THE UNIVERSITY OF MEDICINE AND PHARMACY OF TÎRGU-MUREŞ
DOCTORAL SCHOOL

ABSTRACT OF Phd THESIS:

AUGMENTATION STRATEGIES FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER WITH AN INADEQUATE RESPONSE TO ANTIDEPRESSANT MONOTHERAPY

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Introduction: Despite numerous classes of antidepressants currently available, the rates of remission after the first antidepressant treatment are small (less than 30%) and inadequate response is frequently found [1]. This inadequate response to treatment is associated with an increased risk of relapse [2, 3] and a significant impairment of social and occupational functioning [4]. Numerous studies have shown that atypical antipsychotics have an antidepressant effect, in addition to the antipsychotic effect.

Purpose: The first part of our research - Study 1 aims to evaluate therapeutic options of psychiatrists in Romania and France, about depression in general and depression with inadequate response to monotherapy in particular. Purpose of the study 2 of the thesis is to evaluate the efficacy and safety of quetiapine XR, used as augmentation therapy in patients with incomplete response to antidepressive monotherapy with sertraline, paroxetine or escitalopram.

Methods: Evaluation of therapeutic options of Romanian and French psychiatrists was based on a questionnaire with 18 items, designed by team members. Efficacy and safety of quetiapine XR as augmentation therapy involves a prospective, open, randomized, monotherapy controlled study, with a total of 70 patients from Clinica Psihiatrie I Tirgu Mures, diagnosed with Major Depressive Disorder, Major Depressive Episode, single or recurrent, without psychotic features. The research was conducted from July 2011 to July 2012. Patients were eligible to participate if they showed a HAM- D17 score ≥ 14 after 4-6 weeks of treatment with paroxetine 20-40 mg, sertraline 50-100 mg or escitalopram 10-20 mg daily. Patients were equally randomized to receive quetiapine XR 150 mg / day plus SSRI (group A) or to continue the same antidepressant monotherapy (group B) for 8 weeks. Efficacy was assessed with the HAM- D_{17} , and safety was based on monitoring of vital signs, weight, blood pressure and heart rate, physical examination of the patient,

monitoring and treatment of adverse events, including extrapyramidal signs, at each of the 5 ratings successive (0,1,2,4,8 weeks). Remission rate was evaluated (HAM- D_{17}<7) after 8 weeks of treatment, for each lot. For statistical interpretation of the data we used SPSS -20 for Windows and GraphPad Prism version 6.

Results *Study 1:* The questionnaire was completed by 58 Romanian respondents 27 French respondents. SSRI and SNRI antidepressants are the most commonly used, both in Romania and France. Therapeutic options for first depressive episode are very similar, with one exception - SNRI are most commonly used by psychiatrists in France (27%) compared with Romania (17%). Regarding treatment option for recurrent depression, the percentages obtained are quite similar except for the use of tricyclic antidepressants, much lower in Romania (3%) compared with France (23%). The average duration of maintenance treatment in patients who achieved remission after monotherapy is 7.5 months for our country and 9.2 months for French respondents. Regarding augmentation therapy in first episode depression and in recurrent depression respectively, the results show that the highest weight has augmentation with atypical antipsychotics (36% and 46%), followed by augmentation with mood stabilizers (32% and 39%) and the combination of psychotherapy with drugs (26 % and 16 %). The average duration of antidepressant treatment administration before being considered inadequate response (incomplete response or total lack of response) is 3.7 weeks in Romania and 3.5 weeks in France. Proportion of inadequate response to antidepressant monotherapy for the first episode and recurrent depression is 32% and 48% in Romania and 39 % and 54 % for France. Regarding the efficacy of augmentation therapy in depression in Romania, quetiapine is considered the most effective (an average of 7.2 points out of 10) followed by olanzapine (5.8) and risperidone (2.4). Comparing outcomes with those obtained in France, it is noted that aripiprazole, olanzapine and risperidone have achieved approximately equal scores (6.1, 6.0 or 6.2), while the results obtained for quetiapine are smaller compared to our country (4.2 versus 7.2).

Study 2: 70 patients were included in the study, 35 in group A (22 women, Mage=41.73, 13 men, Mage=44.15) and 35 in group B (24 women, Mage=44.32, 11 men, Mage=43.15). All patients completed the study. In group A depression levels measured on the HAM - D_{17} decreased statistically significantly ($p<0.001$) from moderate ill (M=22.20) to slightly ill (M=8.00), close to remission. In group B, level of depression measured on the HAM - D_{17} decreased statistically significantly ($p<0.001$) from moderate ill (M=21.83) to slightly ill (M=10.57). The use of quetiapine XR as augmentation therapy to treatment with

paroxetine, sertraline and escitalopram in patients with MDD with an inadequate response to antidepressant monotherapy has been shown to be more effective compared with continuing monotherapy with any of the 3 SSRIs ($p<0.05$). At the end of the study, group A achieved a remission rate of 45.7%, significantly higher ($p<0.05$) compared with remission rate in group B - 22.8 %. Adverse effects during the study had a mild severity and did not require discontinuation of medication: somnolence in 34% in group A and 16% in group B, weight gain, 12% in group A and 6% in group B. Extrapyramidal symptoms (parkinsonism, akathisia, dystonia, dyskinesia) occurred in 6% of patients receiving quetiapine XR augmentation .

Conclusions: In the comparative study between Romania and France we have not observed significant differences in terms of treatment options: SSRI and SNRI are the classes of antidepressants most frequently used in depression; in the first depressive episode, SNRI are more frequently used by French psychiatrists compared with the Romanians; in recurrent depression, ADT are more commonly used by French psychiatrists compared to Romanians. In depression with inadequate response to antidepressant monotherapy, augmentation of response with atypical antipsychotics is the preferred method of the psychiatrists. The second part of the research showed that augmentation with quetiapine XR for MDD with an inadequate response to monotherapy with sertraline, paroxetine or escitalopram is an effective and safe method associated with a higher rate of remission for these patients.

Keywords: inadequate response, atypical antipsychotic, treatment options

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