Long-term Treatment of Schizophrenia with Risperdal: An International Multicentre Open Label Trial

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Abstract

Objectives and methods: This open multicentre international trial was designed to investigate the efficacy and safety of risperidone administered once daily during 7 months in subjects with acute exacerbation of chronic or sub-chronic schizophrenia. It was conducted in 10 countries (Cyprus, Egypt, Gulf, Pakistan, Saudi Arabia, Iran, Jordan, Lebanon, Syria, and Turkey). The subject's psychopathology was assessed by the PANSS and clinical response was defined as a reduction of >20% on the total PANSS score compared to baseline. Secondary parameters were the shift between endpoint and baseline of the PANSS subscales, total BPRS and clusters score and the Clinical Global Impression (CGI). Quality of life (QOL) was assessed using the SF-12 questionnaire. Safety evaluation included laboratory analysis (blood biochemistry and haematology, urine analysis), ESR assessments, ECG, and vital signs (weight, blood pressure and heart rate). 809 (68.7% of males) out of the 819 subjects admitted to the study were included in the safety analysis and 797 in the ITT efficacy analysis. The mean daily dose of risperidone averaged 5.9 mg. Early study termination occurred in 22.6% of the subjects of which 3. 1 % were due to adverse events (AEs). Results: Clinical response was seen in 86% of the subjects at endpoint. A 58% clinical improvement in total PANSS was also observed (p<0.0001). Negative and positive PANSS sub -scales improved by 54% and 64% respectively (p<0.0001). Clinical improvement on total BPRS was 58.7% at endpoint (P<0.0001). Based on the CGI, 87% of the subjects ex- perienced an improvement of their condition compared to baseline, and 9% remained unchanged.

Conclusion: These data show that risperidone administered once daily at a mean dose of 5.9 mg / day for up to 7 months significantly reduced the severity of acute exacerbation in subjects with chronic or sub-chronic schizophrenia, with an overall good safety profile.

Key words: *Risperdal — international multicentre — Schizophrenia*

INTRODUCTION

The effectiveness of neuroleptic drugs in the treatment of psychotic disorders is now well established. Conventional neurolepties are effective against the positive symptoms of schizophrenia (hallucination, delusions and thought disorders), but are less effective against negative symptoms (emotional withdrawal, blunted affect, poverty of speech, avolition) of the disease. This shortcoming is important because negative symptoms seriously impair normal interpersonal relationships and make patients less available to psychosocial rehabilitation. (Herz, 1997).

A second limitation of conventional neuroleptics is the induction of extrapyramidal symptoms (EPS). EPS can have a major impact on patient's willingness to take medication, which in turn can influence the relapse rate. It can affect up to 60% of the patients receiving acute antipsychotic medication.

Risperidone is a benzisoxazole derivative with antipsychotic activity characterised by a high selectivity for both serotonin 5-HT_2 and dopamine D_2 receptors (Markowitz, et al. 1999). It also binds to α_1 adrenergic and, with less affinity to H_1, histamine and α_2 adrenergic receptors (Tritsmans, et al. 1996), it was shown to be an effective antipsychotic drug, reducing the severity of both the positive and the negative symptoms of acute and chronic schizophrenia (Bech, et al. 1998).

The aim of this study was to evaluate the efficacy and safety of Risperdal administered once daily in schizophrenic patients treated up to 7 months. The primary objective of the present trial was to evaluate at endpoint the efficacy of Risperdal administered once daily by means of:

1. the shift versus baseline of the PANSS score, 2. the percentage of subjects showing clinical improvement (>20% reduction) as measured on the PANSS scale. The secondary objectives were to evaluate: 1. The efficacy by the shift of the PANSS subscales, by the BPRS scale, by the CGI and its overall change. 2. The safety by the incidence of adverse events, the laboratory (haematology, biochemistry, and urine analysis), the ECG, the vital signs.

MATERIAL AND METHODS

This open multicenter international trial was run by psychiatrists in private practices and hospitals in 10 countries (Cyprus, Egypt, Gulf, Iran, Jordan, Lebanon, Pakistan, Saudi

This study was supported by Janssen Cilag. Middle East and West Asia (MEWA)

Arabia, Syria, and Turkey).

At the first visit, after having given the consent to participate, subjects were examined (physical / neurological examination, psychiatric history), and baseline assessments (demographic data, vitals signs, laboratory, ECG, PANSS, CGI, ESR, SF-12) were performed. The subjects were given the trial medication. Subjects were to be examined after 3, 7, 14, days, then at monthly intervals for up to 7 months.1000 subjects were to be enrolled in this multicentre study, however only 821 entered of which 7 were excluded from the safety analysis (no intake of study medication) and 19 subjects were excluded from the efficacy intent-to-treat analysis. **Inclusion Criteria were:** Age > 15 years, diagnosis according to DSM-IV criteria: acute exacerbation of chronic and sub-chronic schizophrenia (295.XX), total PANSS score at selection of ≥ 60 > , subjects (or their legal guardians) had to give their informed consent in a format, which satisfied the requirements of local ethics committee. **Exclusion Criteria:** Women of reproductive age without adequate contraception (sterilisation, IUD, controlled administration of oral contraceptives, I.M. administration of depot-progestagenes), pregnant or lactating women; subjects who had received a depot neuroleptic within treatment cycle of the time of selection subjects with clinically relevant organic or neurologic diseases, abnormal laboratory tests; abnormal ECG findings, subjects with DSM-IV diagnosis of psychoactive substance abuse with the exception of nicotine related disorders, subjects who have been included in trials with investigational drugs during the 4 weeks preceding this trial, subjects with a history of tardive dyskinesia or neuroleptic malignant syndrome known, sensitivity risperdal, subjects known to be HIV positive, subjects who in the opinion of the investigator are at risk of causing harm to themselves.

The trial medication was to be administrated once daily, in the morning or evening at the discretion of the investigator, around 08:00 h. or 20:00 h. respectively. The chosen time of dosing had, if possible , to remain constant throughout the trial. All antiparkinson and psychotropic drugs had to stopped at selection. EPS treatment could be given, i.e. if a dose reduction of Risperdal did not suffice. Anticholinergics could only be used on a P.R.N basis, at the minimum dose required. Therefore, the routine use of prophylactic drugs was to be discouraged. Benzodiaepine (preferably short acting) could be administrated on a P.R.N. basis, e.g. for sedation, for the shortest possible and at the lowest possible dose.

Results

The schizophrenia was of the paranoid type in 45.3 % of the subjects, disorganized in 20.4%, residual in 6.2% and catatonic in 2.5%. Undifferentiated schizophrenia was diagnosed in 25.6%. A wide range of concomitant disease were reported across the countries. Antiparkinson drugs and psycholeptics were administered most frequently (27.8% and 26.9% respectively) Most of the subjects took between 4 and 8 mg and the overall study dose averaged 5.6 ± 2.1 mg.

At endpoint, 33% of the subjects received between 1 and 4 mg. Another 43% took between 5 and 6 mg. 15% of the subjects were on 8 mg risperidone and only 8% received doses between 10 and 18 mg.

At baseline PANSS data were available for only 740 subjects. The mean score was 99.3 ± 19.4 (minimum = 30 , maximum 210). A significant improvement expressed by a shift of -25.2 ± 20.2.(mean ± STD; $p<0.0001$) of the Total PANSS score for all subjects that was observed already after the first month of treatment. The Total PANSS scores decreased by a mean of 40.4 ± 25.3 at endpoint ($p<0.0001$), to reach 59.1 ± 23.2.

A significant improvement was also observed for each individual country. Both after the first month of treatment and at endpoint. The shift versus baseline at endpoint for the subjects of Egypt (-35.9 ± 18.4), Iran (-21.2 ± 22.1); Saudi Arabia (-32.6 ± 27.8) was less pronounced than for the total of the subjects. On the other hand, again compared to all the subjects, the decrease in severity at endpoint versus baseline was more pronounced for the subjects of Jordan (-54.6 ± 30.42), Lebanon (-51.1 ± 26.9), Pakistan(-48.4 ± 23.1), and Syria (-57.1 ± 21.05) (Table 1)

After the first month of treatment, 72% of all subjects with a PANSS score (n = 740) showed a clinical response (reduction of ≤ 20% of total PANSS). The percentage went up to 94% at month 7 (n 464), with an endpoint value of 86% (n 771).

Table (1): Improvement seen as shift versus baseline at end point per country on the PANSS

Country	Shift versus baseline at end point
Egypt	-35.9 ± 18.4
Iran	-21.2 ± 22.1
Saudi Arabia	-32.6 ± 27.8
Jordan	-54.6 ± 30.42
Lebanon	-51.1 ± 26.9
Pakistan	-48.4 ± 23.1
Syria	-57.1 ± 21.05

$P < 0.0001$

At endpoint, the percent of clinical responders was (64%) in the Iranian patients. (71%) in Saudi Arabian patients compared to the total of all subjects (86%). However, the percentage was higher in the Lebanese (96%) and Cypriots (100%) subject population. At endpoint, 52.5% of all subjects showed a decrease in severity of their total PANSS score ≥60, whereas a deterioration was observed for 4.5% of the subjects.

The improvement, expressed by the negative shift of the clinical improvement averaged -36.2 ± 26.5% at month 1,-53.7 ± 27.6% at month 4, -66.1 ± 26.9% at month 7, and -57.6 ± 31.8% at endpoint. The shift of the clinical improvement on the total PANSS was statistically significant after 1 month of treatment for the total of subjects ($p<0.0001$), as well as for the individual countries ($p<0.0001$).

At baseline, the mean score of the PANSS positive subscale was 24.8 ± 7.8 and decreased (=improved) by 7.5 ± 6.7 after the first month of treatment, by 10.8 ± 7.6 after 4 months, and by 13.2 ± 8.1 after 7 months. The shift averaged -11.4 ± 8.3 at endpoint, and was significant (p<0.0001) after the first month of treatment up to the endpoint for the total of subjects as well as for the individual countries.

At endpoint, the clinical improvement (=decrease in severity) of all subject was 59.3%. The subject population of Iran (43%), showed a less important improvement than the mean of the total of subjects. Whereas the mean improvement was clearly more pronounced for Pakistan (70%), Jordan (76%), Lebanon (81. %) and Syria (79%).

At baseline, the mean score of the PANSS negative subscale was 26.3 ± 8.7 and decreased (=improved) by 6.1 ± 6.7 at month 1, by 9.6 ± 7.7 at month 4, ,and by 12.0 ± 8.6 at month 7. The decrease averaged 10.5 ± 8.5 at endpoint, to a mean of 15.8 ± 7.9. The shift versus baseline was statistically significant from month 1 up to the endpoint (p<0.0001) for both for the total of all subjects and per country.

Table (2): Mean score of PANSS positive and negative subscale decrease from baseline up to end-point

Month	Positive scale	Negative Scale
Baseline	24.8 ± 7.8	26.3 ± 8.7
Decrease at month 1	7.5 ± 6.7	6.1 ± 6.7
Decrease at month 4	10.8 ± 7.6	9.6 ± 7.7
Decrease at month 7	13.2 ± 8.1	12.0 ± 8.6
Decrease at endpoint	-11.4 ± 8.3	10.5 ± 8.5

P< 0.0001

At endpoint , the overall clinical improvement (=decrease in severity) was 47.7% the subject population of Iran (28%) and Turkey (41%) showed a less important improvement of the severity of the PANSS negative subscale than the mean of the total of the subjects. On the other hand, the subject population of Syria (71%), Pakistan (61%) , Jordan (74.5%) and Lebanon (67%) showed a more pronounced decrease in severity.

At endpoint, a significant improvement of the primary parameters was observed for the total of all subjects and for each individual country. Total PANSS severity decreased from 99.3 ± 19.4 at baseline by 40.4 ± 25.3 or 40.7% down to 59.1 ± 23.2 at endpoint. The clinical improvement at endpoint (taking the minimum score at baseline into account) was 57.6% ± 31.8%. 72% of the subjects showed clinical improvement (reduction of ≥ 20% of Total PANSS) already after 1 month of treatment, with 86% subjects clinically improved at endpoint.

A significant decrease of all PANSS clusters (positive, negative, general and total BPRS) was observed reflecting the clinical improvement already expressed by the changes of the primary parameters. At baseline, the mean score of the BPRS subscale was 54.9 ± 11.5 and decreased (=Improved) by 14.0 ± 11.1 (p<0.0001) after the first month of treatment, by 20.5 ± 12.4 after 4 months, and by 25.5 ± 13.4 after 7 months, showing a mean shift versus baseline of -22.1 ± 14.1 (p<0.0001), to reach 33.0 ± 12.4 at endpoint. When calculating the clinical improvement, the decrease in severity averaged 58.7% ± 32.6% (p<0.0001). The number of subjects with clinical response (decrease of ≥ 20% on total BPRS) was 86%. A clearly less important improvement of the total BPRS subscale was observed at endpoint for the subject population of Iran (37%). On the other hand, the improvement was more pronounced for the subjects from Jordan (69%), Lebanon (71%), Pakistan (66%) and Syria (79%).

At baseline the mean score for the anergia cluster was 12.0 ± 4.3. It decreased (= improved) by 2.6 ± 3.1 after the first month of treatment, and by 4.4 ± 4.0 at endpoint, to average 7.7 ± 3.4

The severity of the activation BPRS cluster averaged 8.0 ± 2.9 at baseline, and decreased by 3.1 ± 2.8 at endpoint, to a mean of 5.0 ± 2.2

At baseline the mean score of the BPRS factor scores "depression" was 10.1 ± 4.1. The severity decreased by 3.4 ± 3.7 at endpoint down to an average of 6.7 ± 2.9.

The severity of the cluster "paranoid / belligerence" averaged 10.2 ± 3.7 at baseline and decreased by 4.5 ± 4 at endpoint down to a mean of 5.5 ± 2.9.

The severity of the cluster "thought disturbance' was 14.5 ± 4.7 at baseline and improved (= decreased) by 6.5 ± 4.8 at baseline down to an average of 8.1 ± 4.1 .

Table (3): Baseline and endpoint scores of BPRS clusters

Cluster	Baseline	Endpoint
Anergia	12.0 ± 4.3	7.7 ± 3.4
Depression	10.1 ± 4.1	6.7 ± 2.9
Paranoid /Belligerence	10.2 ± 3.7	15.5 ± 2.9
Thought disturbance	14.5 ± 4.7	8.1 ± 4.1
Activation	8.0 ± 2.9	5.0 ± 2.2

(Clinical Global Impression (CGI), (Overall severity) a baseline, 75% of the total of all subjects (n 797) were at least markedly ill. This percentage dropped to 1 8% after the first month of treatment , to reach 12% at endpoint, with 52% of all the subjects either "not ill" or "very mildly" ill.

The parametric analysis of the CGI (mean of scores instead of percent of subjects per categories) showed a mean severity at baseline of 4.4 ± 1.3, which decreased to 3.4 ±1.25 at month 1 and to 2.6 ± 1.4 at endpoint. The change over time was statistically significant both for the total of subjects and for the individual countries (p=0.001). An improvement was already noticed after three days of treatment with 22% of the subjects minimally or much improved. At day 14, already 72% of the subjects were at least minimally improved, and 3% worsened.

Until month 7, a steady improvement could be noticed with 95% improved. Only 4% of the subjects remained unchanged and 2% experiencing a worsening of their condition. At endpoint, 87% experienced an improvement, 9% remained unchanged and 15 subjects (2%) showed a worsening of their condition The improvement over time is statistically significant both for the total of subjects and for each country ($p<0.0001$). The parametric analysis (mean of scores instead of percent of subjects per category) showed a mean of 3.8 ±0.54 after three days of treatment (unchanged =4). The mean severity decreased to 2.6 ± 0.8 after one month and to 1.8 ± 0.9 after 7 months of treatment. The endpoint value averaged 2.2 ± 1.2 . As recorded by the CGI scale, at baseline, 75% of all subjects were at least markedly ill. At endpoint, only 12% of all subjects were still at least markedly ill, whereas 52% were either not ill or very mildly ill, and 37% mildly to moderately ill. When compared to baseline, 87% of all subjects experienced improvement, for 9% remaining unchanged and only 2% worsened.

Safety results: ESRS showed a slight decline during treatment. No clinically consistent ECG, vitals signs, and laboratory abnormalities were observed, except for a significant increase in body weight (+2.5kg). Adverse Events (AEs) were reported in 38.8% of the subjects, 3.1% leading to study withdrawal. EPS were seen in 11.7%, agitation in 5.4% and insomnia in 5.2%. 86% of the EPS episodes received a concomitant treatment. The drug was withdrawn for 6 patients, because of adverse effect , two from cardiovascular complaints, 3 from sever E.P.S and one suicidal attempt.

Regarding the Quality of life the Physical Component Score (PCS-12) averaged 44.9 ± 10.7 at baseline and improved significantly to 50.4 ± 7.7 at endpoint. This represents a mean improvement versus baseline for the total of subjects of 5.7 ± 10.8 ($p<0.001$), which is more important than the mean improvement of the subject population of Iran (3.0 ± 7.5, $p<0.05$), Lebanon (1.2 ± 11 NS), and Saudi Arabia (1.9 ± 9, NS). On the other hand, the improvement for Cyprus (17.1 ± 9.4, $p<0.001$) and Pakistan (10.7 ± 10.8, $p<0.001$) was more pronounced than for the total of all subjects.

The Mental Component Score (MCS-12) averaged 37.1 ± 11.36 at baseline and improved significantly to 47.2 ± 10.57 at endpoint. The improvement for the subject population of Iran (1.6 ± 11.8, NS) was lower than the mean improvement of 10 ±13.6 ($p<0.001$) for the total of subjects. Yet, the improvement was more pronounced for Cyprus (20.9 ± 14.5, $p<0.00$ 1), Lebanon (16.9 ± 17, $p<0.001$) and Pakistan (15.1 ± 13, $p<0.001$). (Table 4)

Table (4): Quality of life physical and mental component scores

	Physical Component	Mental Component
Baseline	44.9 ± 10.7	37.1 ± 11.36
Endpoint	50.4 ± 7.7	47.2 ± 10.57

P < 0.001

DISCUSSION

This open multicentre international trial was designed to evaluate the clinical efficacy and safety of risperidone administered once daily. The rationale for this evaluation was based on pharmacokinetic data showing that the active moiety of risperidone has a half-life of about 24 hours.

- Markowitz, J., Brown, G., Moore, T., et al. (1999): Atypical Antipsychotics Part 1: pharmacology, Pharniacokinctics, and Efficacy. The Annals of ptiarmacotherapy, 33: 73-85.

During the course of the trial, Nair et al. (1998), published the results of a double-blind trial comparing 8 mg o.i.d. to 4 mg b.i.d administration, which we also will refer to in the discussion. 809 subjects were included in the safety and 797 in the efficacy analysis. Clinical response of >= 20% reduction on the PANSS score was obtained in 86% of the subjects. This percentage is higher than the 33% to 81% in the review by Tritsmans et al. (1996), the 72.7% by Chouinard et al. In a double-blind comparison with haloperidol and the 72% to 76% reported by Nair et al. (1998), in the once versus twice daily administration comparison[3,16,7]. When considering the clinical improvement, the mean reduction on the Total PANSS reported by Tritsmans et al. (1996), Ranged from 22.5 to 47.4%, and by 41% as calculated from Nair et al. (1998),compared to 58% in our study. At baseline, the Total PANS S in our study was slighly lower than in Nair et al. (1998), study (99.3 versus 103.6 to 106.1), but was in the range of the other studies reviewed by Tritsmans et al. (1996), (89.6 to 124.4).

In our study, a significant clinical improvement by 64% on the positive and by 54% on the negative PANSS subscales was observed. Tritsmans et al. (1996), reported a reduction on the positive PANSS subscale ranging from 30.5 to 56.8% and from 19.3 to 36.8% on the negative subscale. The improvement with a once daily administration was 34% on 7 the negative and 48% on the positive subscale. In our subject population, the severity of the psychosis measured on the General Psychopathology subscale was also significantly reduced at endpoint with a decrease by 57.4%, which is also somewhat higher than the 43% calculated from Nair et al. (1998), and the 35.4 to 42.8% from Tritsmans et al. (1996).

Total BPRS decreased by 59.3% at endpoint, compared to the 45% calculated from Nair et al. (1998), and the 30% to 45% from Tritsmans et al. (1996).

The CGI showed that 87% experienced an improvement of their condition, and 9 % remained unchanged, which is also in line with the 77% and 9% reported by Nair et al. (1998).

In our study, the incidence of adverse events was lower than in the once daily arm in Nair et al. (1998) study (38.8% versus 70%) and concerned mainly EPS disorders (11.7%), agitation (5.4%) and insomnia (5.2%). These particular AEs were also found more often than other AEs in Nair et al. (1998) study,

but with a higher incidence (31%, 14%, 17% resp.). Umbricht et al. (1995) in his review reports that the most comment AEs found in North American trials were insomnia (26%),
- Kasper S. et al. (1998): Risperidone and olanzapine: optimal dosing for efficacy and tolerability in patients with schizophrenia. Internat Clin Psychopharmacol, 13: 253-262.
agitation (22%), EPS (17%), headache (17%), anxiety (12%) and rhinitis (10%). Kasper et al. (1998) reports an overall incidence of EPS for risperidone of 16%. In our study, 86% of the EPS episodes received a concomitant treatment, which represents 9-11% of the subjects. Previous studies showed the low prevalence of EPS in Egyptian population with conventional antisychotics, Okasha et al. (1986). With resperidone there may be some ethnic variation in response of patients.

ESRS severity declined during the study, although not significantly which is in line with the conclusion by Tritsmans et al. (1996), that "pre-existing ESRS scores declined over time or were stable."

Early study termination occurred in 22.6% of the subjects of which 3.1 % were due to AEs. These figures are between the 13% from Nair et al. (1998) and the 33% from Chinchilla et al. (1996). The AEs leading to study discontinuation were mainly CNS or psychiatric disorders. Serious adverse events affected 6 subjects (0.7%) of which 3 deaths, one suicide, one death due to coronary disease and another due to circulatory collapse. Of the vitals signs, heart rate, blood pressure remained stable during the study, however with a significant increase in body weight by 2.5 kg. This finding has already been described by Tritsmans et al. (1996), who reports weight increases from previous studies ranging from 0.2 to 3.4 kg, as well as by Chinchilla et al. (1996). (+2.2 kg) and by Umbricht et al. (1995), (+2.3 kg).

The once daily administration did not seem to induce consistent hypotension through the alphalytic activity of risperidone. It has however to be noted that a transient but significant increase in heart rate at the beginning of the trial has been observed. Heart rate decreased steadily afterwards to slightly below baseline values at endpoint.

No consistent relevant changes in ECG findings were seen. Laboratory data were available only for 79% of the subjects and do therefore not reflect the whole subject population. In this group of subjects no consistent clinically relevant abnormalities were observed.

The mean dosage in our study was 5.9 mg, which is lower than the 8 mg o.i.d or 4 mg b.i.d fixed dose used by Nair et al. (1998), and could explain the lower incidence of AEs and the equivalent or even better efficacy observed in our study. This is in line with Kasper et al (1998), who has shown that 6 mg/d was the optimal dose for maximal efficacy.

- Lemmens, P., Wyffels, V., Smet, A., Boucique, E., et al (5/1999): Medical Expert Statement on Adjustment of Risperidone Dosing. Instruction for Adults with Schizophre- nia. Lanssen Research Foundation.; Clinical Expert Report N 137404.
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Lemmens et al (1999), in a recent expert report confirmed that increasing the dose from 4 mg 2 to 8 mg is not accompanied by a significantly better therapeutic response. The once daily administration was also well tolerated without a clinically relevant increase in hypotension, tachycardia or dizziness.

CONCLUSIONS

In this open multicentre study, 809 subjects took risperidone for up to 7 months. A significant decrease in severity by 58% was measured on the total PANSS. This is confirmed by a decrease in severity by 64% on the positive, by 54% on the negative and by 57% the general PANSS subscales. Clinical response (≥20% decrease in total PANSS) was observed in 86% of the subjects. According to the clinical impression (CGI) of the treating psychiatrists, 87% of the subjects were improved at the end of treatment. No consistent clinically relevant changes in vital signs, laboratory and ECG measurements were found except for a significant increase in body weight (+2.5 kg). The overall dropout rate was 23%, of which 3.1 % were due to AEs.

These data show that risperidone administered once daily at a mean of 5.9 mg daily up to 7 months is well tolerated with an efficacy at least as good as reported in previous trials. The absence of an active or placebo control has to be taken into consideration when interpreting these data.

ACKNOWLEDGMENT

We are grateful to the investigators in the RIS-INT-36 study group

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الملخص العربي

علاج طويل الأجل للفصام بالريسبردال: تجربة دولية مفتوحة متعددة المراكز

الأهداف والطرق: هذه التجربة المفترضة الدولية متعددة المراكز تمت لفحص كفاءة وسلامة الريسبردال المقدم في جريمة واحدة خلال سبعة أشهر لأشخاص يعانون من تفاقم حاد لفصام مزمن ، وتحت المزمن وقد جرت في عشر دول (قبرص ومصر والخليج وباكستان والعربية السعودية وايران والأردن ولبنان وسوريا وتركيا) . تم تقدير المرضية النفسية بواسطة مقياس الأعراض الإيجابية والسلبية وتعريف الاستجابة السريرية بانخفاض أكبر من ٢٠% من حاصل هذا المقياس مقارنا بما قبل التجربة. وأتخذ التغير في مقاييس الأعراض منفردة عن نقطتي بدء ونهاية التجربة وحاصل مقاييس المقابلة النفسية القصيرة ولانطباع السريري الكلي كمحكات ثانوية . وتم استخدام استبعاد تقدير نوعية الحياة . وقد شمل تقدير الأمان فحوصات معملية (كمياء الدم وفحص الدم والبول وسرعة الترسيب وتخطيط القلب والعلامات الحيوية (الوزن وضغط الدم ومعدل ضربات القلب) . واشترك فيه ٨٠٩ مريضا (٦٨,٧% من الذكور) من ٨١٩ مريضا شملتهم التجربة وشارك ٧٩٧ في تحليل الكفاءة . وكان متوسط جريمة ريسبريدون ٥,٩ مم يوميا و لم يستكمل التجربة بعد بدايتها ٢٢,٦% كان منهم من أنهوها (٣,١%) بسبب الأعراض الجانبية .

النتائج: تحقق التحسن السريري في ٨٦% من أداء العينة عند نهاية التجربة . ولوحظ التحسن في مقياس الكلي للأعراض الإيجابية والسلبية في ٥٨% وبالنسبة للأعراض السلبية في ٥٤% والأعراض الجانبية في ٦٤% وعلي اختبار المقابلة النفسية القصيرة ظهر التحسن السريري في ٥٨,٧% عن نقطة النهاية وكلها بدلالات إحصائية بالغة (أقل من ٠,٠٠١) وأوضح ٨٧% من مرضي التجربة تحسنا بالمقاومة بنقطة البداية من خلال الانطباع السريري الكلي بينما بقي ٩% بدون تغير .

الخلاصة: تظهر هذه المعلومات نجاح تناول الريسبريدون بجرعة يومية واحدة متوسط ٥,٩ مم مدة سبعة أشهر مع تقليل التفاقم الحاد لمرضى الفصام المزمن وتحت المزمن مع انطباع شامل بأمان جيد.