Comparison of Risperidone and Olanzapine in the Control of Negative Symptoms of Chronic Schizophrenia and Related Psychotic Disorders in Patients Aged 50 to 65 Years

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Background: This analysis compares the efficacy of risperidone and olanzapine in controlling negative and positive symptoms of chronic psychosis in older patients.

Method: Post hoc assessments were made in a subset of risperidone-treated (N = 19) and olanzapine-treated (N = 20) older patients (aged 50 to 65 years) from a large international, multicenter, parallel, double-blind, 28-week study of patients aged 18 to 65 years (N = 339) randomly assigned to receive risperidone (4–12 mg/day) or olanzapine (10–20 mg/day). Assessments were made using repeated-measures analysis.

Results: At both 8 weeks and 28 weeks, the magnitude of changes in Positive and Negative Syndrome Scale (PANSS) positive symptom subscale scores did not differ between treatment groups (8 weeks: risperidone, –6.5; olanzapine, –6.8, p = .866; 28 weeks: risperidone, –6.5; olanzapine, –7.0; p = .804). However, by the 8-week timepoint, olanzapine had reduced PANSS negative subscale scores significantly more than risperidone (–8.8 vs. –4.9, p = .032). By the 28-week endpoint, olanzapine had continued to maintain significantly greater reduction in baseline-to-endpoint PANSS negative scores (–8.1 vs. –3.5, p = .032) and led to significantly greater reduction in scores on the Scale for the Assessment of Negative Symptoms (SANS) dimensions of affective flattening (–5.2 vs. –0.6, p = .033) and alogia (–3.8 vs. –0.3, p = .007). Patients in the olanzapine treatment group also demonstrated numerically greater reduction of both SANS summary (–3.7 vs. –1.0, p = .078) and SANS composite scores (–14.1 vs. –4.1, p = .075).

Conclusion: These data demonstrate that, in older patients with schizophrenia and related psychotic disorders, risperidone and olanzapine have approximately equal efficacy in controlling positive symptoms. However, olanzapine appears to be more efficacious in maintaining control over negative symptoms.

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In older patients with schizophrenia, severity of negative but not positive symptoms is correlated with greater impairment of adaptive skills and cognition.[1,2] While positive symptoms tend to lessen in severity with age, negative symptoms are persistent.[3] Conventional antipsychotics have shown efficacy in controlling the positive symptoms of psychosis but are considered to have limited ability to control negative symptoms.[4–7] Moreover, their use is associated with a number of side effects to which older patients are particularly susceptible, most notably extrapyramidal symptoms (EPS) such as parkinsonism and tardive dyskinesia.[8–11] This, in turn, may exacerbate negative symptoms further, or indirectly appear to, through an induction or worsening of hypertonia or bradykinesia.[4,12] In contrast, the newer atypical antipsychotics have been shown to have greater efficacy than the conventional antipsychotics in treating the negative symptoms of psychosis and are characterized by their lower propensity to induce extrapyramidal symptoms.[7,13]

Two atypical antipsychotics, risperidone and olanzapine, are the most commonly prescribed atypical antipsychotics currently in use for the treatment of psychosis. However, few studies have actually compared the efficacy of these 2 atypical antipsychotics in older adults with schizophrenia or related psychotic disorders. It was therefore of interest to compare risperidone and olanzapine in their abilities to control the negative symptoms of psychosis in older patients with schizophrenia and related psy-

chotic disorders. We report here the results of a subgroup analysis of data from a large international, double-blind study[14] that compared the efficacy and safety of risperidone versus olanzapine in patients with psychosis. The design of the parent study included an age "cap" of 65 years. The current analysis focuses on the older patients in this study, identified as those aged 50 years or older.

METHOD

Patient Population

This report presents the results of a post hoc subgroup analysis of data from a 28-week international, multicenter, parallel, double-blind study of the efficacy and safety of risperidone and olanzapine.[14] The overall population (N = 339) included patients, aged 18 to 65 years, with schizophrenia, schizophreniform disorder, or schizoaffective disorder, based on DSM-IV criteria as assessed by the clinical investigator. Patients must have had an initial score of at least 42 on the Brief Psychiatric Rating Scale (BPRS),[15] extracted from the Positive and Negative Syndrome Scale (PANSS),[16] at both enrollment and randomization (visits 1 and 2, respectively). This analysis focuses on changes in positive and negative symptoms in the oldest patients in the overall study, those aged 50 to 65 years (N = 39).

Study Design

Prior to participation, each patient signed an informed consent document approved by the study site's institutional review board. Patients were randomly assigned in a 1:1 ratio to one of 2 treatment groups, risperidone (4–12 mg/day) or olanzapine (10–20 mg/day). Exclusion criteria included treatment with an injectable depot antipsychotic within 2 weeks prior to randomization or within less than 1 dosing interval between injections prior to randomization, as well as treatment with an oral antipsychotic less than 48 hours prior to randomization. Study period I consisted of a 2- to 9-day washout period, starting at study entry (visit 1) and continuing to randomization (visit 2), during which all oral antipsychotic medications were discontinued. The double-blind therapy period (study period II) began with randomization at visit 2 and continued through visit 15. During the 28-week double-blind treatment period, patients were assessed weekly for the first 8 weeks and every 4 weeks thereafter. Risperidone was titrated from 1 mg b.i.d. on day 1 to 2 mg b.i.d. on day 2 and 3 mg b.i.d. on day 3, up to visit 3. Treatment with olanzapine began at an assigned initial dose of 15 mg/day at visit 2. Daily doses of study drugs could then be adjusted upward or downward by 1 dosing increment (risperidone, 1 mg/day; olanzapine, 5 mg/day) within the final allowed dose ranges at the discretion of the clinical investigator. Concomitant medications with primarily central nervous system activity were disallowed. However, subjects undergoing chronic treatment with benzodiazepines were permitted to remain on the fixed dose they were receiving at enrollment, but were allowed to increase their dose only if they manifested some new symptom or a worsening of a previously existing symptom. Anticholinergic medication (benztropine mesylate or biperiden) could be given up to 6 mg/day if EPS occurred, but use of anticholinergics as prophylaxis was prohibited.

Assessments

Efficacy measures used in this analysis included the PANSS total score and positive, negative, and general psychopathology subscale scores; the Scale for the Assessment of Negative Symptoms (SANS)[17] composite and summary subscale scores; and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[18] The PANSS consists of 30 items scored on a scale of 1 = absent to 7 = extreme. The SANS measures 5 dimensions of negative symptomatology, each covered by several independent items, scored using a range of 0 = none to 5 = severe, and 1 global or summary item. Each global or summary item score focuses on overall severity of the symptoms for that dimension. The SANS summary score is the sum of all 5 global items of the SANS. The SANS composite score is the sum of the 19 independent items of the SANS scale and ranges from 0 to 95. The CGI-S is used to rate severity of mental illness on a scale of 1 = normal to 7 = extremely ill.

EPS were assessed with the Simpson-Angus Scale,[19] Barnes Akathisia Scale,[20] and Abnormal Involuntary Movement Scale[18] (AIMS). Medical history, psychiatric assessment, physical examination, and electrocardiography (ECG) were obtained at screening, and the physical examination and ECG were repeated at endpoint or on discontinuation. Other safety assessments included vital signs (blood pressure, pulse, weight, temperature) and clinical laboratory tests (chemistry, electrolytes, hematology). Efficacy and safety were assessed at each visit and on discontinuation.

Statistical Methods

Primary analyses were performed on an intent-to-treat basis, as defined by Gillings and Koch.[21] All hypotheses were tested using a 2-sided α level of .05. Patients with a baseline and at least 1 postbaseline measurement were included in the analyses of change scores. All total scores from rating scales were derived from the individual items. If any of the individual items were missing, then the total score was omitted. Continuous variables, including measures of efficacy and EPS, were analyzed by a maximum-likelihood repeated-measures analysis using PROC MIXED in SAS,[22] with fixed covariate of baseline value and class effects of visit week, therapy, and the interaction between visit week and therapy. Extra covariance between records from the same subject was modeled with a

random effect of patient with an unstructured covariance matrix. This method accounts for differences between visits due to selective dropout and provides less biased estimates of difference in treatment response than those obtained from last-observation-carried-forward or observed-case models. Treatment differences were tested for the week 8 and week 28 contrasts using the Satterthwaite approximation. The Fisher exact test was used for categorical analyses (patient disposition, anticholinergic use, laboratory values, vital signs, ECG parameters, and treatment-emergent adverse events). Response rates were analyzed using the Pearson chi-square test and the Cochran-Mantel-Haenszel statistic, stratified by geographic region.

RESULTS

In the overall investigation,[14] 339 patients aged 18 to 65 years had been studied at 35 sites in 7 European countries, South Africa, and the United States between April 1995 and January 1997. From this patient sample, a subgroup of 39 patients aged 50 years and older (actual range, 50 to 64 years) was identified and examined in depth for the current analysis. Of these, 19 had been randomly assigned to treatment with risperidone and 20 to treatment with olanzapine. The majority of patients in this analysis (71.8%) were outpatients. The patient subgroup sample was mostly white (92.3%), but was approximately evenly divided between men (56.4%) and women (43.6%), although there was a slightly, but not significantly, higher proportion of women in the risperidone group relative to the olanzapine group (Table 1). Thirty-two patients (82.1%) were diagnosed with schizophrenia; the remaining 7 were diagnosed with schizoaffective disorder. Most patients presented at baseline with paranoid symptoms (59.0%), and the majority had prominent negative symptoms (64.1%), as assessed by the investigators using DSM-IV criteria. Baseline measures indicated moderate severity of overall psychopathology and of both positive and negative symptoms. No significant differences were found between treatment groups in any demographic characteristic or baseline illness rating. Only numerical, nonsignificant differences were seen between completion rates for the 2 treatment groups for the entire 28-week treatment (risperidone, 47.4%; olanzapine, 60.0%; p = .527), as well as in rates of discontinuation due to either adverse events (risperidone, 21.1%; olanzapine, 10.0%; p = .408) or lack of efficacy (risperidone, 10.5%; olanzapine, 10.0%; p > .99).

The mean modal dose of risperidone throughout the entire study was 7.8 ± 2.8 mg/day (N = 19) and the mean dose at endpoint (week 28) was 8.9 ± 2.3 mg/day, while the mean modal dose for olanzapine was 18.0 ± 3.0 mg/day (N = 20) and the mean dose at endpoint was 18.8 ± 3.1 mg/day. Mean doses of risperidone and olanzapine at the 8-week interim timepoint (8.8 ± 1.7 mg/day and 18.7 ± 3.0 mg/day, respectively) were essentially the same as at endpoint. Use of anticholinergic agents was approximately equal in the 2 treatment groups, both in the mean daily doses required (benztropine equivalents: risperidone, 1.64 ± 1.44 mg; olanzapine, 1.38 ± 0.84 mg; F = 0.10, df = 13, p = .755) and in the percentages of patients requiring their use (risperidone, 7/19 [36.8%]; olanzapine, 9/20 [45.0%]; p = .748).

Table 1. Patient Characteristics[a]

Characteristic	Risperidone (N = 19)	Olanzapine (N = 20)	p Value
Age, mean (SD), y	57.2 (4.5)	56.9 (4.1)	.750
Sex			.111
Male	8 (42.1)	14 (70.0)	
Female	11 (57.9)	6 (30.0)	
Racial origin			.356
African	0 (0.0)	2 (10.0)	
White	19 (100.0)	17 (85.0)	
Other	0 (0.0)	1 (5.0)	
Paranoid subtype	10 (52.6)	13 (65.0)	.523
Prominent negative symptoms[b]	11 (78.6)	14 (82.4)	> .99
Length of current episode,[b] mean (SD), d	119.9 (155.5)	60.7 (46.9)	.352
No. of previous episodes, mean (SD)	10.7 (6.5)	9.0 (5.9)	.393
Age at onset, mean (SD), y	28.2 (10.7)	30.8 (11.4)	.484

[a]Values shown as N (%) unless otherwise noted.
[b]Assessments were not available for all patients.

By the 8-week timepoint, both atypical antipsychotic treatments had considerably improved patients' levels of psychopathology (Table 2). On the PANSS total, risperidone treatment led to a 21.0-point decrease (SD = 4.1) from baseline in the risperidone group compared with a 27.2-point decrease (SD = 3.9) for olanzapine, a difference that did not reach statistical significance (F = 1.19, df = 16.7, p = .290). Improvements in PANSS positive and general psychopathology subscale scores were also similar in the 2 treatment groups, as were changes in CGI-S scores. In contrast, PANSS negative subscale scores were decreased significantly more during olanzapine treatment than during risperidone treatment (mean ± SD change: olanzapine, –8.8 ± 1.2; risperidone, –4.9 ± 1.3; F = 5.09, df = 28, p = .032). Virtually every subscale and dimension score on the SANS showed numerically greater improvement in the olanzapine group, but none of the differences in SANS scores were statistically significant at 8 weeks.

At 28 weeks, the magnitude of improvement in both treatment groups was roughly the same as at 8 weeks on nearly all measures of psychopathology (Table 3). Baseline-to-endpoint reductions were again not significantly different between treatment groups in PANSS total scores or in positive symptom or general psychopathology subscores. Mean changes in CGI-S scores were also not statistically different between treatment groups. How-

Table 2. Summary of Efficacy Results at 8 Weeks[a]

	Risperidone		Olanzapine		
Measure	Baseline	Change	Baseline	Change	p Value[b]
PANSS					
Total	96.1 (12.7)	–21.0 (4.1)	95.1 (15.5)	–27.2 (3.9)	.290
Positive	22.4 (4.9)	–6.5 (1.2)	22.3 (4.9)	–6.8 (1.2)	.866
Negative	27.7 (4.5)	–4.9 (1.3)	26.4 (6.6)	–8.8 (1.2)	.032
General psychopathology	46.0 (8.7)	–10.0 (2.4)	46.4 (7.2)	–10.8 (2.2)	.825
SANS					
Summary	13.8 (3.9)	–2.1 (0.9)	12.8 (4.3)	–3.6 (0.9)	.283
Composite	46.9 (15.1)	–6.5 (4.5)	46.9 (16.3)	–13.0 (3.2)	.160
Affective flattening	14.1 (5.4)	–2.3 (1.2)	14.3 (5.7)	–4.5 (1.2)	.193
Alogia	8.4 (4.6)	–1.4 (0.8)	7.9 (3.8)	–3.2 (0.8)	.133
Avolition/apathy	7.6 (2.7)	–1.0 (0.6)	7.9 (3.6)	–1.9 (0.6)	.291
Anhedonia/asociality	11.9 (4.2)	–0.5 (0.8)	12.8 (4.6)	–2.2 (0.7)	.126
Attention	4.9 (2.2)	–1.1 (0.4)	4.1 (2.2)	–1.2 (0.4)	.823
CGI-S	4.8 (0.8)	–0.7 (0.2)	4.6 (0.7)	–0.8 (0.2)	.760

[a]Mean (SD) change from baseline to 8-week timepoint, derived from mixed-model repeated-measures analysis.
[b]Treatment difference, risperidone vs. olanzapine.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

Table 3. Summary of Efficacy Results at 28 Weeks[a]

	Risperidone		Olanzapine		
Measure	Baseline	Change	Baseline	Change	p Value[b]
PANSS					
Total	96.1 (12.7)	–17.2 (4.9)	95.1 (15.5)	–25.0 (4.5)	.260
Positive	22.4 (4.9)	–6.5 (1.5)	22.3 (4.9)	–7.0 (1.4)	.804
Negative	27.7 (4.5)	–3.5 (1.5)	26.4 (6.6)	–8.1 (1.3)	.032
General psychopathology	46.0 (8.7)	–9.6 (3.1)	46.4 (7.2)	–8.7 (2.9)	.837
SANS					
Summary	13.8 (3.9)	–1.0 (1.1)	12.8 (4.3)	–3.7 (1.0)	.078
Composite	46.9 (15.1)	–4.1 (4.0)	46.9 (16.3)	–14.1 (3.5)	.075
Affective flattening	14.1 (5.4)	–0.6 (1.6)	14.3 (5.7)	–5.2 (1.3)	.033
Alogia	8.4 (4.6)	–0.3 (0.9)	7.9 (3.8)	–3.8 (0.8)	.007
Avolition/apathy	7.6 (2.7)	–1.4 (0.8)	7.9 (3.6)	–2.3 (0.7)	.382
Anhedonia/asociality	11.9 (4.2)	–0.8 (1.0)	12.8 (4.6)	–2.7 (0.8)	.146
Attention	4.9 (2.2)	–1.0 (0.7)	4.1 (2.2)	–1.4 (0.5)	.618
CGI-S	4.8 (0.8)	–0.8 (0.3)	4.6 (0.7)	–0.7 (0.2)	.843

[a]Mean (SD) change from baseline to 28-week endpoint, derived from mixed-model repeated-measures analysis.
[b]Treatment difference, risperidone vs. olanzapine.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

ever, the reduction in the PANSS negative subscore was again significantly greater in the olanzapine group than in the risperidone group (olanzapine, –8.1 ± 1.3; risperidone, –3.5 ± 1.5; F = 2.63, df = 16, p = .032). On the SANS, the magnitudes of the decreases of the summary and composite scores in the olanzapine group were more than 3 times those of the corresponding scores in the risperidone group. However, these differences only approached, but did not achieve, statistical significance. Nevertheless, differences in the SANS dimension scores for affective flattening (olanzapine, –5.2 ± 1.3; risperidone, –0.6 ± 1.6; F = 5.10, df = 23.8, p = .033) and alogia (olanzapine, –3.8 ± 0.8; risperidone, –0.3 ± 0.9; F = 8.56, df = 26.1, p = .007) were significant. Response rates taken as a ≥ 30% improvement in PANSS total scores at endpoint were not different between treatment groups (risperidone, 2/19 [10.5%]; olanzapine, 7/20 [35.0%]; p = .127), but were significantly higher in the olanzapine group if assessed as a ≥ 30% improvement at any time during the study (olanzapine, 13/20 [65.0%]; risperidone, 5/19 [26.3%]; p = .025).

Rates of adverse event reporting in the 2 groups were, for the most part, not significantly different, with the exception of weight gain, which, as a spontaneously reported adverse event, occurred significantly more often in the olanzapine group (risperidone: 0%; olanzapine: 25%; p = .047). However, for treatment-group differences in overall mean changes in weight, statistical significance could not be established (risperidone: +0.6 kg [1.3 lb], SD = 4.6 [10.2], N = 19; olanzapine: +4.7 kg [10.4 lb], SD = 5.8 [12.9], N = 20; F = 4.09, df = 1, p = .052). Adverse events with an incidence greater than 20% in either group included somnolence (risperidone: 32%; olanzapine: 25%; p = .731), agitation (risperidone: 21%; olanza-

pine: 10%; p = .407), and anxiety (risperidone: 5%; olanzapine: 30%; p = .091). Measures of extrapyramidal symptoms were comparable between the 2 treatment groups both at 8 weeks and at endpoint. Little change from baseline to the 28-week endpoint was seen in either AIMS scores (risperidone: –0.7, SD = 0.6, N = 9; olanzapine: 0.0, SD = 0.6, N = 12; F = 1.80, df = 29, p = .403) or Barnes Akathisia Scale scores (risperidone: –0.1, SD = 0.2, N = 9; olanzapine: 0.1, SD = 0.2, N = 12; F = 1.05, df = 34.5, p = .449), whereas Simpson-Angus scores were slightly decreased in both groups (risperidone: –0.4, SD = 1.0, N = 9; olanzapine: –1.3, SD = 0.9, N = 12; F = 1.23, df = 45.2, p = .545). Both vital signs and laboratory measures likewise were unremarkable and not significantly different between treatment groups.

DISCUSSION

To our knowledge, this analysis is the first to make a direct head-to-head comparison of the 2 leading atypical antipsychotics, risperidone and olanzapine, in a randomized clinical trial involving older patients with schizophrenia. The findings indicate that both agents significantly improved general psychopathology and the positive symptoms of psychosis in patients aged 50 to 65 years. This is in agreement with the majority of studies involving administration of these 2 atypical agents to younger adults with schizophrenia.[14,23,24] However, as revealed by PANSS negative-symptom cluster scores, olanzapine reduced the negative symptoms of psychosis to a significantly greater degree than did risperidone, both at the 8-week timepoint and at the 28-week endpoint. SANS negative scores were also decreased more by olanzapine, although this treatment difference merely approached, but did not achieve, statistical significance, presumably due to insufficient powering from the small sample sizes. A previously conducted path analysis determined that the improvement in negative symptoms by olanzapine is due to a direct effect and is not merely secondary to a reduction in the severity of positive symptoms or side effects.[25] These findings are similar to those in the overall parent study of patients aged 18 to 65 years,[14] of whom the patients in this secondary analysis are a subset. In the parent study, in which the overall patient sample had similar baseline PANSS positive and negative scores to those in this analysis, olanzapine improved SANS summary and PANSS depression scores significantly more than did risperidone, although the greater decrease of PANSS negative scores seen in the olanzapine group did not achieve statistical significance. However, among patients in the overall sample who successfully completed the trial, significantly greater improvement in PANSS positive scores was seen with olanzapine treatment, while improvement in PANSS negative scores was not different between treatment groups.[26]

The current findings are also somewhat consistent with those of the Canadian Collaborative Group for Research on Cognition in Schizophrenia.[24] The group's analysis compared risperidone, olanzapine, and haloperidol in patients aged 18 to 65 years in a 54-week, double-blind study. The results demonstrated significant improvement in PANSS negative scores by treatment with olanzapine (p = .04) but not with risperidone (p = .62) or haloperidol (p = .16). However, between-group pairwise comparisons showed that the treatment-group differences did not reach statistical significance. This latter finding contrasts with the significant treatment-group differences obtained in the current study. One possible explanation for this difference in findings is the degree of impairment among the patients studied. In the Collaborative Group's study,[24] patients were within the first 5 years of their illness, whereas those in the current analysis were several decades into their illness. Older patients tend to have more persistent negative symptoms compared with patients who are in the early stages of the illness, and the severity of negative symptoms is known to increase over time.[27] Thus, the patients in the current analysis may have had a profile of negative symptoms that were more severe and more refractory to treatment. This in fact is reflected in the treatment groups' baseline mean PANSS negative scores of 26.4 (olanzapine) and 27.7 (risperidone) in the current analysis, compared with scores of 16.8 (risperidone), 18.7 (olanzapine), and 22.4 (haloperidol) in the Collaborative Group's study.

Despite the agreement between the current results and those of the parent analysis and the Canadian Collaborative Group's study, previous comparisons of risperidone and olanzapine have led to somewhat mixed results. An investigation comparing risperidone, olanzapine, and clozapine[28] in younger adult patients with schizophrenia found olanzapine to bring about nearly twice as great an improvement as risperidone in the PANSS total and negative cluster, while only a numeric advantage was seen for olanzapine in the positive cluster. By contrast, separate investigations have indicated that risperidone and clozapine may be equally effective in reducing negative symptoms.[29] One unrandomized, hospital-based study of aggressive and psychotic symptoms in a limited number of male geriatric patients showed no significant difference between risperidone and olanzapine in their ability to improve negative symptoms, and only a slight numeric advantage was seen for olanzapine in the PANSS total and positive cluster.[30] Similarly, in a large-scale, 8-week, randomized, double-blind study in younger adults, endpoint change scores associated with the 2 antipsychotics were virtually identical between treatments, with PANSS positive score decreases of 4.8 points for risperidone and 4.3 for olanzapine (p = .48) and a PANSS negative score decrease of 2.9 points for both (p = .72).[31]

Some limitations of the current analysis bear mentioning. The first, and perhaps most obvious, is that the

sample sizes in this analysis were limited, which led to the uncovering of statistical "trends" that did not quite reach significance. Due to its post hoc subsampling of a parent study, this analysis was not sufficiently powered to permit extensive statistical testing. It might have been instructive to have had a large enough sample to permit the conduction of subgroup analyses, allowing us to examine, for example, whether sex differences could be seen in the responsiveness to treatment of patients' positive symptoms, as has been reported previously in studies involving middle-aged and elderly patients.[32] This point notwithstanding, the results were sufficiently robust to reveal significant treatment differences. A second limitation is that this study focused on patients that might be considered "young old" adults rather than "elderly." Their physiologic and psychiatric state might therefore represent more of a transition stage toward the condition of geriatric schizophrenia, and these results might not be readily extrapolated for the care of the elderly patient. To its credit, however, the study on which this analysis was based was a truly randomized and blinded trial, which should serve to reduce the potential influence of any sampling biases. Moreover, the current study was carried out over an extended period of 28 weeks. Many studies have been hampered by the short duration of their observation periods, leaving open to question whether some of the changes that are seen are due to random fluctuations in patients' clinical conditions or whether the improvements that are seen can indeed be sustained.

Another possible criticism of this study is that the doses used were somewhat higher than those used to treat elderly patients in usual clinical practice. The mean dose for risperidone in this subgroup was 7.8 mg/day and that for olanzapine was 18.0 mg/day. These doses, which were well within the treatment guidelines established by the pharmaceutical manufacturers at the time this study was initiated (ca. 1995), are nevertheless substantially higher than the mean doses of 5.4 mg/day and 13.0 mg/day, respectively, that are used in current practice,[33] and this could have affected the outcome of this study. This may have been particularly the case for risperidone, as doses much above the recommended 4 mg/day[34] are likely to produce unnecessarily high D_2 receptor occupancy, leading to an increased risk of extrapyramidal effects[35] and poorer overall outcomes.[36] Bradykinesia and rigidity could, in turn, lead to a misdiagnosis of increased psychomotor retardation or apathy, or the induction of EPS may itself lead to the development of negative symptoms,[4,7] resulting in an underestimation of the efficacy of the administered antipsychotic for those negative symptoms. Alternatively, the clinician may recognize adverse reactions for what they are and be prompted to adjust the dose of antipsychotic downward, potentially leading to a decrease in efficacy. Arguing against this as a possible confounding variable in the current analysis, however, is the observation that use of anticholinergic agents was not significantly different between treatment groups, nor was there a difference in the incidence of treatment-emergent EPS between treatment groups, indicating that, if EPS were a factor, they most likely affected both groups equally. These findings contrast with those in the parent analysis, in which anticholinergic use was considerably lower, on the order of 20% to 50% of that in this older subsample. This observation may therefore be an indication of the greater susceptibility of these older patients to the potential extrapyramidal effects of antipsychotic agents.

In summary, the results of this post hoc analysis show that, in a subsample of older patients with chronic psychosis, risperidone and olanzapine have approximately equal efficacy in controlling positive symptoms. However, olanzapine appears to be better able to improve and maintain control over the negative symptoms of psychosis. Given the persistent nature of negative symptoms in the older patient, this finding suggests that olanzapine may confer considerable advantage in treating the older patient with chronic schizophrenia.

Drug names: benztropine (Cogentin and others), biperiden (Akineton), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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