Health-Related Quality of Life in Patients With Schizophrenia During Treatment With Long-Acting, Injectable Risperidone

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Background: We investigated the impact of treatment with long-acting, injectable risperidone versus placebo on health-related quality of life (HRQoL) in patients with schizophrenia. Results are discussed in the context of HRQoL in the general U.S. population.

Method: Patients with DSM-IV schizophrenia entered a randomized, double-blind, placebo-controlled trial. After screening, previous antipsychotics were discontinued, and oral risperidone was titrated up to a dose of 4 mg/day over 1 week. Patients were then randomly assigned to receive placebo [N = 92] or long-acting risperidone (25 [N = 93], 50 [N = 97], or 75 mg [N = 87] every 2 weeks) for 12 weeks. HRQoL was measured using the Medical Outcomes Study Short-Form 36-item questionnaire (SF-36).

Results: At week 12, patients receiving long-acting risperidone had improved significantly ($p < .05$) in 5 domains of the SF-36 (bodily pain, general health, social functioning, role–emotional, and mental health) compared with patients receiving placebo. The effect was greatest for the 25-mg group, with significant improvement versus placebo in 6 domains ($p < .05$). At baseline, all SF-36 domain scores except bodily pain were significantly lower ($p < .05$) than normal values in all groups. With placebo, scores in all 8 domains remained below normal values after 12 weeks, while patients receiving long-acting risperidone showed improvement in HRQoL toward normal levels, with clinically meaningful improvements in all mental-health domains. In the 25-mg group, scores in 7 domains were not statistically different from normal values after 12 weeks.

Conclusions: Long-acting, injectable risperidone improved HRQoL toward normal levels. After 12 weeks, HRQoL of patients receiving 25 mg was not significantly different from normal.

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The concept of health-related quality of life (HRQoL) has always been of substantial importance to patients but is now starting to gain acceptance among physicians and those responsible for reimbursement of medications and medical interventions as a valid, measurable treatment outcome. In several chronic medical conditions, the impact of the disease on HRQoL can clearly be observed. Indeed, studies have confirmed that HRQoL is adversely affected in a wide range of such disorders, including osteoarthritis, diabetes mellitus, and migraine.[1–3] Although the reliability of patients' self-reports has sometimes been questioned, a number of studies have confirmed the reliability of such reports and have consistently shown that patients with schizophrenia do experience reduced HRQoL compared with the general population, as assessed by both objective and subjective measures.[4–6]

Improvements in HRQoL often represent evidence of a good treatment outcome for patients with schizophrenia. Moreover, consistent adherence to medication regimens can lead to good HRQoL if symptoms abate and few side effects occur; HRQoL in schizophrenia is most severely impacted by the negative symptoms of the condition (such as depression and emotional withdrawal) and the side effects of conventional antipsychotic agents, particularly tardive dyskinesia.[7,8] With long-term treatment,

however, most patients are not fully adherent to their treatment regimen—it has been estimated that 75% will be nonadherent over 2 years.[9]

The "atypical" antipsychotics, which first became widely available in the 1990s, have advantages over the first-generation "conventional" agents. The efficacy of atypical antipsychotics, particularly with regard to negative symptoms, but also in terms of positive symptoms and overall disease severity, has been demonstrated in a number of clinical trials and meta-analyses.[10–12] The side effect profile of atypical antipsychotics is also superior to that of the conventional agents, notably with regard to the incidence of extrapyramidal symptoms, and there is also some evidence that the incidence of tardive dyskinesia is reduced.[11–14] Thus, it is likely that oral atypical antipsychotics could have beneficial effects on the HRQoL of patients with schizophrenia. Oral agents are, however, associated with a number of disadvantages, such as low adherence to treatment regimens,[15] fluctuating serum drug levels,[16] and a high level of first-pass metabolism.[17]

The impact of long-acting "depot" antipsychotics on quality of life has not been formally assessed. However, depot formulations of conventional agents have been shown to have several advantages over their oral equivalents, including a superior pharmacokinetic profile and an improved level of treatment adherence.[17] These features, in turn, lead to a decrease in rates of relapse and hospitalization during long-term maintenance treatment[18] and can therefore be expected to have a positive effect on patients' HRQoL. Moreover, patients who are established on treatment with depot formulations have a high degree of acceptance and satisfaction with their medication.[19]

Long-acting risperidone injection is the first long-acting, injectable formulation of an atypical antipsychotic to become available. The aim of the present study was to measure the impact of treatment with long-acting risperidone injection compared with placebo on HRQoL—particularly on domains related to mental health—in patients with schizophrenia. In addition, the results are discussed in the context of HRQoL in the general population of the United States.

METHOD

Data on HRQoL were collected as part of a 12-week, multicenter, randomized, double-blind, parallel-group trial to evaluate the efficacy and safety of long-acting risperidone injection (25, 50, or 75 mg, every 2 weeks). Full details of the inclusion and exclusion criteria and trial design have been published elsewhere.[20]

Patients

Patients were required to be aged between 18 and 55 years and have a diagnosis of schizophrenia according to DSM-IV criteria.[21] Patients were also required to have baseline scores on the Positive and Negative Syndrome Scale (PANSS) of between 60 and 120, inclusive. Participants in the trials could be outpatients or hospital inpatients at baseline.

Written informed consent was obtained from each patient or the patient's guardian or legal representative. The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and its subsequent revisions.

Trial Design

After a 1-week screening period and a 1-week, open-label run-in, during which previous antipsychotics were discontinued and patients were titrated up to a dose of 4 mg/day of oral risperidone, patients were randomly assigned to receive intramuscular injections of placebo or long-acting risperidone, 25, 50, or 75 mg, every 2 weeks. Randomization was performed by a dynamic method, using interactive voice response system.[22] For the first 3 weeks of the double-blind phase, patients in the placebo group received an oral placebo, while those randomly assigned to long-acting risperidone received supplementation with oral risperidone according to their dose of long-acting risperidone.

The efficacy and safety results from this trial have been reported previously.[20]

Health-Related Quality of Life

HRQoL was measured using the Medical Outcomes Study Short-Form 36-item questionnaire (SF-36),[23] a widely used, generic HRQoL questionnaire for which normative data are available. The SF-36 consists of 8 domains that assess the following: bodily pain (BP), general health (GH), general mental health (MH), physical functioning (PF; limitations in physical functioning because of health problems), role–emotional (RE; role limitations because of emotional problems), role–physical (RP; role limitations due to physical health problems), social functioning (SF; limitations in social activities because of physical or emotional problems), and vitality (VT; energy and fatigue).

Possible scores range from 0 to 100, with higher scores indicating a better quality of life; a change of 5 points in any domain is considered to be clinically meaningful.[23] From the 8 domains, physical component summary (PCS) and mental component summary (MCS) scales can be constructed. The PCS and MCS are constructed such that they have a mean score of 50 and a standard deviation of 10 in the general U.S. population. Thus, scores above or below 50 represent HRQoL that is above or below average.

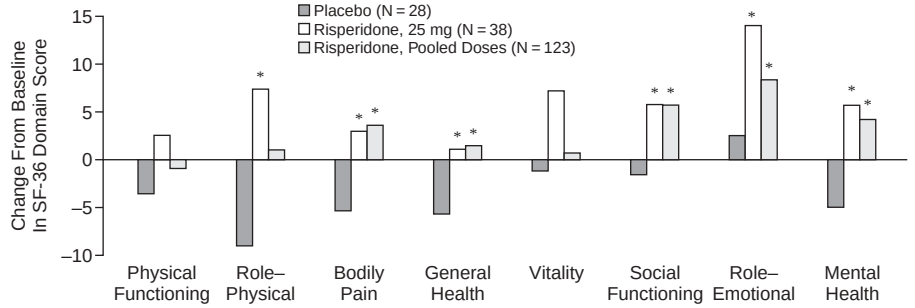
Training in the administration of the SF-36 was performed at the investigator meeting and followed up with training sessions at the study sites. SF-36 scores were collected at randomization and at either week 12 or study dis-

Table 1. Baseline Demographics for Patients Receiving Placebo or Injectable Risperidone, 25, 50, or 75 mg

Characteristic	Placebo (N = 92)	Risperidone 25 mg (N = 93)	Risperidone 50 mg (N = 97)	Risperidone 75 mg (N = 87)
Age, mean ± SE, y	38.2 ± 0.9	38.9 ± 1.0	36.0 ± 1.0	39.0 ± 1.1
Sex, N (%)				
Male	75 (82)	64 (69)	79 (81)	57 (66)
Female	17 (18)	29 (31)	18 (19)	30 (34)
Race, N (%)				
Black	34 (37)	39 (42)	37 (38)	45 (52)
White	44 (48)	35 (38)	44 (45)	35 (40)
Hispanic	11 (12)	12 (13)	10 (10)	6 (7)
Asian	0 (0)	4 (4)	3 (3)	0 (0)
Other	3 (3)	3 (3)	3 (3)	1 (1)
Schizophrenia type, N (%)				
Catatonic	0 (0)	0 (0)	1 (1)	0 (0)
Disorganized	2 (2)	1 (1)	6 (6)	3 (3)
Paranoid	72 (78)	71 (76)	72 (74)	65 (75)
Undifferentiated	18 (20)	21 (23)	18 (19)	19 (22)
Age at onset, mean ± SE, y	22.2 ± 0.7	22.7 ± 0.8	21.3 ± 0.7	20.8 ± 0.7
Baseline PANSS score, mean ± SE	82.13 ± 1.40	83.15 ± 1.27	83.09 ± 1.27	82.00 ± 1.47

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 1. Change From Baseline in SF-36 Scores at Week 12



*p < .05 vs. placebo.
Abbreviation: SF-36 = Medical Outcomes Study Short-Form 36-item questionnaire.

continuation. Scores were compared with normative data for the general population (aged 35–44 years) in the United States. These normative data were constructed from the SF-36 Health Survey to yield scores that would be useful in understanding population differences in physical and mental health status.[23]

Data Analysis

Analysis of HRQoL was carried out in patients who received at least 1 injection during the double-blind phase and had at least 1 postbaseline HRQoL assessment. At week 12, SF-36 scores were analyzed on an "observed case" basis (i.e., patients with data at baseline and week 12). Analysis of change from baseline for within-group comparisons was performed using a paired t test, while comparisons between the placebo group and each of the active-dose groups or pooled data from all 3 active-dose groups were made by employing an analysis of covariance model controlling for pooled investigator, baseline value, randomization group, and PANSS score stratum. Dunnett's method was used to correct for multiple comparisons versus placebo. A 2-sample t test was used to compare the health status of patients from each of the treatment groups in the present trial versus the general U.S. population.

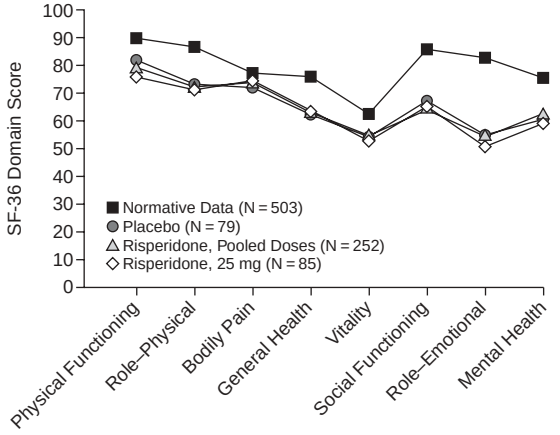
RESULTS

At baseline, 369 patients were randomly assigned to treatment (placebo: N = 92; 25 mg: N = 93; 50 mg: N = 97; 75 mg: N = 87). Baseline demographics were comparable for all groups (Table 1).

Placebo Comparison

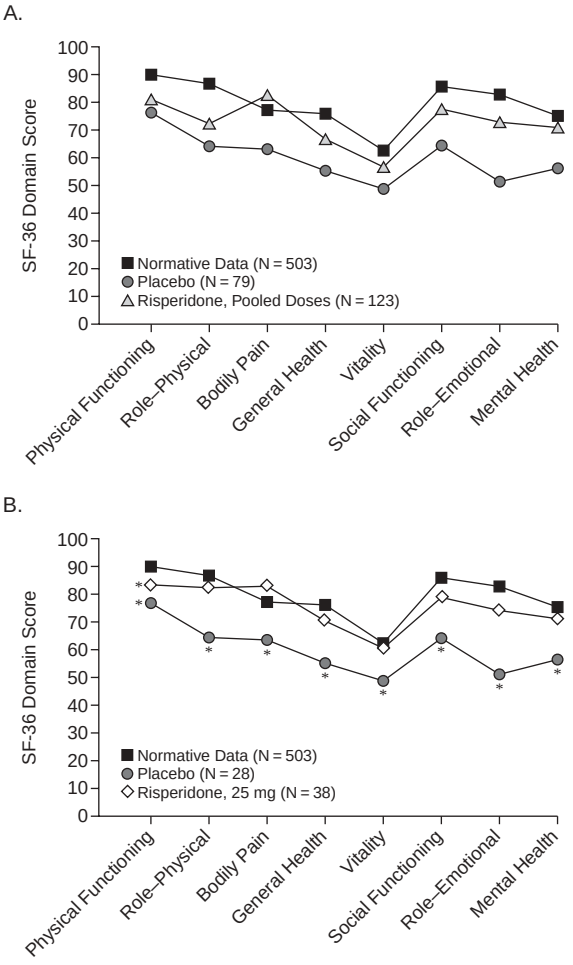
At week 12, patients receiving placebo showed worsening of HRQoL from baseline in 7 of the 8 domains of the SF-36 ($p > .05$; Figure 1). In 1 domain (RE), there was a small, nonsignificant improvement of 2.38 points.

Figure 2. SF-36 Domain Scores at Baseline



Abbreviation: SF-36 = Medical Outcomes Study Short-Form 36-item questionnaire.

Figure 3. SF-36 Domain Scores at Week 12 in the (A) Pooled Risperidone Treatment Groups and (B) Risperidone 25-mg Group Compared With Normative Data and Placebo



*p < .05 placebo vs. normative data.
Abbreviation: SF-36 = Medical Outcomes Study Short-Form 36-item questionnaire.

By contrast, patients receiving long-acting risperidone showed significant improvement from baseline compared with placebo in 5 domains (BP, GH, SF, RE, and MH; $p < .05$ vs. placebo; Figure 1). The effect was largest in 3 of the mental-health domains (SF: 5.59; RE: 8.40; MH: 4.13), leading to a significant improvement in MCS score after 12 weeks (2.37 vs. –0.29 for placebo; $p < .05$). In the 25-mg group, an improvement of at least 5 points was seen in all 4 mental-health domains (Figure 1). Of the physical-health domains, only RP showed at least a 5-point change from baseline. Changes from baseline were statistically significant versus placebo ($p < .05$) in 6 of the 8 domains (Figure 1). Patients in the 50- and 75-mg groups showed significant improvement compared with placebo in 2 and 3 domains, respectively (50 mg: BP, MH; 75 mg: BP, SF, RE; $p < .05$ vs. placebo; data not shown). As with the 25-mg group, improvements versus placebo were observed in both higher dose groups in almost all domains, with the exception of nonsignificant deteriorations in PF and RE in the 50-mg group and VT in the 75-mg group.

Results in the Context of Normative Data

Baseline SF-36 domain scores were similar in the risperidone groups and the placebo group and were significantly lower than for the general U.S. population ($p < .05$) for all domains except BP (Figure 2). The largest differences from the normative data were observed in the mental-health domains, ranging from 27.73 (risperidone) and 27.63 (placebo) for RE to 8.50 (risperidone) and 9.34 (placebo) for VT (Figure 2).

No improvement in domain scores was observed in patients treated with placebo. Scores in all 8 domains in these patients remained below those of the general U.S. population at week 12, with the difference between normative scores and those in patients receiving placebo ranging from 13.85 (VT) to 31.57 (RE) in the mental-health domains (Figure 3). After 12 weeks of treatment with long-acting risperidone, HRQoL showed an improvement toward normal values (Figure 3A). The greatest improvements in risperidone-treated patients were seen in the domains relating to mental health, in which the deficit compared with the general U.S. population was approximately halved. At week 12, the differences between scores in the general U.S. population and the risperidone groups ranged from 4.17 (MH) to 9.86 (RE).

Improvements seen with the lowest risperidone dose (25 mg) were of similar magnitude to those seen in the pooled population, with the differences from the general population ranging from as little as 2.16 (VT) to 9.08

(RE). All but one of the domains (PF) were no longer significantly different from the general U.S. population after 12 weeks of treatment with long-acting risperidone, 25 mg (Figure 3B). In the 50-mg and 75-mg groups, 2 domains (BP and MH) and 6 domains (PF, RP, MH, VT, RE, and SF), respectively, were no longer statistically significantly different from normal values after 12 weeks of treatment (data not shown).

DISCUSSION

After 12 weeks of treatment, HRQoL in patients who received long-acting risperidone injection was improved toward the level seen in the general U.S. population. The effect was most pronounced in the group receiving long-acting risperidone, 25 mg, in which scores in 7 of the 8 domains of the SF-36 were not significantly different from those in the general population at week 12. Moreover, all of the mental-health domains showed at least a 5-point improvement from baseline, a change that is considered to be clinically meaningful.[23] These data support the efficacy and safety results from the present trial,[20] suggesting that long-acting risperidone, 25 mg, may afford the best combination of efficacy and improved quality of life.

No significant improvement in HRQoL was seen in patients who received placebo. Indeed, the decrease in SF-36 scores for some domains, such as GH or MH, was similar to or greater than the increase seen in the patients receiving risperidone. As HRQoL in individuals with schizophrenia is most severely affected by the symptoms of the disorder, particularly negative symptoms, and the side effects of antipsychotics, it seems likely that the improvements in HRQoL in this study reflect the control of positive symptoms, a significant effect on negative symptoms, and the minimal side effects that are seen with long-acting risperidone injection.[20] One limitation of the current study, however, is its relatively short duration. Longer-term studies will be necessary to assess fully the benefits of maintenance treatment with long-acting, injectable risperidone on HRQoL.

The SF-36 is a widely used instrument for the assessment of HRQoL and has been extensively validated in patients with schizophrenia.[24,25] As might be expected, the domains relating to mental health are more severely affected in mental health disorders, including schizophrenia, compared with physical disorders such as osteoarthritis or diabetes mellitus.[1] In the present trial, the mental-health domains of the SF-36 were also those that showed the greatest difference from normal values at baseline, a finding that is in agreement with previous studies in patients with schizophrenia.[4,5] Moreover, the greatest improvements during treatment with long-acting risperidone were seen in the SF-36 domains related to mental health (MH, RE, VT, and SF). This finding was perhaps to be expected, as the physical domain scores were similar to those of the general population at baseline—it is the reduced HRQoL in the mental-health domains that is more debilitating in schizophrenia, preventing normal functioning and integration into society. Unlike patients receiving long-acting risperidone, those receiving placebo experienced worsening in the mental-health domains of the SF-36 during the trial. Although the efficacy data from the trial show that patients receiving placebo did experience improvements in their total PANSS score,[20] this was not the case for the negative subscores, which have been shown to be more closely related to perceptions of well-being and quality of life.[7] Improvements in negative symptoms were, however, observed in all 3 treatment groups and may be reflected in the HRQoL findings.

In conclusion, improvements in HRQoL were demonstrated in patients who received long-acting risperidone injection (25, 50, or 75 mg) every 2 weeks for 12 weeks. In the 25-mg group, clinically meaningful improvement was seen in all mental-health domains, and HRQoL after 12 weeks was not significantly different from that of the general U.S. population. Thus, long-acting risperidone not only leads to improvements in the symptoms of schizophrenia, but also improves HRQoL.

Drug name: risperidone (Risperdal).

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