Abstract of the PhD thesis:

THERAPEUTIC ACTUALITIES IN DEPRESSIVE MOOD DISORDERS ASSOCIATED WITH DIABETES MELLITUS

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Introduction. In medical clinical practice, we frequently encounter comorbidity between mental disorder and a disorder of organic nature, this type of disorder requires inter-disciplinary approach in order to achieve a quickly and efficient therapeutic response. There is currently little evidence of randomized controlled trials showing that treating only depression improves glycemic control in diabetes, even if treatment improves the mood state.

These concerns related to finding effective treatment methods for this comorbidity, have been long in the attention of international medical and scientific environment due to adverse implications on social life, family and work, which are severely affected in these patients.

Based on these premises, we investigated effective forms of treatment to have multiple and causal actions. Thus, we compared the effect of two substances, the first one from the SNRI Group sites, and the second from the group of SSRIs, to see which one of the two substances are effective in this disorder. Finally, we compared the quality of life of the patients regarding the two types of treatment.

We could say that although there is a high interest about this topic, the book is up to date because it compares the therapeutic efficacy of two antidepressants, and finally investigated the relationship between each type of care and also the quality of life.

Purpose. Investigating the relationship between depression and type 2 diabetes patients under the evaluation of the diabetologist, in collaboration with the psychiatrist to facilitate a correct diagnosis, early management of depressive disorders, followed by a customized prophylactic strategy to improve their quality of life.

Material and methods. This study is a prospective component conducted in 2011-2013. The research took place between 2011 - 2013,at MEDIAB Center in Targu Mures in collaboration with the specialists from the first Clinic of Psychiatry, on a total of 1486 patients diagnosticated with Type 2 diabetes.

To investigate the presence or the absence of depressive disorder in the first stage we have used the anxiety and depression scales. (Hospital Anxiety and Depression Scale) (Keedwell and Snaith, 1996). In the second stage the 256 patients who achieved scores over 11 at the HADS scale (Appendix 1) were referred to the outpatient clinic of Psychiatry. Following the specialist medical examination we have diagnosticated patients with major depressive disorder according to DSM criteria - IV -TR. To assess the severity of depression there was used the 17 -item Hamilton scale. In the third stage subjects were administered questionnaire for assessing quality of life, short form, for patients with diabetes, the requirement being to indicate their quality of life status for the last month. Also there were determined, both initially and at the end of the study, the levels of glycosylated hemoglobin (HbA1c) to monitor glycemic control. All patients had diabetes therapy or oral antidiabetic or insulin and oral antidiabetic led by diabetologist.

Results. Of the total of 1486 patients held in evidence by the diabetologist, diagnosed with type 2 diabetes, 256 patients, representing 14.7 % were diagnosed with depression associated with diabetes. The sample of patients suffering from depression and diabetes consists of 256 patients: 170 female and 86 male, the average age per patient group being Mage = 59.75 years. The group of patients with diabetes is composed of 256 patients: 178 female and 78 male, the general age per patient group being Mage = 61.39 years. In terms of gender backgrounds and the majority of patients from the both groups (depression and diabetes, diabetes) were women from urban areas. The data presented show that, in all patients in both groups depression diabetes associated with diabetes (men, women), the majority are retired. As antidiabetic treatment in patients with depression and diabetes group, 136 women,18 men, were on oral antidiabetic agents and 68 men and 34 women had both insulin and oral anti-diabetic treatment, and in the diabetic patients group,140 women 14 men were only on oral antidiabetics and 64 men and 38 women had both oral antidiabetic and insulin treatment. The 256 patients with comorbid depression diabetes were divided in two groups depending on antidepressant therapy recommended: duloxetine 60 mg and SSRI in equivalent dose. As antidepressant treatment for the patients with depression and diabetes group, 80 women, 48 men had duloxetine 60 mg and 90 women and 38 men were treated with SSRIs. Reported on test interpretation (HAM -D) in patients treated with duloxetine, we can say that the depression was moderately high into the Baseline phase before treatment (M = 23.60) and then decreased to the level of sub-

clinical in the third stage (M = 7.15) per whole group and in the group treated with SSRIs we can say that the depression level was moderate in the second phase (M = 19.35) and remained moderate in the third phase (M = 16.35) per whole group. Average scores on all quality of life questionnaire items stood at around 31.6 in the group who was selected to receive duloxetine and 30.5 in the group who was selected to receive SSRI, which means a significant reduction in quality of life. After one year the difference between the values obtained from QOL questionnaire, the group with duloxetine had an average of M = 8.42 and the group with SSRI an average of M = 13.25. Patients have been given daily doses of duloxetine and SSRIs during the study, and at the end of the study the HAM- D questionnaire was applied and have been reviewed the levels of glycosylated hemoglobin (HbA1c) for monitoring the glycemic control in response to antidepressant treatment. Analyzing the distribution of HbA1c values determined in patients in the duloxetine group in the initial phase, we obtained an average value around M = 9.02 and in the group treated with SSRI, M = 9. After one year of treatment with two antidepressants, in the duloxetine group the average value of HbA1c was M = 6.25 and in the group with SSRI M = 7.8.

Discussion. In a placebo- controlled study with notriptiline, Lustman has demonstrated the benefits of medication on the depressive symptoms but also noted a hyperglycemic effect on the tricyclic agent. In the same study by Lustman et al., Fluoxetine demonstrated a positive impact on depression and improvement on glycemic control although of the study was short. A recent randomized study of maintenance was performed on 152 patients, who recovered after the administration of sertraline, either sertraline or placebo for up to 52 weeks. In our study, depressive symptoms significantly decreased after the administration of antidepresive medication. The difference is higher in the group of patients treated with duloxetine versus the group of patients treated with SSRIs.

Studying the impact of depression on quality of life of patients with diabetes in Nigeria, Bawo OJ, et al, in 2010 found that major depression (MDD) was diagnosed in 30 % of patients. MDD was associated with lower scores on all items of the questionnaire of quality of life, WHOQOL - Bref, but without statistical significance on the items tied to physical health (p = 0.67), mental health (p = 0.59), medium (p = 0.70), or social relationships. The study we conducted showed that the prevalence of depression in the population with diabetes was 14.7%, a percentage that approaches the percentages described in the literature. The difference between the values obtained from QOL questionnaire in the group with Duloxetine where M = 8.42 and SD = 2.31 and the values obtained from QOL questionnaire in the group with SSRI where M = 13.25 and SD = 1.79, is 4.82. The confidence interval for the difference of 4.31 to 5.33 was 95%. The difference is important at the level of significance, where $p < 0.001$, such that treatment with duloxetine is superior to SSRIs in improving the quality of life in patients with depression associated with diabetes. The continuum in diabetes begins with insulin resistance, glucose intolerance and diabetes as a result of the inability of insulin secretion in type 2 diabetes. Generally, most patients with diabetes should have HbA1c levels below 7 %.

In a meta-analysis, whose objective was to highlight the association of depression with a low glycemic control in patients with type 1 or type 2 diabetes, Lustman et al, in 2000 [197] found that depression was significantly associated with hyperglycemia ($Z = 5.4$, $P < 0.0001$), treatment of depression increasing proportion of patients with optimal control of blood glucose at 41-58 %. The results that we have obtained have shown that depressive episode is associated with an imbalance in blood glucose translated with elevated HbA1C.Finally, as the depression lowers, the values of HbA1C normalize. In the group treated with duloxetine the depressive symptoms were submitted (M = 7.1), concomitent with the normalizing of the HbA1c values (M = 6.25) and for the group treated with SSRI the remission was incomplete, depressive symptoms had decreased slightly from the level (m = 16.4), and the HbA1c values ranged from an average of M = 7.8.

Conclusions. Duloxetine in doses of 60 mg reduced depression scores on the HAM –D scale which is considered superior to SSRI therapy, where the depression level dropped to moderate after 6 months, and was maintained after 1 year of treatment.

The treatment of depression is an important link to improve the quality of life of patients with diabetes and has reduced by more than 70 % of the scores of all items of the quality of life questionnaire, which means improved quality of life.

There is a statistically significant positive correlation demonstrating that depressive episode is associated with an imbalance in blood glucose in the investigated group.

Treatment of depressive symptoms with duloxetine has the effect of improving glycemic control translated by HbA1c levels below 7 %, and being superior to SSRI treatment.

Serotonin and noradrenaline re-uptake inhibitors (SNRI) should be the first line drugs in the treatment of depression in patients with diabetes.

Collaboration is necessary between the psychiatrist and diabetologist to detect comorbid affective disorders in patients with diabetes and to increase the quality of services provided to these patients.

Keywords: depression, quality of life, type 2 diabetes.