THE IMPORTANCE OF ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF BIPOLAR DISORDER

DOCTORAL DISSERTATION - ABSTRACT

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Craiova
2010
I. General Part

The bipolar disorder is part of the category of mood disorders, subsequently reframed as manic-depressive psychosis and then further as manic-depressive disorder. It is a chronic condition in which patients experiment manic or hypo-manic episodes and depression with a relative mood stability between episodes. It is associated with cognitive difficulties and behavioral disorders, and in severe cases patients may also show psychotic symptoms. It represents the third cause for mortality among the young population aged between 15-24 years, 25% of the bipolar patients have at least one suicidal attempt during their lifetime (10). At the same time it represents the sixth cause for disability among the population aged 15-44 years and the fourth cause for disability among the neuro-psychic disorders (27).

The severity of the disease is highlighted by psychiatric and somatic comorbidities:

- The substance abuse is associated with the bipolar disorder in 60% of cases (15); 46% of bipolar patients have an alcohol addiction, and 40% have an abusive consumption or drug addiction (7);
- Anxiety disorders: panic disorder, social phobia;
- Post-traumatic stress disorder;
- Obsessive – compulsive disorder;
- Impulse control disorders: gambling, kleptomania;
- Attention deficit and hyper-activity, associated in 11% of the bipolar children (7);
- Cardiovascular diseases - 44% of the bipolar patients have coronary decisions and two thirds are obese while one third suffers from high blood pressure (9);
- Diabetes is presents in 26% of the bipolar patients (16).

These comorbidities, together with the social and economic implications, increase the direct and indirect costs of the disorder. If in 1985, in the United States, the total costs related to bipolar disorder were estimated at 20.8 billion dollars and in 1990 at 30.4 billion dollars, these costs have increased in 1991 to 45 billion dollars, out of which 84.5% represent indirect expenses (37.8% due to incapacity to work, 6.7% illness pensions, 6.7% costs due to institutionalization, 17.8% suicide related costs and 13.3% care costs) (17; 28). The costs for a manic episode amount to 11.720 dollars in the US, for a treatment resistant case they amount to 624.785 dollars and the costs for newly diagnosed cases during one year is estimated at 24 billion dollars (2). In the United Kingdom the direct costs for the treatment of the bipolar disorder amount to 2 billion per year or 6900 pounds per person, while the indirect costs due to work incapacity amount to 1.510 million pounds (5).

The biologic treatment is essential in the management of the bipolar disorder, with a decisive influence in the evolution of the disorder. The medical treatment is represented by mood stabilizers, conventional and atypical antipsychotics, antidepressants. Mood stabilizers were for a long time the first line in the treatment of the bipolar disorder, but currently these tend to be replaced by atypical antipsychotics. Atypical antipsychotics represent an efficient alternative both in the treatment of acute episodes (depressive, manic or mixed) and in the maintenance treatment (6).
The current dissertation attempts to evaluate the weight of the atypical antipsychotics in succeeding to improve the disorder evolution in reducing the frequency and severity of recurrences, with positive consequences on the social impact, on the direct and indirect costs, in comparison with conventional antipsychotics.

II. Objectives and method of the study

Main objective
- Evaluation of long term evolution of patients with bipolar disorder type I, treated with conventional and atypical antipsychotics, compared with those treated only with atypical antipsychotics.

Secondary objective
- Research of the relationship between individual characteristics and the typology of affective episodes within each lot.

The study was done retrospectively on a lot of patients (N=100) with bipolar disorder type I, registered in the records of the Mental Health Centre (MHC) Craiova, in the interval 1990-2009.

Recorded data
- Gender
- Age
- Residence environment
- Education level
- Couple relationship or family support
- Occupational status
- Debut age
- Number, type and duration of affective episodes
- Number of hospitalization days
- Type of psychotropic treatment: conventional (AC) or atypical (AA) antipsychotics
- Associated treatments: mood stabilizers or antidepressants.

Instruments
- NIMH Life Chart for Recurrent Affective Illness
- SCID-I (Research Version) Structured Clinical Interview for DSM Disorders

Work groups
- Lot A – n₁ = 50 patients with bipolar disorder type I, registered in the MHC Craiova in 2009, taking treatment with conventional antipsychotics and then with atypical antipsychotics for periods between 54 and 240 months.
- Lot B – n₂ = 50 patients with bipolar disorder type I, registered in the MHC Craiova in 2009, taking treatment from debut only with atypical antipsychotics, for periods between 12 and 120 months.

Inclusion criteria:
- Diagnosis of bipolar disorder type I according to DSM IV TR criteria, with at least one affective, manic or mixed episode with or without psychotic elements, congruent or incongruent with mood;
- Residence in Dolj county;
- Acceptance for participation (informed consent);
- Registration in records in the interval 1989-2008 and existence in records at the end of the period;
- Completeness of data.
Exclusion criteria:

- Refusal to participate in the study (informed refusal of consent);
- Reduced compliance, without constant maintenance treatment, but just sporadic, during acute episodes;
- Diagnosis of personality disorder on axis II DSM IV TR.

III. Results and discussions

Within lot B, the average of affective episodes per year was 0.77, lower than the average of affective episodes per year for the entire treatment period in lot A - 1.1, but also than the average of affective episodes per year for the treatment with conventional antipsychotics of patients in lot A - 1.38 episodes and compared with the average of affective episodes per year for the treatment with atypical antipsychotics of patients in lot A - 0.83 episodes.

The therapy for bipolar patients with atypical antipsychotics from the debut of the disorder determined the reduction of affective recurrences with 44.2%, compared with the treatment with conventional antipsychotics, and the change of conventional with atypical antipsychotics determined also a decrease in the number of affective episodes by 39.85%. Globally the recurrence in lot B with 30% lower compared with lot A. The decrease in affective recurrences, in the case of atypical antipsychotics, is determined by the increase in the relapse time of good quality remissions, compared with conventional antipsychotics, allowing for a complete social and professional and family reintegration, a determining factor in the reduction of affective recurrences. The superiority of atypical antipsychotics in the reduction of affective recurrences, including the forms of bipolar disorder with rapid cycle and resistant, is in accordance with the results of the clinical studies (1, 4, 5, 8, 12, 20, 24, 25, 26).

Regarding the average of the depressive episodes per year, in lot B this was 0.27 episodes/year, lower than the average of the number of depressive episodes per year for the entire treatment period for the patients in lot A, 0.4 episodes/year, but also than the average of the number of depressive episodes per year for the period of treatment with conventional antipsychotics in lot A, 0.44 episodes/year and compared with the average of the number of depressive episodes per year for the period of treatment with atypical antipsychotics from lot A 0.33 episodes/year.

Consequently, the treatment with atypical antipsychotics on the disorder debut determines a recurrence of depressive episodes 38.6% lower than with conventional antipsychotics, and the change of conventional with atypical determines the reduction of depressive recurrences by 25%. Globally, the recurrence of depressive episodes was 32.5% lower in lot B, compared with lot A. This result is in accordance with the specialised literature; the conventional antipsychotics can generate depression, increasing the number of depressive recurrences, while the atypical antipsychotics have an antidepressant effect through their mood stabilizing action, determining the reduction of depressive recurrences (3, 19, 23).

The average of the number of hypomanic episodes/year in lot B was 0.32 episodes/year, lower than the average number of hypomanic episodes for the entire treatment period on the patients in lot A, 0.38 episodes/year, but also lower than the average number of manic-hypomanic episodes/year for the treatment period with conventional antipsychotics for patients in lot A, 0.57 episodes/year and higher than the average number of manic-hypomanic episodes/year for the treatment period with atypical antipsychotics of patients in lot A, 0.23 episodes/year.

Consequently, the treatment with atypical antipsychotics from the disorder debut determines a recurrence of the manic-hypomanic episodes 43.86% lower than conventional antipsychotics, and the change of conventional with antipsychotic determines the decrease in manic-hypomanic recurrences by 59.65%. Globally, the recurrence of manic-hypomanic episodes was 15.79% lower in lot B, compared with lot A. As a paradox, the recurrence of manic-hypomanic episodes in the treatment period with AA in lot A was 28.15% lower than in the AA treatment period in lot B.

The anti-manic effect of atypical antipsychotic is thus very well emphasized by the decrease in the number of manic recurrences on changing from conventional to atypical antipsychotic, in lot A.
This result is in accordance with the clinical studies that proved the superior efficacy of atypical antipsychotics in the treatment of mania acute phase, compared with the conventional ones (11, 13, 14, 18, 21, 22, 26).

Within lot B, the average in the number of mixed mood episodes per year was 0.19/year, lower than the average number of mixed mood episodes/year for the entire treatment period for patients in lot A, 0.31/year, but also lower than the average of mixed mood episodes/year for the treatment period with conventional antipsychotics, 0.36/year and the average of mixed mood episodes/year for the treatment period with atypical antipsychotics in the patients from lot A – 0.27/year.

The treatment with atypical antipsychotics on disorder debut determines a mixed episodes recurrence that is 47.22% lower than with conventional antipsychotics, and the change from conventional to atypical determines the reduction of mixed recurrences by 25%. Globally the recurrence of mixed episodes was 38.7% lower in lot B, compared with lot A. As in the case of manic-hypomanic episodes, the superior efficacy of atypical antipsychotics compared with conventional ones is in accordance with the results from clinical studies (11, 13, 14, 18, 21, 22, 26).

The average of disease months per year in lot B was 1.33, lower than the average of disease months/year for the entire treatment period for patients in lot A, 2.2 months/year, and lower than the average of disease months/year for the treatment period with conventional antipsychotics for patients in lot A, 2.91 months/year and the average of disease months/year for the treatment period with atypical antipsychotics for patients in lot A, 1.45 months/year.

The treatment with atypical antipsychotics on disorder debut determines a decrease in the duration of affective episodes by 54.3% compared with the conventional antipsychotics treatment, and the switch from conventional to atypical determines a decrease in the duration of affective episodes by 50.17%. Globally, the duration of affective episodes was 39.54% shorter in lot B compared with lot A. This result is in accordance with the clinical studies (8, 11, 13, 14, 18, 20, 21, 22, 25) and it is explained through the mood stabilizing action of atypical antipsychotics, which unlike the conventional ones, don’t allow for oscillations in the sense of mood elevation or depression. The more rapid effect of atypical is due to a smaller quantity of side effects: sedation, concentration difficulties, extra-pyramidal phenomena, which allow for a faster and better quality social-professional and family reinsertion.

Within lot B, the average of depression months/year was 0.49 months, lower than the average of depression months/year for the entire treatment period of patients in lot A – 0.81 months, but also than the average of depression months/year for the treatment period with conventional antipsychotics of patients in lot A – 0.93 months and compared with the average of depression months/year for the treatment period with atypical antipsychotics for patients in lot A – 0.81 months (Fig. 41).

The treatment with atypical antipsychotics in the disorder debut determines a decrease in the duration of depressive episodes by 47.3% compared with the conventional antipsychotic treatment, and the switch conventional – atypical determines the reduction of the depressive episodes duration by 38.7%. Globally, the duration of depressive episodes was 39.5% shorter in lot B compared with lot A. The results correspond with the data in the specialised literature based on clinical studies (3, 19).

In lot B the average of manic-hypomanic months/year was 0.52, smaller than the average of manic-hypomanic months/year for the entire treatment period for patients in lot A, 0.78 months/year, but also compared with average of manic-hypomanic months/year for the treatment period with conventional antipsychotics of patients in lot A, 1.24 months/year and higher than the average of manic-hypomanic months/year for the treatment period with atypical antipsychotics of patients in lot A, 0.38 months/year.

Consequently, the treatment with atypical antipsychotics on disorder debut determines a decrease in the duration of manic-hypomanic episodes by 58.06% compared with the conventional antipsychotic treatment, and the change from conventional to atypical determines the reduction in the duration of manic-hypomanic episodes by 69.35%. Globally, the duration of manic-hypomanic episodes was 33.3% shorter in lot B compared with lot A. The result corresponds with data from specialised literature based on clinical studies (11, 13, 14, 18, 21, 22, 26).
The average of months with mixed mood/year in lot B was 0.34, lower than the average of mixed mood months/year for the entire treatment period for patients in lot A, 0.64 months/year, but also than the average of mixed mood months/year for the treatment period with conventional antipsychotic for patients in lot A, 0.77 months/year and lower than the average of mixed mood months/year for the treatment period with atypical antipsychotic for patients in lot A, 0.5 months/year.

The treatment with atypical antipsychotics on disorder debut determines a decrease in the duration of mixed episodes by 55.84% compared with conventional antipsychotics treatment, and the switch from conventional to atypical determines the reduction in the mixed episodes duration by 35.06%. Globally, the duration of mixed episodes was 46.87% shorter in lot B, compared with lot A. The result is in accordance with data from specialised literature based on clinical studies (11, 13, 14, 18, 21, 22, 26).

Within lot B, the average number of hospitalization days/year was 1.33 days/year, lower than the average of hospitalization days/year for the entire treatment period for patients in lot A, 2.2 days/year, but also compared with the average of hospitalization days/year for the treatment period with conventional antipsychotics for patients in lot A, 2.91 days/year and compared with the average of hospitalization days/year for the treatment period with atypical antipsychotics for patients in lot A, 1.45 days/year.

The treatment with atypical antipsychotics on disorder debut determines a decrease in the duration of hospitalization by 59.53% compared with conventional antipsychotics treatment, and the switch from conventional to atypical determines the reduction in hospitalization by 51.72%. Globally, the duration of hospitalization was 43.1% shorter in lot B compared with lot A. The faster effect of atypical on mood stabilization, the reduced number of side effects: sedation, concentration difficulties, extra-pyramidal phenomena, determine the reduced duration or even need for hospitalization and allow for a faster and better quality social-professional and family reinsertion. Through the significant reduction in hospitalization duration, the efficiency – cost rate is increased in the favour of atypical antipsychotics, the hospitalization cost and temporary work incapacity having the largest weight in the costs for treatment of bipolar disorder (2, 5, 17, 28).
IV. Conclusions

1. The treatment with atypical antipsychotics (Lot B), compared with the treatment with conventional antipsychotics followed by treatment with atypical antipsychotics (Lot A), in the patients with bipolar disorder type I, has reduced significantly the statistical average number of episodes/year by 30%, and the disease duration, expressed in the average number of disease months per year by 39.5%.

2. The decrease in the number of episodes, statistically significant, was at 32.5% for the depressive, and 38.7% for the mixed ones, while the reduction in disease duration meant 39.5% for depression, 33.3% for mania and 46.9% for mixed episodes.

3. By direct comparison between the treatment periods with conventional and atypical antipsychotics on debut, the result obtained is a statistically significant reduction in the relapses/recurrences by 44.22%, meaning 38.6% for depressive episodes, 43.9% for manic episodes and 47.22% for mixed episodes.

4. The change in treatment from conventional to atypical antipsychotics in the evolution of lot A determined a significant decrease in duration by 50.2%, respectively 38.7% for depression, 69.3% for mania and 35.06% for mixed episodes.

5. The average number of hospitalization days/year recorded in the patients treated from debut with atypical antipsychotics (Lot B) was by 43.1%, statistically significant, lower than for the patients treated initially with conventional antipsychotics and then with atypical antipsychotics (Lot A).

6. The switch from treatment with conventional antipsychotics to treatment with atypical antipsychotics determined in the evolution of lot A a significant reduction of 51.7% in the average number of hospitalization days.

7. The prevalence of depressive and mixed episodes is directly and significantly correlated with the debut age in the bipolar disorder type I.

8. The age of the patients is directly correlated with the number and duration of depressive episodes only in the patients treated with conventional antipsychotics and then with atypical antipsychotics (Lot A).

9. The higher education level is closely correlated statistically significant – 99.8%, with a lower number of affective episodes, especially depressive – 95.1%.

10. The stable couple relationship is closely correlated statistically significant – 97.8%, with a lower number of affective episodes.

11. The use of novel atypical antipsychotics represents a therapeutic option with highly superior efficacy for bipolar disorder type I both for the acute periods and for the maintenance and prevention of recurrences.

12. Ensuring early and wide access to atypical antipsychotics for the patients with bipolar disorder type I can produce an important improvement in their life quality, but also a decrease in direct and indirect costs, on medium and long term.
V. References

15. NIMH. Bipolar disorder research at the National Institute of Mental Health (2000). NIH publication number 00-4502.


