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Efficacy and safety of long-acting injectable risperidone in maintenance phase of bipolar and schizoaffective disorder

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Introduction. Our aim was to evaluate treatment safety, tolerability, efficacy and compliance of long-acting injectable risperidone (LAIR) as maintenance treatment in a bipolar and schizoaffective inpatients sample with torpid course due to poor compliance to oral therapy.

Methods. 22 inpatients, 14 with a diagnosis of bipolar disorder and 8 with a diagnosis of schizoaffective disorder, were included in this study. They were treated with LAIR, 1 dose every 14 days, and were evaluated for 40 weeks with the Young Mania Rating Scale (YMRS), Hamilton Scale for Depression (HAM-D), UKU-Side Effect Rating Scale and Clinical Global Impression Severity of Illness Scales (CGI).

Results. Average YMRS scores were reduced significantly from 10.5 at baseline interview to 2.5 at week 40 ($p < 0.001$). HAM-D and UKU scales did not reach a statistically significant reduction. CGI-S scores were reduced from 3.8 at baseline to 1.5 at week 40 ($p < 0.001$).

Conclusions. LAIR could be an effective maintenance therapy for bipolar and schizoaffective patients with poor compliance to oral treatment.

Key words:
Bipolar disorder. Schizoaffective disorder. Risperidone. Long-acting antipsychotic. Adherence.

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Eficacia y seguridad de risperidona inyectable de larga duración en fase de mantenimiento del trastorno bipolar y esquizoafectivo

Introducción. Este estudio tiene como objetivo evaluar la seguridad, tolerabilidad, eficacia y cumplimiento del tratamiento utilizando una formulación de risperidona inyectable de larga duración (RILD) como terapia de mantenimiento en un grupo de pacientes bipolares y esquizoafectivos con evolución tórpida debido a una mala adherencia al tratamiento por vía oral.

Metodología. Veintidós pacientes, 14 de ellos con diagnóstico de trastorno bipolar y 8 con diagnóstico de trastorno esquizoafectivo, fueron incluidos en este estudio. Recibieron una inyección de RILD cada 14 días y fueron evaluados durante 40 semanas utilizando la *Young Mania Rating Scale* (YMRS), la *Hamilton Scale for Depression* (HAM-D), la *Udvalg Für Kliniske Undersogesler* (NKU) y las *Clinical Global Impression Scales* (CGI).

Resultados. Las puntuaciones de la YMRS se redujeron significativamente de 10,5 (promedio) en la entrevista basal a 2,5 (promedio) en la semana 40 ($p < 0,001$). En las puntuaciones de la HAM-D no hubo variación estadísticamente significativa, así como tampoco en las de la escala UKU para efectos adversos. Las puntuaciones en la escala CGI-S se redujeron de 3,8 (entrevista basal) a 1,5 (semana 40) ($p < 0,001$).

Conclusiones. RILD podría ser eficaz como tratamiento de mantenimiento en pacientes bipolares y esquizoafectivos con particular dificultad para adherirse de manera adecuada al tratamiento por vía oral.

Palabra clave:
Trastorno bipolar. Trastorno esquizoafectivo. Risperidona. Antipsicoticos larga duración. Adherencia.

INTRODUCTION

The natural course of the disease in many patients diagnosed of bipolar disorder (BD) and schizoaffective disorder (SD) is generally characterized by a risk of relapse and low rate of maintained recovery. The risk of recurrence at 5 years is approximately 73% in spite of conventional drug therapy.[1] This is even clearer in those patients who lack adequate adherence to treatment due to factors such as, for example, little or no disease awareness, predominance of relapses in manic phase, comorbidity with any personality disorder, toxic consumption, weak family support, severity of their symptoms, etc. (table 1).

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The prognosis in this group of patients is generally dismal and is characterized by frequent relapses and multiple hospitalizations.[2] In recent times, there has been increasingly more evidence that typical antipsychotics (AAs) such as risperidone, olanzapine, quetiapine and ziprasidone, are also effective in the treatment of manic symptoms. These antipsychotics seem to have mood stabilizing properties in bipolar and schizoaffective patients with the presence or not of commitment psychotic symptoms,[3] so that they are generally used during maintenance treatment.

Within the currently available group of AAs, oral risperidone received the approval of the Food and Drug Administration (FDA) in the year 2003 for treatment of acute mania episodes and mixed episodes associated with bipolar mania. Several studies have established its efficacy and safety in the treatment as monotherapy or in combination with mood stabilizers.[4-7] The presentation of long-acting risperidone opens up a new possibility for us regarding treatment in maintenance phase of bipolar and schizoaffective patients with specific difficulty for good therapeutic compliance.

Taking into consideration that one of the main causes of relapses in bipolar and schizoaffective patients is precisely treatment noncompliance, we think that a certain group of patients with these diagnoses and difficulty for good therapeutic compliance could be benefited by a long acting treatment that assures adequate administration of the drug. Some studies have demonstrated the efficacy and safety of long acting risperidone in bipolar patients.[8,3] Thus, the purpose of this open label, observational study was to provide more information on this subject.

The need for randomized and placebo-controlled studies to reach final conclusions is clear. However, some of the advantages of an open label, observational study such as this one are its greater similarity with clinical reality, greater time of follow-up and greater extension in regards to inclusion criteria. The present study has aimed to evaluate the efficacy, safety, tolerability and greater treatment adherence with long acting risperidone in the maintenance phase as monotherapy or in combination with some mood stabilizer in bipolar and schizophrenic patients.

METHODS

A total of 22 patients between 19 and 63 years of age were included in the present open label, observational study. All of the patients signed an informed consent to form a part of the study. Fourteen of them met diagnostic criteria for bipolar disorder 1 and 8 for schizophrenic disorder according to the DSM-IV-TR. The most outstanding characteristics of these types of patients were lack of treatment compliance and their frequent relapses that derived in the corresponding hospitalization. Table 2 shows the inclusion criteria used for admission to the study.

Table 1 Inclusion Criteria

1	Meet DSM – IV TR diagnostic criteria of bipolar disorder and/or schizoaffective disorder
2	Be over 18 years
3	Absence of severe physical disease
4	Presence of relapses due to poor therapeutic compliance
5	Signing of informed consent

Prior to initiating the study, all the patients except one were under treatment with some oral antipsychotic agent. Eight patients were receiving risperidone, 4 quetiapine, 3 amisulpride, 2 olanzapine, 2 haloperidol, 2 ziprasidone and 1 was not receiving any antipsychotics. During the baseline interview, 18 patients received 25 mg and 4 received 37.5 mg of intramuscular LAIR. The oral antipsychotic dose was slowly reduced over the 3 weeks following the baseline visit, so that all the patients only receive LAIR every 14 days and a mood stabilizer (except in two cases where they only received an antipsychotic drug) after week 4. Regarding the mood stabilizers, 9 patients received valproic acid, 8 lithium carbonate, 3 carbamazepine and 2 did not use any. All the patients received LAIR every 14 days intramuscularly for 40 weeks. The minimum dose used was 12.5 mg in one patient and the maximum was 75 mg, also in a single patient, each dose being established according to the symptoms and the response of each patient. Mean dose at the end of the study was 30.68 mg. The interviews were made on the day of the initiation of the study and then at weeks 2, 4, 8, 16, 24, 32 and 40. In order to evaluate the efficacy, the Young Mania Rating Scale (YMRS)[9] and the Hamilton Rating Scale for Depression (HAM-D)[10] were used as tools at baseline evaluation and at weeks 4, 16, 32 and 40. In addition, the Clinical Global Impression - Severity of Illness scale (CGI-S)[11] was used in the baseline evaluation and at weeks 2, 4, 16, 32 and 40 and the CGI - Efficacy (CGI-E) at weeks 2, 4, 8, 16, 32 and 40. The Udvalg Für Kliniske Undersogesler (UKU)[12] was used at weeks 2, 16, 32 and 40 to evaluate adverse effects.

Regarding the statistical analyses, Friedman's non-parametric tests for abnormal distribution variables was used. When the Friedman's test revealed significant changes, the Wilcoxon test with Bonferroni correction test was used, comparing posttreatment values (week 0 compared to week 40). For age, the Student's T parametric test for related samples was used. The value of $p < 0.05$ was considered significant. The data were processed with SPSS 12.0.

RESULTS

A total of 22 patients (11 men and 9 women) formed a part of the present study. One patient was excluded due to his difficulty to be able to come to the interviews in a time-

ly way. Average age of the 21 remaining patients was 36.71, the youngest being 19 years old and the oldest 63. Average weight was 79.71 in the first week and 79.95 at week 40, so that this mild increase was not significant (Student's T test for paired samples, p = 0.717) as can be seen in Figure 1.

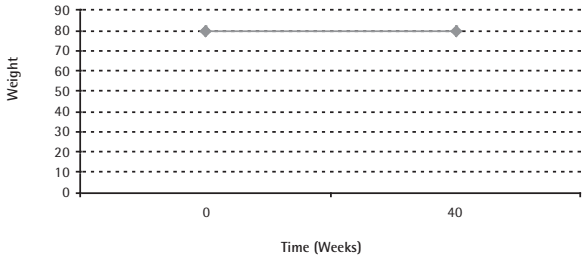

Figure 1 *Weight at onset and end of this study.*

The YMRS demonstrated a constant and significant reduction during the 40 weeks of this study in regards to efficacy (Friedman's test, p < 0.001; Wilcoxon, p < 0.001; Figure 2).

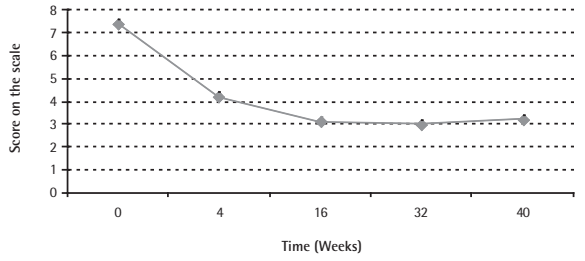

Figure 2 *YMRS mania or euphoria symptoms scale (Young Mania Rating Scale).*

No appearance of depressive symptoms during the follow-up time was observed. The HAM-D scale did not show a significant variation during the 40 weeks of the study, as can be observed in Figure 3 (Friedman's test, p = 0.779).

The CGI-S demonstrated a constant and significant reduction (Friedman's Test, p < 0.001; Wilcoxon, p < 0.001; Figure 4) while the CGI-E demonstrated an increase during the follow-up. However, when week 0 was compared with week 40, this increase was not significant (Friedman's test, p = 0.016; Wilcoxon, p = 0.124; Figure 5).

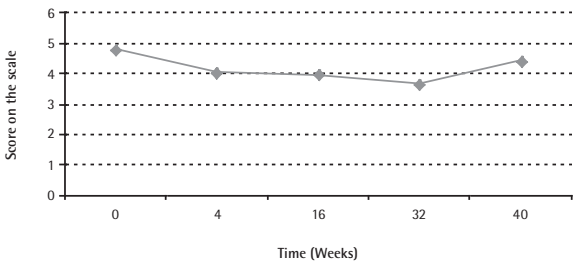

Figure 3 *Hamilton's depression rating scale.*

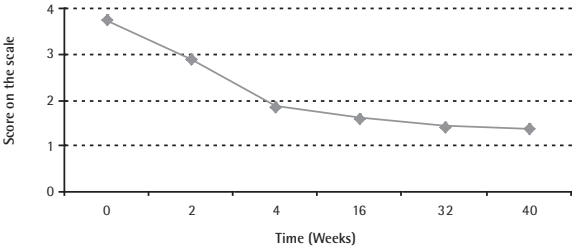

Figure 4 *Clinical Global Impressions Scale - Severity (CGI-S).*

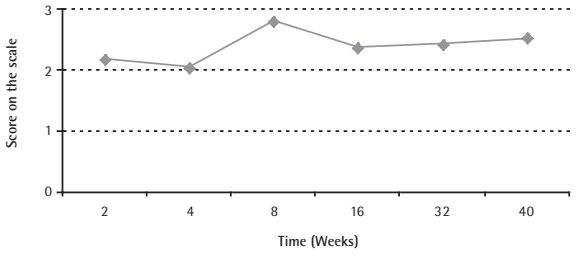

Figure 5 *Clinical Global Impressions Scale -Efficacy (CGI-E).*

The adverse effects scale (UKU) showed a constant reduction. However, the score of adverse effects is so low that the difference between score 1 and score 0 is not significant (Friedman's test, p = 0.108 (Figure 6).

DISCUSSION

By means of this open label, observational study and in accordance with our results, a clinical improvement could be seen in the combination of bipolar and schizoaffective patients, so that the YMRS scores have significantly de-

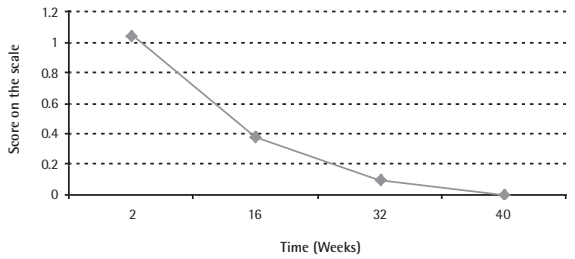

Figure 6 *Adverse effects scale (UKU).*

creased ($p < 0.001$) without the appearance of depressive symptoms as shown by the HAM-D scores ($p < 0.779$). Furthermore, the CGI-S scores were also statistically significantly decreased ($p < 0.001$) and there was no variation regarding weight between week 1 and week 40. In addition no relevant adverse effects appeared, as is observed in the UKU scale scores.

In a study carried out in the year 2007, Changsu Han et al.[3] demonstrated that LAIR could be useful to assure more adequate therapeutic compliance in a group of patients. We have been able to find some similarities with that study, such as, for example the fact that no potentially depressive symptoms related with the treatment appeared, reduction in the CGI-S scores, absence of significant adverse effects and good tolerability to the drug. In regards to the differences, the YMRS maintained low scores in the Changsu Han et al. study while the scores were significantly reduced in our case ($p < 0.001$). It is important to consider that when we initiated our study, the YMRS scores were greater in comparison to those obtained by the Korean-American group. It should also be stressed that our group of patients came from a program to care for bipolar patients that was attended by especially severe and complex patients, a reason why the severity of the symptoms may be greater. In addition, we consider the information on weight important since, as demonstrated, there was no significant variation (this also coinciding with the Changsu Han et al. study) between week 1 and week 40.

In accordance with our clinical experience, it is clear that there is a subpopulation of bipolar and schizoaffective patients with greater difficulty for treatment adherence in relationship to the rest of the patients. As we have previously mentioned, there are several factors that influence poor compliance in this patient group (considering the previously described, we believe that the principal benefit of using a long acting antipsychotic agent could be that of assuring adequate compliance of the drug in order to prevent frequent relapses and hospital admissions. Furthermore, we consider that another one of the benefits would be the safety and certainty to determine if a patient is adequately complying or not with the treatment since, if the patient does not come to the appointment, we will know immediately that the patients did not receive the corresponding dose of LAIR.[3]

It is important to mention that neurocognitive deterioration may also play a very important role in the capacity of certain patients to adequately adhere to treatment. Low or null awareness of disease could have a partial relationship with the neurocognitive deterioration presented by some patients.[13] Thus, larger studies would be needed to determine the grade of relationship existing between some mild cognitive dysfunctions and adequate therapeutic compliance.

Table 2 **Factors that participate in poor treatment adherence**

1	Little or null awareness of disease
2	Predominance of relapses and manic phase
3	Comorbidity with personality disorders
4	Consumption of toxic agents
5	Weak family support
6	Severity of the symptoms

The need for randomized and placebo-controlled studies to reach more solid conclusions is clear. However, we consider that the characteristics of such a study as this one approaches us a little more to the clinical reality of our daily work because, for example, the greater follow-up time and greater extension in regards to the inclusion criteria. Finally, our results show that LAIR could be useful in the management of complex schizoaffective and bipolar patients who have a special difficulty for adequate treatment adherence.

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