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## Report of three cases that received maintenance treatment with risperidone as a mood stabilizer

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### Abstract

**Introduction:** The current study is a short report of 3 cases of bipolar patients.

**Material and methods:** Three bipolar patients were prospectively followed up. All were partial responders to lithium therapy alone, and unresponsive to other therapies (anticonvulsants, antidepressants, typical antipsychotics, various combinations).

**Results:** All manifested complete remission of symptoms after combination therapy with lithium (plasma levels above 0.8 mEq/l) plus 1–3 mg of risperidone daily. The two of them are still free of symptomatology during the maintenance period for 28 and 38 months respectively. The third patient, after several months during which she was free of symptomatology discontinued lithium against the psychiatrist's advice and received only 3 mg of risperidone daily. For the next 15 months the patient was under risperidone monotherapy and free of symptomatology. She discontinued therapy to become pregnant, the illness recurred several times during pregnancy and after the delivery the patient restarted risperidone therapy. She was free of symptoms for the following 9 months until her last follow-up.

**Discussion:** The current study provides preliminary evidence concerning the long term efficacy of risperidone in the treatment of bipolar patients

### Introduction

The treatment of bipolar disorder includes the treatment of psychotic symptoms, of the manic, of the depressive phase and the long-term prophylactic treatment.

The efficacy of lithium in maintenance therapy is well established, while that of antiepileptic drugs or antidepressants is less well proved. The response rate to maintenance therapy is limited to nearly 50% of bipolar patients, depending on their clinical subtype [1].

The use of atypical antipsychotics has expanded beyond schizophrenia to include a variety of mental disorders [2,3]. Atypical antipsychotics are being increasingly used to control acute manic episodes, and data are emerging to support their mood-stabilizing and antidepressant properties. However, while their efficacy concerning the acute manic phase is well documented [4], sufficient data are lacking concerning their usefulness in the maintenance phase and no data exist beyond 6 months of follow-up.

The current study reports three cases of refractory bipolar I patients with a follow up of 28, 38 and 15 plus 9 months. Two of them received risperidone as adjunctive therapy to lithium and one as monotherapy. To our knowledge these are the longest reported follow-up cases in the literature.

They were the first ones recruited by the authors in the frame of a larger study. No selection bias concerning their (beneficial) response to treatment is present, and they underwent a full laboratory investigation including blood and biochemical tests and EEG.

### Case 1

The patient is a 31 years old unmarried bipolar I female. At the age of 20 she manifested a manic episode with auditory hallucinations, about 1 month duration. Five more manic episodes followed, with a seasonal pattern (spring). Depressive episodes followed manic ones (ratio 1:1) and the patient reported that she continuously felt depressed with only manic episodes braking depression.

During the first assessment (April 13, 2000), the patient had severe depression, and was under 600 mg lithium (0.6 mEq/Lt), 3 mg Risperidone, 60 mg mianserin and 225 mg clomipramine per os daily. Response to treatment was unsatisfactory. She was put on 900 mg lithium (Lithiofor), 1 mg Risperidone and 60 mg mianserin per os daily. Serum lithium levels rose to 1.00 mEq/Lt by April 29, 2000 response to treatment was compete.

During the next few months, the patient was free of symptomatology, although she reported mild subclinical 'misery'. She was unable to return to normal functioning. Lithium was gradually discontinued and topiramate was gradually titrated up to 400 mg per day. She also continued to receive 1 mg risperidone and 150 mg clomipramine per os daily was also added. By November 25, 2000 the patient reported complete recovery and lost 15 kilograms.

From December 18, 2000 to January 16, 2001 the patient manifested a manic episode and got hospitalized. During her hospitalization she was treated with the combination of haloperidol 5 mg, plus chlorpromazine HCl 25 mg, and biperiden 5 mg i.m. The episode remitted completely and the patient was released. She was put to lithium 1200 mg (0.9 mEq/Lt) and Risperidone 1 mg per os daily.

Since then the patient was stable until her most recent follow-up (April 5<sup>th</sup>, 2004), that is for 38 months. There are mild periods of 'misery' and 'happiness' that cannot be considered as clinically significant and remit spontaneously.

Conclusively, the patient achieved maximum response under lithium 1200 mg (0.9 mEq/Lt) and Risperidone 1 mg per os daily, but this maximum response took several months to appear.

### Case 2

The patient is a 25 years old unmarried bipolar I female patient with psychotic features, student of Architecture. At the age of 16 she experienced a psychotic-like episode. She was agitated, verbally and physically aggressive and had the delusional belief that her father was planning to kill her. She had neither hallucinations, nor euphoric mood. She was treated with haloperidol. The episode lasted for about 1.5 months. No maintenance treatment was prescribed.

At the age of 19 while facing important exams at school she developed severe depression. The episode remitted without treatment within weeks. Six months later she developed a typical manic episode. She received lithium (0.5–0.6 mEq/Lt). and risperidone and the duration was 2 months.

The patient was reluctant to follow the prescribed treatment and many times refused to take the medication. Soon she discontinued treatment completely.

Since then she suffered from recurrent episodes of mania lasting 1–2 months followed by depression which was lasting for several months. The rate was 1:1 and both phases were appearing once per year. She was prescribed with carbamazepine, lithium (0.5–0.6 mEq/Lt), oxcarbazepine and fluvoxamine with poor results. In spite of these difficulties she managed to enter the School of Architecture at the University.

The patient was first assessed in August 28, 2001 and reported unremitted depression for the past 8 months. She had given up her studies at the University. The patient was put under lithium (900 mg) plus risperidone 1 mg per os daily.

An important element of her medical file was a history of hyperprolactemia (successfully treated) and polycystic ovaries. By September 13, 2001 the patient's condition was unchanged but lithium level was 0.6 mEq/Lt. Lithium increased to 1200 mg per os daily.

In October 4, 2001, the patient reported that she felt much better and she has returned to her studies. Her lithium level was 0.8 mEq/Lt and serum prolactin levels were 408  $\mu$ U/ml (within the normal range). By November 12, 2001 the patient reported that her illness was in full remission. There was only a slight fatigue and concentration difficulty left.

The patient was stable until the most recent follow-up (April 4th, 2004) that is for about 28 months.

### Case 3

The patient is a 35 years old married bipolar I female patient with psychotic features.

At the age of 23 (August 12, 1991) she was hospitalized because of persecutory delusions without hallucinations. In the next couple of months two more similar episodes occurred and all lasted less than two weeks each. During this period she received various agents including haloperidol, thioridazine, chlorpromazine, sulphiride and others.

From 1991 to 1995 she was under psychoanalytically oriented psychotherapy and suffered from one more episode. In 1991 she graduated from University and soon after she started another course of studies. In summer 1995 she was caught cheating at the examinations at the University and a new similar episode occurred. However, after this episode, she manifested mood liability. Carbamazepine treatment was tried but discontinued because of adverse effects. Her mood became depressed, she was feeling fatigue, loss of interest, despair and deep pessimism. Medication changed to imipramine 75 mg and alprazolam 2 mg per os daily. Soon the symptoms partially remitted and the patient was released.

In 1996 she graduated from the Kindergarten Teachers' School.

In January 1997 she manifested a depressive episode. Her prolactin plasma levels were 2375  $\mu\text{U}/\text{ml}$  (normal values below 600  $\mu\text{U}/\text{L}$ ). Soon afterwards she manifested rapid shifts of mood from hyperthymic-agitated to depressed. Spontaneous remission occurred two weeks later.

During the following year, the patient suffered from chronic mild depression. She was put on 1200 mg lithium (0.90–1.00 mEq/Lt). Response was unsatisfactory.

Three months latter she was hospitalised again, because of a mild manic episode. Risperidone 2 mg per os daily was added. The patient manifested almost complete remission of symptoms one month later. The medication remained unchanged during the maintenance phase.

A year latter, still in full remission she got married. A few months latter she was appointed as a teacher at a high school and started working full time, on a regular basis.

After a year the patient discontinued any medication in an effort to stay pregnant. Soon afterwards a new manic episode appeared. After restarting medication, she responded within one week.

In January 15, 2000 the patient was readmitted to the hospital suffering from severe anxiety and restlessness. However no overt psychotic or manic symptomatology was present. She recovered completely within less than one week. However her prolactin levels were high again ( $>2000 \mu\text{U}/\text{L}$ ) and the patient also suffered from amenorrhoea (the rest of hormonal investigation and brain MRI were normal). Risperidone was substituted by olanzapine first and then by quetiapine, but both agents were discontinued because of adverse effects. The patient demanded to return to risperidone.

While being free of symptomatology, in June, 2001, and against the advice of her therapist, the patient gradually stopped taking lithium. She refused to continue receiving it because she felt that it caused sedation. He accepted to receive only 3 mg of risperidone daily.

Since then she was on risperidone monotherapy. She reported that her mind was clear, she was able to concentrate and felt that this is the most suitable therapy for her. No side effects were evident and her quality of life was the best in the last ten years.

Since then the patient had been stable until the follow-up visit of October 10<sup>th</sup>, 2002, for a total period of 18 months, and for 15 of them she was under risperidone monotherapy. Then the patient decided to discontinue medication in order to become pregnant (again against her therapist's advise). In the following months, she suffered from several but brief and mild manic episodes, but managed to become pregnant. She firmly refused to receive any kind of medication and along with her husband decided to keep the baby. She suffered from a further series of similar manic episodes and was hospitalized several times until the delivery, in July 2003. Then the patient started receiving 2 mg Risperidone daily and was free of symptoms since her last follow up in April 1<sup>st</sup>, 2004, that is for 9 months.

### Discussion

Atypical antipsychotics and especially risperidone block 5-HT<sub>2</sub> receptors which lead to an increase of dopamine activity in the frontal cortex, and thus they manifest antidepressant activity, while simultaneously they block D<sub>2</sub> activity in the mesolimbic system and thus manifesting an antimanic effect. The biochemical profile of risperidone suggests that it could serve as a mood stabilizer, preventing both manic and depressive phases of bipolar illness [5].

Double-blind and open-label studies support the usefulness of risperidone either alone or in combination with mood stabilizers in treating acute mania by [6]. Additionally it is suggested that approximately 20% more patients

respond by week 3 to the combination in comparison to a mood stabilizer alone [7].

However, all these studies concern acute treatment. The longest study concerning risperidone is a six-month open study [8]. Data concerning longer periods of time and maintenance treatment are lacking.

The current paper reports three cases of refractory bipolar I patients successfully treated with a combination of lithium and risperidone or risperidone alone, and followed-up for 28, 38 and 15 plus 9 months, which is the longest reported follow-up period in the literature until now.

Until today, only olanzapine has received official approval as monotherapy for the maintenance phase of bipolar illness. Our data suggest that further research is necessary to investigate the long term efficacy of the other atypical antipsychotics as mood stabilizers.

### Conflict of interest

All authors have received funding by Janssen Pharmaceuticals which is the manufacturer of Risperdal (risperidone), Eli Lilly, Sanofi-Synthelabo and AstraZeneca to attend several conferences.

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