cognitive index derived from the six domain scores. Olanzapine showed an advantage over risperidone in the amount of change in the general cognitive index from baseline to end point ($p=0.04$).

Amisulpride versus Risperidone. Sechter et al. (38) conducted a six-month, double-blind, randomized study to evaluate the efficacy, safety and functional effects of amisulpride (N=152) and risperidone (N=158) in patients with chronic schizophrenia. Both medications were comparable in terms of decrease in PANSS, BPRS and Bech Rafaelsen Melancholia Scale from baseline.

Olanzapine versus Quetiapine versus Risperidone versus Ziprasidone versus Perphenazine. In a comprehensive double-blind study by Lieberman et al. (39) authors compared several SGAs and perphenazine. A total of 1493 patients with schizophrenia were recruited and randomly assigned to receive olanzapine (N=336), perphenazine (N=261), quetiapine (N= 337), or risperidone (N= 341) for up to 18 months. Ziprasidone (N=185) was included later on in the course of the trial. The antipsychotics differed significantly in terms of the time to the discontinuation of treatment. There was significantly longer time to the discontinuation for any cause in the olanzapine group than in the quetiapine ($p < 0.001$) or risperidone ($p=0.002$) group, but not in the perphenazine ($p=0.021$) or ziprasidone ($p=0.028$) group after adjustment for multiple comparisons.

Open Trials

Olanzapine versus Risperidone. The long-term effectiveness of risperidone and olanzapine in resistant or intolerant schizophrenic patients assessed Soholm et al. in an open-label study (40). The aim of the study was to retrospectively evaluate the long-term effectiveness of antipsychotic treatment before and after switching from treatment with conventional antipsychotics or clozapine to newer atypical antipsychotics

because of treatment resistance or intolerance. The data of patients switched were recorded for two periods: before and after the day of switching. The patients in olanzapine group (N=45) and risperidone group (N=10) were followed for a mean study period of 3.1 ± 0.2 years. There were no significant differences in the ratio of responders/non-responders between the subgroups. A responder to treatment was defined as a patient with a significant effect of drug treatment with one of the newer atypical antipsychotics and without discontinuation of treatment for one reason or another. The treatment was considered significant, if either a) both the treating psychiatrist and the patient considered the treatment to be effective, or b) there were reports of improvement in the record.

Ascher-Svanum et al. (41) evaluated patients with schizophrenia-spectrum disorders initiated on olanzapine (N=159, mean daily dose 14.5 mg) or risperidone (N=112, mean daily dose 4.5 mg) in a three-year prospective, nonrandomized, naturalistic study. The outcome measures were: hospitalization rate, duration of hospitalization and time to hospitalization after initiation of given treatment. Compared to risperidone, olanzapine-treated patients had significantly lower hospitalization rates, (21.4% vs. 14.4%, respectively, $p=0.04$) and significantly fewer hospitalization days (14.5 days vs. 9.9 days respectively, $p = 0.035$).

Second-line Antipsychotics Second-generation: Clozapine

Open Trials

Clozapine versus Olanzapine. Meltzer et al. (42) conducted a randomized, open-label two-year study compared the risk for suicidal behavior in patients treated with clozapine (N=490) against olanzapine (N=490) in patients with schizophrenia or schizoaffective disorder with high risk of suicide, 26.8% of whom were refractory to previous treatment. Suicidal behavior occurred to a significantly lower extent in patients treated with clozapine compared to olanzapine (hazard ratio, 0.76; 95% confidence interval, 0.58–0.97, $p = .03$).

DISCUSSION

Notable limitations of the head-to-head trial comparisons between first-line atypical antipsychotics included in this review are the different numbers of subjects, variable outcome measures and imbalance of dose comparisons. Another source of methodological limitations derives from different assessment scales used in those studies, each of which measures slightly different variables in different ways. Thus, assessment data of patients taking medications may vary depending upon which scale was used, and the assessment scores derived from each scale are not fully interchangeable, though they may be roughly but not directly comparable. Needless to say that number of randomized controlled trial data on possible efficacy

differences within this group of modern antipsychotics is substantially limited.

The clinical efficacy differences have been most extensively studied between olanzapine and risperidone. Seven double-blind and seven open-label studies indicated comparable clinical efficacy in primary outcome measures in both medications, although minor differences were found in secondary outcome measures. Risperidone was also compared with aripiprazole, amisulpride and ziprasidone in double-blind randomized trials. Olanzapine was compared to ziprasidone and amisulpride. These studies do not indicate important advantages of the above-mentioned SGAs over risperidone or olanzapine. Moreover, direct head-to-head comparisons of the other first-line SGAs except for olanzapine and risperidone have not been assessed either in double-blind or open trials. However, Lieberman's double-blind study (39) that compared olanzapine, quetiapine, risperidone, ziprasidone and perhenazine brings an important point of view in this field and to some extent fills in the gap.

Clozapine has shown substantial superiority to several first-generation antipsychotics in a number of head-to-head comparisons (43). Six double-blind studies included in this review compared clozapine (total N=269) with risperidone (total N=269). Two short-term trials showed similar clinical efficiency although clozapine was superior to risperidone for BPRS positive symptom score in one study. Of four intermediate length trials, one large double blind study confirmed quite robust superiority in efficacy of clozapine over risperidone. Another smaller study found at least minor efficacy advantage over risperidone in PANSS subscale. Regarding the differences between clozapine and olanzapine, there were no significant differences in clinical outcome measures in two intermediate length double-blind randomized trials. Two-year open-label study that compared the risk for suicidal behavior in patients treated with clozapine and olanzapine proved clozapine superiority over olanzapine in high-suicide risk patients (42). Since even more apparent differences in clinical efficacy between clozapine and first-generation antipsychotics were observed with prolonged treatment (43), long-term trials are urgently needed to assess the advantages and disadvantages of clozapine in comparison to each SGA.

Our knowledge about differences between novel atypical drugs is insufficient. More evidence-based information to make everyday clinical decision is necessary. Filling this gap could be one important step in individualized treatment approaches based on conceivable specific clinical advantages of those drugs and specific side effect profile. Possible new studies should focus on efficacy, long-term effects, including cost-effectiveness, quality of life, social functioning and service utilization.

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