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Long-Acting Risperidone in Young Adults with Early Schizophrenia or Schizoaffective Illness

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Background. *Treatment with long-acting injectable risperidone was evaluated in young adults likely to be in the early stages of schizophrenia or schizoaffective disorder.*
Method. *An open-label 50-week trial included young adults (men aged 18–25 years and women aged 18–30 years).*
Results. *Sixty-six young adults received at least 1 injection of long-acting risperidone (25 or 50 mg) every two weeks; 64% of the patients completed the 50-week trial. A mode dose of 25 mg/14 days was received by 23 patients and 50 mg/14 days by 43 patients. Mean PANSS scores improved significantly from baseline at each time point, with 64% of the patients showing clinical improvement (≥20% reduction in PANSS total scores) at endpoint. Patient-rated quality of life (SF-36 scores) improved and patients' attitudes toward the medication were positive (DAI scores). Severity of movement disorders (ESRS) and injection-site pain ratings were low throughout the trial. Results were similar in the population of other (older) patients.*
Conclusions. *Long-acting risperidone was associated with clinical benefits in stable young adults with early schizophrenia or schizoaffective illness.*

Keywords Long-acting risperidone, Schizophrenia, Schizoaffective disorder, Young adult patients

INTRODUCTION

Early intervention with antipsychotic medications can improve long-term outcome in patients with schizophrenia experiencing their first psychotic episode (1). Most first-episode patients are likely to be young adults since the peak age at onset of schizophrenia is in the early 20s for men and early 30s for women (2) and modal ages range from 18 to 25 years for men and 25 years to the mid-30s for women (3). High rates of treatment response and symptom remission have been reported in first-episode patients (4). However, among first-episode patients who initially responded to treatment, relapse rates of >80% during a 5-year follow up have been reported (5). The risk for a first or second relapse in these patients was almost 5 times greater when not taking than when taking medication (5). Relapse rates are also dependent on the type of medication. In a recent long-term study of patients with a first episode of psychotic illness (median duration of treatment was 206 days), Schooler et al (6) reported that, among patients who had met a predefined clinical improvement criterion, the relapse rate was significantly lower in patients receiving risperidone than haloperidol (42% versus 55% relapsed, $P < 0.01$).

Acceptance of treatment and medication adherence are key issues in the successful management of patients with early illness. The patients' sense of quality of life and their attitudes toward the medications they are receiving are also important correlates of treatment adherence (7,8). A long-acting atypical antipsychotic may benefit these patients by offering continuous

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delivery for a guaranteed duration of time of a well-tolerated treatment, potentially improving adherence. The efficacy, safety, and tolerability of long-acting injectable risperidone (Risperdal® Consta®) have been demonstrated in recent trials (9–13). The objective of the present report was to assess the effects of long-acting risperidone in young adults—men aged ≤25 years and women aged ≤30 years—with early schizophrenia or schizoaffective illness who had been maintained on oral and depot antipsychotics before participating in a large 50-week open-label study (10,11).

METHODS

A 12-month, open-label international trial has been conducted to evaluate the long-term effects of long-acting risperidone given every 2 weeks in patients aged 18–84 years (10,11). The trial was conducted in accordance with current ICH-Good Clinical Practice guidelines and the Declaration of Helsinki and its subsequent revisions. The subjects of the present analysis are the young adults with schizophrenia or schizoaffective disorder who received 25 mg or 50 mg of long-acting risperidone every 2 weeks. The characteristics of the 351 other adults (men aged >25 years and women >30 years) who received 25 or 50 mg of long-acting risperidone in the 50-week trial are also reported, together with efficacy and safety data for this population.

Patients

Patients selected for the analysis were clinically stable outpatients or hospital inpatients, men aged 18–25 years and women aged 18–30 years, with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Each patient had received a stable dose of an antipsychotic for at least 4 weeks preceding the initial screening and was judged by the investigator to be symptomatically stable. Inclusion criteria included a baseline Positive and Negative Syndrome Scale (PANSS) (14) total score of 60–120 and good general health with standard laboratory test results within acceptable reference ranges. Patients were excluded from the analysis if they had a diagnosis of substance dependence, a history of tardive dyskinesia or neuroleptic malignant syndrome, a clinically significant ECG abnormality, or if they were pregnant, likely to become pregnant, or nursing. Written informed consent consistent with local regulations was obtained from each patient or guardian or legal representative.

Dosing

Patients who had received oral or depot antipsychotics other than risperidone completed a 2-week run-in period of flexible doses of oral risperidone (1–6 mg). All patients were then switched to long-acting risperidone but continued to receive oral risperidone for 2–3 weeks after the first injection to maintain blood drug concentrations during the transition. Each patient was assigned to a dose of long-acting risperidone based on his/her prior oral risperidone dose and clinician judgment. Clinicians could adjust the dose as deemed necessary. In the original studies (9,10), patients received 25, 50, or 75 mg of long-acting risperidone. The 75-mg dose, however, showed no greater benefit over the lower doses and the 75-mg formulation is now not commercially available. Thus the focus of the present analysis is on patients with a modal dose of 25 or 50 mg of long-acting risperidone.

Efficacy Assessments

Psychotic symptoms were assessed with the PANSS (14) every 3 months. PANSS total scores and scores on each PANSS factor (15) (positive symptoms, negative symptoms, disorganized thoughts, anxiety/depression, and uncontrolled hostility/excitement) were recorded. Overall symptom severity was assessed monthly using the Clinical Global Impressions severity (CGI–S) scale (16). Remission was defined according to the criteria of Andreasen et al (17). The definition requires the simultaneous attainment of a score of 3 (mild), 2 (minimal), or 1 (absent) for at least 6 months for all of the following symptoms (PANSS items): Delusions (P1), Concept disorganization (P2), Hallucinatory behavior (P3), Unusual thought content (G9), Mannerisms and posturing (G5), Blunted affect (N1), Passive/apathetic social withdrawal (N4), and Lack of spontaneity and flow of conversation (N6). This analysis assessed the percentage of nonremitted patients at baseline (by the severity component only) who attained symptom remission (mild to absent on all 8 items) for at least 6 months during treatment with long-acting risperidone.

Assessments of Quality of Life and Drug Attitudes

Patient-rated health status was assessed at baseline and every 3 months and at the last visit using the self-administered 36-Item Short Form Health Survey (SF–36) that measures patient-rated functioning and well-being (18). The SF–36 contains the following eight domains: physical functioning, body pain, role physical, general health, vitality, social functioning, role emotional, and mental health. US national normative values of SF–36 scores for men and women aged 18–24 years are also reported (18).

The patients' attitudes toward the medication were assessed at baseline and every 3 months and at the last visit by means of the 10-item Drug Attitude Inventory (DAI) (19). DAI scores range from –10 to +10 with a negative total score representing a negative subjective response and a positive total score representing a positive subjective response.

Adverse Events and Movement Disorders

Spontaneously reported adverse events were recorded every 2 weeks. Patient- and physician-rated movement disorders were evaluated with the Extrapyramidal Symptom Rating Scale (ESRS) (20) completed monthly for the first 3 months and subsequently every 3 months. The ESRS was used to provide measures of the patients' overall subjective assessment of movement disorders (questionnaire) and the physician rating for parkinsonism, dyskinesia, dystonia, and akathisia. Patients rated injection-related pain using a 100-mm visual analogue scale (from 0 mm=no pain to 100 mm=unbearable pain) at the time of the injection and at each visit.

Data Analysis

Patients who had received at least 1 injection of risperidone and had at least 1 post-baseline PANSS assessment were evaluated for efficacy. Patients who had received at least 1 injection of risperidone were evaluated for safety. PANSS, CGI–S, SF36, DAI, and ESRS data were analyzed using a last-observation-carried-forward (LOCF) analysis. Mean changes on the PANSS, SF36, and ESRS between baseline and each scheduled time point and endpoint were analyzed using a paired *t* test. An analysis of covariance was used to compare mean changes from baseline between the two groups (young adults and all other adults), with group as the main effect and baseline value as a covariate. Clinical improvement was defined as a reduction in total PANSS score of ≥20%.

RESULTS

Baseline characteristics of the young adults and all other adults are listed in Table 1. Few between-group differences were evident; the only significant between-group differences were in age and duration of prior treatment as expected. Baseline PANSS total scores and scores on the 5 PANSS factors (positive symptoms, negative symptoms, disorganized thoughts, anxiety/depression, and uncontrolled hostility/excitement) were similar in the 2 groups.

The 50-week trial was completed by 42 of the 66 young adults (64%), a rate slightly less than that of all other adults (252/351; 72%). The reasons for discontinuation among the young adults and all other adults were similar and included consent withdrawal (11% and 15%, respectively), adverse event (9% and 5%), insufficient response (5% and 3%), noncompliance (3% and 1%), and other reasons (9% and 5%).

Concomitant psychotropic medications initiated during the study period included benzodiazepines received by 23 patients, antidepressants by 16, sedative/hypnotic/anxiolytics by 12, antiparkinsonians by 5, anticonvulsants by 2, mood stabilizers by 1, and antipsychotics by 1.

Table 1 Patient Characteristics

	Young Adults (N=66)	All Other Adults (N=351)
Age, mean ± SD years*	23.3 ± 3.3	47.6 ± 13.5
Men	42 (64%)	220 (63%)
Women	24 (36%)	131 (37%)
Race		
White	58 (88%)	332 (95%)
Other	8 (12%)	19 (5%)
Diagnosis		
Schizophrenia	56 (85%)	292 (83%)
Schizoaffective disorder	10 (15%)	59 (17%)
PANSS total score, mean ± SD	65.3 ± 18.8	64.7 ± 17.6
Previous treatment		
Risperidone	42 (64%)	162 (46%)
Depot conventionals	15 (23%)	100 (28%)
Mixed conventionals	5 (8%)	40 (11%)
Oral conventionals	2 (3%)	32 (9%)
Other/none	2 (3%)	17 (5%)
Prior treatment duration*		
Mean ± SD days	131.0 ± 164.7	502.3 ± 831.6

*P < 0.001 between groups.

Efficacy

PANSS total scores and scores on each of the 5 PANSS factors improved significantly from baseline to endpoint (Figure 1, Table 2). Almost two-thirds (64%) of these clinically stable young adults showed clinical improvement at endpoint, ie, a reduction of ≥20% in PANSS total score. The percentages of patients with CGI-S ratings of "not ill," "very mild," and "mild" increased from 41% at baseline to 65% at endpoint (Figure 2). Among the patients who did not meet criteria for remission at baseline (severity component only), remission for 6 months or longer was achieved by 9/32 (28%) of the young adults and 44/175 (25%) of the other adults.

Patient-Rated Health Status and Drug Attitudes

According to the patients' ratings on the SF–36 scale, improvements were noted in 7 of the 8 mental and physical health-related subscales (Figure 3). No change was seen on the body-pain subscale—scores were at the US normative value both at baseline and endpoint (Figure 3). Clinically significant improvements from baseline (>5 points) were noted on the social-functioning, role-emotional, physical-functioning, and role-physical subscales. As shown in Figure 3, patients' scores on both the mental and physical health-related domains approached mean US normative values at endpoint.

The patients expressed positive attitudes toward the medication. Their mean (±SD) scores on the DAI were 3.7 ± 4.8 at baseline and 3.7 ± 4.9 at endpoint. DAI scores range from –10 to +10 (most positive).

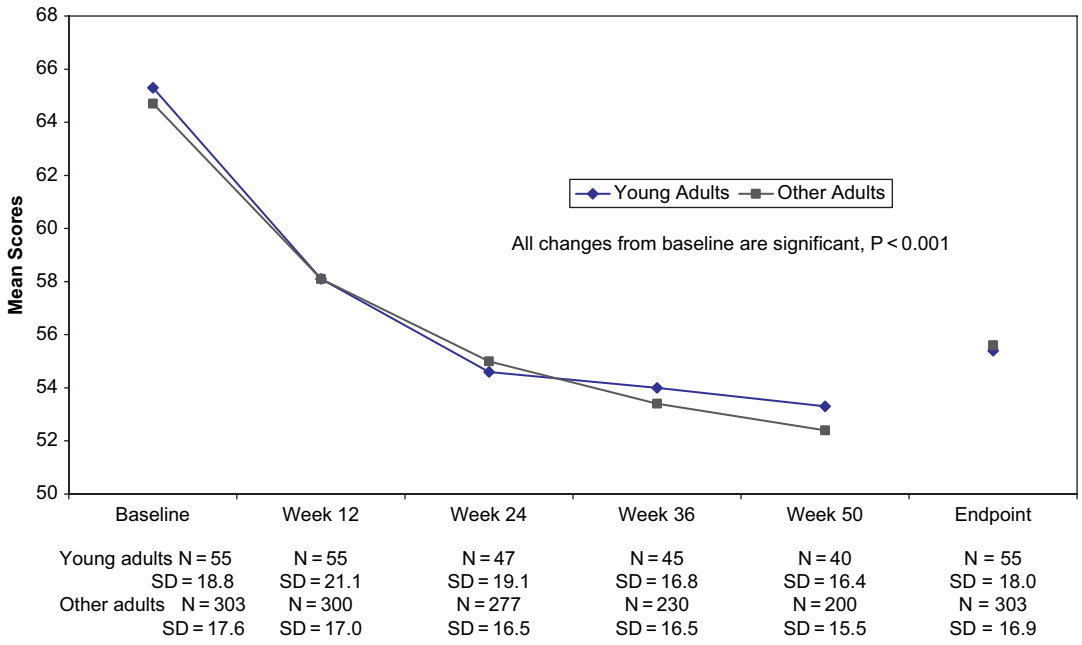

Figure 1 Mean PANSS Total Scores in Young Adults and Other Adults.

Table 2 PANSS Total and Factor Scores at Baseline (Mean ± SD) and Adjusted Changes at Endpoint (mean ± SE) in the Young Adults and in All Other Adults*

	Young Adults(N=55)	All Other Adults(N=351)
PANSS total		
Baseline	65.3 ± 18.8	64.7 ± 17.6
Change at endpoint	–9.7 ± 1.7	–9.1 ± 0.7
Positive symptoms		
Baseline	17.6 ± 7.2	17.0 ± 6.4
Change at endpoint	–2.9 ± 0.6	–2.3 ± 0.3
Negative symptoms		
Baseline	18.3 ± 6.8	18.7 ± 6.8
Change at endpoint	–3.4 ± 0.6	–3.2 ± 0.3
Disorganized thoughts		
Baseline	14.4 ± 5.6	14.7 ± 5.2
Change at endpoint	–1.7 ± 0.5	–1.7 ± 0.2
Anxiety/depression		
Baseline	8.9 ± 3.2	8.4 ± 3.3
Change at endpoint	–1.3 ± 0.4	–1.3 ± 0.2
Uncontrolled hostility/ excitement		
Baseline	6.2 ± 2.6	5.9 ± 2.4
Change at endpoint	–0.4 ± 0.3	–0.6 ± 0.1

*All within-group changes from baseline are significant (P < 0.001) except Uncontrolled hostility/excitement scores in the young adults (P=0.194).

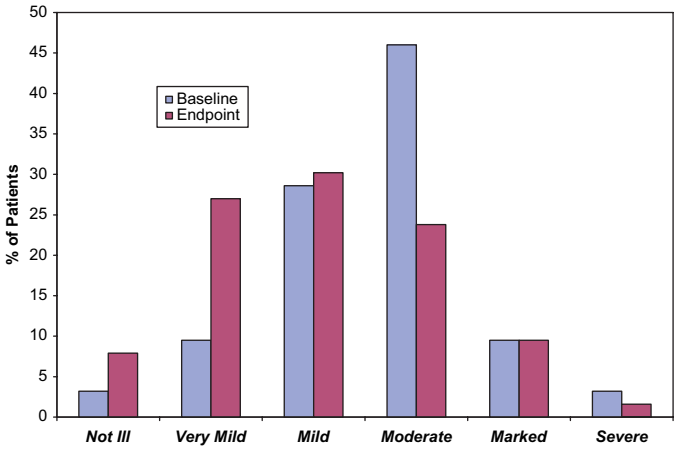

Figure 2 Clinical Global Impressions of Severity at Baseline and Endpoint in the Young Adults.

Adverse Events

The most commonly reported adverse events among the young adults were insomnia (29%), anxiety (21%), headache (21%), hyperkinesia (20%), and rhinitis (18%) (Table 3).

Patient ratings of injection site pain were low throughout the study and declined over time: mean VAS scores (0=no pain to 100=unbearably painful) decreased from 25.0 ± 24.2 at baseline to 14.2 ± 16.8 at endpoint (P < 0.001). The patients' ratings of body pain (as measured by the SF–36) were close to the US normative value at baseline and endpoint (Figure 3). Two patients, each with a history of paranoid schizophrenia, died during the study. Both deaths were considered suicides and related to the patients' underlying psychiatric illness and not to the study medication according to the clinical investigators.

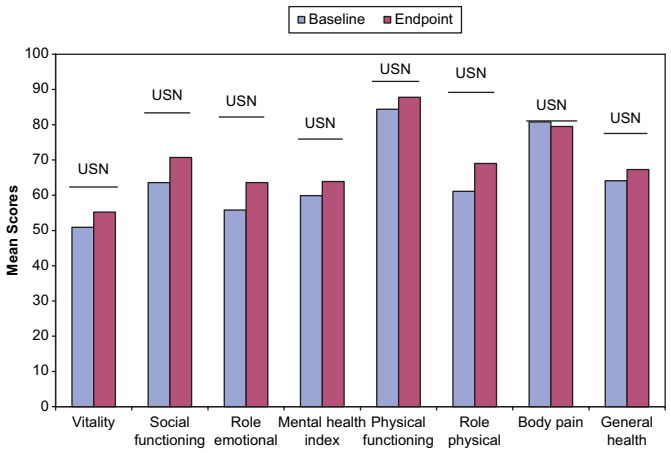

Figure 3 SF–36 Scale Scores at Baseline and Endpoint in the Young Adults USN = mean US national norms (men and women aged 18–24 years).

Table 3 Adverse Events Reported in ≥ 10% of the Young Adults and in All the Other Adults

Adverse Event	Young Adults (N=66)%	All Other Adults (N=351)%
Insomnia	29	19
Anxiety	21	23
Headache	21	11
Hyperkinesia	20	11
Rhinitis	18	11
Depression	17	14
Fatigue	15	7
Psychosis	12	12
Nausea	12	3
Somnolence	12	5
Vomiting	11	3

Movement Disorders

Severity of movement disorders (ESRS scores) was low throughout the study. Scores on the patients' subjective severity ratings (ESRS questionnaire; scores range from 0–36, items 0–11) and the physicians' ratings of parkinsonism (ESRS parkinsonism scale; scores range from 0–48, items 13–30) were significantly improved. Mean (±SD) questionnaire scores were reduced from 3.1 ± 3.2 at baseline to 1.6 ± 2.4 at endpoint ($P < 0.0001$), while parkinsonism scores were reduced from 2.2 ± 2.4 to 1.1 ± 1.8 ($P < 0.0001$). Physician ratings of dyskinesia, akathisia, and dystonia were low throughout the study (mean score <1 for each).

Comparisons between Young Adults and Other Adults

Few substantial differences in efficacy or safety data between the two groups were evident. Mean PANSS total scores were similar at baseline, as were the changes at endpoint (Table 2). At endpoint, improvements of ≥20% in PANSS total scores were seen in 64% of the young adults and 56% of the other adults; improvements of ≥40% in 44% and 37%, respectively; and improvements of ≥60% in 22% and 19%.

Mean SF–36 mental-health domain scores were similar in the 2 groups at baseline. Improvements at endpoint were seen in both groups ($P < 0.05$ vs baseline in the other adults). Mean (±SD) baseline scores on the physical functioning subscale were 84.4 ± 19.7 in the young adults and 74.3 ± 24.9 in the other adults. Mean (±SE) changes at endpoint were 6.4 ± 2.5 in the young adults and –0.35 ± 1.1 in the other adults ($P=0.014$). Mean (±SD) DAI total scores at baseline were 3.7 ± 4.8 in the young adults and 4.8 ± 4.4 in the other adults ($P=0.0174$). Mean (±SE) changes at endpoint were –0.5 ± 0.6 in the young adults and 1.0 ± 0.2 in the other adults ($P=0.017$).

More of the young adults than the other adults tended to report adverse events (Table 3). ESRS scores were similar in the two groups with somewhat lower parkinsonism scores in the young adults (6.2 ± 6.7 versus 8.0 ± 9.2 in other adults). Changes at endpoint were similar in the two groups.

DISCUSSION AND CONCLUSIONS

The efficacy of long-acting risperidone in schizophrenia and schizoaffective disorder has been established in previous studies (9–13). It has also been shown that symptomatically stable schizophrenia patients can be safely switched directly to long-acting risperidone from both oral conventional antipsychotic medications (21) and conventional depot antipsychotics (13). The present results in young adults are compatible with these findings, and with those of studies of risperidone in first-episode psychotic patients (22–26). Long-acting risperidone was generally well tolerated in this study; movement disorder ratings (via ESRS scores) were very low throughout the trial

The mean age of the young adults of this analysis—23 years—indicates that many would have been experiencing their first episode of psychosis when treatment with the previous oral or conventional depot antipsychotics was initiated. Robinson et al (27) have noted that most patients who recover from a first episode of schizophrenia or schizoaffective disorder experience psychotic relapse within 5 years. A number of issues influence the risk of relapse, foremost of which are the duration of untreated psychosis in early illness and poor compliance with medication (28). Early intervention with an effective antipsychotic can improve outcomes in first-episode psychosis, and the use of an atypical antipsychotic can optimize medication compliance and reduce morbidity associated with repeated relapses (4). Attitudes toward the medication were generally positive among the young patients of the present study, increasing the likelihood of their continued acceptance of treatment. Long-acting risperidone could thus be an important tool in the treatment of early schizophrenia and schizoaffective illness. It has been suggested (29,30) that the prevalence of adverse events is higher in first-episode than in chronic schizophrenia patients; a

somewhat higher rate was seen in the young adults than the other adults of the present study (Table 3).

Improvements in these patients' self-rated functioning and well-being suggest that even stable schizophrenia patients can experience further benefits in health-related quality of life. Underlying causes of impaired quality of life in schizophrenia patients include higher levels of negative symptoms, depression/anxiety, extrapyramidal symptoms associated with antipsychotic use, and negative attitudes and feelings toward medication (31–35). The reduction in negative and affective symptoms observed in this study provides a rationale for the improvements in mental-health status reported by these patients.

In this trial, 15% of the young adults had schizoaffective disorder, for which optimal treatment must address affective as well as psychotic symptoms. The results to date with risperidone in schizoaffective disorder indicate that it is efficacious for both psychotic and mood symptoms (11,36,37).

Limitations of this analysis include the open-label study design so that it cannot be established that the observed improvements were not due to nonspecific effects. The improvements, however, are continual and rather dramatic for a stable group of patients with low PANSS and CGI scores at entry. Second, the duration of the patients' illness before entering the study was not recorded and thus low age (18–25 years for men and 18–30 years for women) was used as a proxy for early illness. These age ranges, however, are consistent with those suggested by DSM–IV for the onset of schizophrenia. Finally, only 66 young adults were the subjects of the analysis because the study was not designed to look at early illness. However, even with this low number, significant results were observed.

In summary, young clinically stable patients switched from oral or conventional depot antipsychotics to long-acting risperidone experienced significant benefits comparable to those reported in other patient populations (9–13). Symptom severity measured by both the PANSS and CGI scores was substantially reduced, and patients' self-assessed mental health status improved. Moreover, the patients expressed positive attitudes toward long-acting risperidone, which was well-tolerated and with little injection site discomfort. The results indicate that a long-acting atypical antipsychotic may be an important new treatment option for young adults with schizophrenia or schizoaffective disorder who may be in the early stages of their psychotic illness.

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