Prevention of relapses in the bipolar I disorder: a comparative study between quetiapine monotherapy vs. quetiapine-valproate combined therapy

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Abstract: - Although bipolar disorder is one of the most devastating of all psychiatric disorders in terms of risk for suicide, need for hospitalization, and suffering, the available pharmacologic agents for its treatment, until relatively recently, have been quite limited. Although some estimates suggest that the lifetime prevalence of bipolar disorder in the world wide is between 1% and 1.5%, this rate would be higher if patients with bipolar spectrum disorders beyond bipolar I and II disorder were included. The public health importance of this disease is heightened by the high rate of suicides and the high economic toll it can take, including lost work days and cost of care, as well as poor financial decision-making characteristics of the manic phase of the illness [1]. We tried to evaluate whether quetiapine monotherapy reduces the rate of relapse, compared with combined therapy quetiqpine-valproate in patients with bipolar I disorder.

Key-Words: - relapse, bipolar disorder, quetiapine, valproate

1. Introduction

Although the efficiency of the quetiapine treatment has been scientifically documented in many clinical research studies, there are still insufficient data regarding the long-term efficacy in preventing the relapses in the bipolar disorders. The prospective naturalist studies have reported a 44% relapse rate in the first year after a mood episode and a 75-85% relapse rate in the next 5 years [2, 3]. For almost 30 years, Lithium was the basic treatment for the prevention of the mood episodes relapse. Lithium is the most researched mood-stabilizer; it's efficacy is recognized for the prophylactic treatment of the bipolar disorder. Other therapeutic alternatives are: valproate, lamotrigine, carbamazepine and antipsychotics. A number of studies have demonstrated that quetiapine is effective in the treatment of acute mania. A double-blind, placebo-controlled trial comparing quetiapine (flexibly dosed up to 800 mg/day), haloperidol (up to 8 mg/day), and placebo in the treatment of acute mania demonstrated significant separation from placebo on YMRS scores for haloperidol as early as day 4, and for quetiapine starting at day 21 [4]. A second study, which pooled results from 2 separate monotherapy trials with quetiapine (up to 800 mg/day), demonstrate significant improvement as early as day 4 [5].

Our prospective observational study has compared the efficacy of the quetiapine monotherapy versus quetiapine- valproate associated therapy.

2. Method

The patients enrolled in our study were males and females aged 18 to 60 years, who gathered the DSM IV criteria for bipolar disorder- current episode manic or mixed, with at least 2 previous mood episodes. Patients with a history of ineffective quetiapine or valproate treatment were excluded from the study. Patients with a diagnostic of neoplasia, patients with an unstable medical condition or with a substance addiction were also excluded.

The study gathered 30 patients diagnosed with Bipolar I Disorder, who went into clinical remission by the following criteria:

(1) Syndromic remission

(a) Mania: all the A and B DSM IV criteria for current manic episode – mild gravity (≤3 on a 1 to 7 scale) and less than 3 B criteria with a "mild" scoring (3 on a 1 to 7 scale);

(b) Depression: all the A and B DSM IV criteria for current depressive episode – mild gravity (≤3 on a 1 to 7 scale) and less than 3 A criteria with a "mild" scoring (3 on a 1 to 7 scale).

(2) Symptomatologic remission

(a) Mania: total score ≤ 12 on the YMRS scale;

(b) Depression: total score ≤ 8 on the MADRS scale.

The study occurred between August 2007 and May 2009 in the clinical department of the Psychiatry and Neurology Hospital of Brasov. The patients who went into clinical remission continued the support treatment with either quetiapine monotherapy or quetiapine- valproate associated therapy on a 1:1 ratio. The examination of patients was made during a 12 months period through 12 visits. The scales used in this study were the CGI, YMRS, MADRS, SAS, BARS and AIMS. The eligible subjects received a treatment with Quetiapine 300-800 mg daily dosage and Valproate 300-1800 mg daily dosage.

3. Results

As illustrated by the table below, the study revealed no significant differences concerning the time to relapse between the monotherapy group and the associated therapy group. The proportion of subjects that completed the study was practically similar in the two groups.

Table 1. Groups' characteristics

Characteristics	**Quetiapine (N=14)**		**Quetiapine-Valproate (N=16)**	
	N	**%**	**N**	**%**
Males	6	42,8	8	43,7
Females	7	57,2	9	56,3
Average quetiapine dosage (mg)	557,1		462,7	
Average valproate dosage (mg)	0		1218,7	
Average age (years)	43,2		41,6	
Average debut age (years)	23		25	
Duration of the index episode (days)	58,3		57,6	
Average duration to symptomatologic relapse (days)	45,3		70	
Mania	59		78	
Mixed	22		47	
Depression	55		85	
Average duration to syndromic relapse (days)	90		104	
Mania	70		90	
Mixed	85		100	
Depression	115		122	
Number of patients who completed the study	6	42,8	7	43,7
Males	2	33,3	3	42,8
Females	4	66.7	4	57,1

Table 2. The mood episode relapse risk according to the type of treatment

The type of relapse	**Quetiapine (N=14)**		**Quetiapine-Valproate (N=16)**	
	N	**%**	**N**	**%**
(1)Symptomatologic relapse	4	28,5	4	25
Mania	2	50	1	25
Mixed	1	25	1	25
Depression	1	25	2	50
(2)Syndromic relapse	9	57,1	9	56,25
Mania	5	62.5	5	55.5
Mixed	1	12.5	2	22.25
Depression	2	25	2	22.25

1) A total score ≥15 on the YMRS or MADRS scale
2) DSM IV TR criteria are met for a manic, mixed or depressed episode.

Table3. Adverse effects

Adverse effects	Quetiapine (N=14)		Quetiapine -Valproate (N=16)	
	N	%	N	%
Depression	3	21,4	4	25
Somnolence	4	28,5	4	25
Weight gain	2	14,2	3	18,7
Anxiety	2	14,2	3	18,7
Tremor	2	14,2	2	12,5
Asthenia	1	7,1	2	12,5
Constipation	2	14,5	3	18,7

The adverse effects of the medication have not determined the patients to discontinue the study, as they were of mild to moderate intensity. Somnolence and constipation are common adverse effects attributed to quetiapine.

4. Conclusions

Our study has investigated the potential of an atypical antipsychotic administered as a monotherapy, compared to the combined treatment with antipsychotic-valproate, in preventing relapses in the bipolar I disorder. The quetiapine monotherapy has shown no statistical difference, according to the DSM IV criteria, concerning the syndromic relapse, compared to the quetiapine-valproate associated therapy, but it has proven to be inferior in the case of symptomatologic relapse. We

conclude the necessity of a maintenance treatment in the bipolar disorder that associates a second generation antipsychotic and a mood stabilizer.

Despite the advances in the management of acute mania, the treatment of bipolar depression remains a formidable challenge. There is increasing evidence that the largest part of the disability of bipolar disorder stems from the manic phase of the illness [6]. Patients were symptomatically ill approximately 47% of the time over the 12-year period they were followed, spending nearly 3-fold more time experiencing syndromal or subsyndromal manic symptoms as compared with depressive symptoms [7,8]. Currently, we have a clear demonstration of the efficacy of the atypical antipsychotics, with quetiapine and the quetiapine/valproate combination, in the treatment of bipolar disorder.

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