RISK FACTORS FOR EVOLUTION OF DEPRESSIVE DISORDER IN WOMEN

ABSTRACT

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Keywords: differentiated therapeutical response, incomplete remission, somatic and psychiatric comorbidities, cognitive deficit, unfavorable evolution.
INTRODUCTION

Interest in the study of depression in women is justified primarily on epidemiological data, which reveal a frequency of 2-3 times higher depressive disorder in women and an unfavorable evolution rate significantly higher than in men. [1] Furthermore, there is insufficient data to show the differences between men and women at genetic, neurobiological, neurobiochemical, cognitive and psychosocial levels, arguing once again the option for a differentiated study of depression in women and a psychopharmacological response anticipated by particularities of female brain. [2]

Depression in women has a specifically psychoendocrine vulnerability, objected by hyperactivity of HPA axis, coupled with a tendency to exaggerated response at stressors through hypercortisolemia. The same vulnerability is linked with hyperprolactinemia, more often as a consequence of therapy with certain antidepressants or antipsychotics. High levels of cortisol are related to vulnerability of neurobiological structures involved in cognition and depression (hippocampus, cingulate cortex, frontal cortex, amygdala), but is also an important factor in the occurrence of somatic comorbidities significantly altering prognosis and reducing the patient’s quality of life (obesity, cardiometabolic syndrome and cardiovascular risk, diabetes) that can be amplified by hyperprolactinemia. [3] Psychosocial factors act in a differentiated manner, resulting in a response to stress that generates hypercortisolemia, being the primary factor of female depression. Therefore the existence of psychotraumatical events in adolescence may be an important indicator for predicting the occurrence of depression in adult women. [46]

Women have particular clinical forms represented by premenstrual dysphoric syndrome, depression during pregnancy, postpartum blues, postpartum psychotic depression and perimenopausal depression. Depressive disorder in women is a risk factor for cognitive deficit and an indicator for prediction of Mild Cognitive Impairment (MCI). Evolution of depression in women is unfavorable, recurrence of first episode at 2 years after remission is 35%, and for the next 12 years by 60%. The high rate of recurrence is associated with an evolution of poor quality, the presence of somatic comorbidities and significant increase of suicidal tendency, this being the most serious complication of depressive disorder (15-20% of depressed commit suicide).

Therapeutic particularities of depression in women

- risk of obesity, diabetes mellitus and metabolic syndrome for both antidepressants and antipsychotics; [5]
- risk of cardiovascular disease, especially during perimenopausal or in connection with hyperprolactinemia;
- presence of hyperprolactinemia raises serious issues of risk for breast or genital cancer;
- higher risk of cognitive impairment than in male patients;
- high rate of recurrence due to vulnerability to stressors, reduced adherence and incomplete remission;
the need of multidisciplinary strict surveillance, especially in postpartum depression.

Outlining the epidemiological and etiopathogenical arguments involving neuropsychoeendocrine components, also the relationship between neuroprotection and neurogenesis that differs in male patients, depressive disorder in women shows a possible neurobiological model, supported by the high vulnerability of hippocampal and prefrontal structures [6] and reduced neuroprotection induced by antidepressant medication in animal model studies.

METHODOLOGY
Working hypothesis
The double prevalence of depressive disorder in women that in males [7] and unfavorable evolutionary trend constitutes a genuine public health problem. Based on these assumptions, the study of particularities of therapeutic response to antidepressant medication and their correlation with disease progression would allow us to reveal the evolutionary risk factors for depression in women, in order to improve therapeutic strategies in the field.

Objectives
1. Highlighting of clinical features of depressive disorder in women hospitalized in the Clinic of Psychiatry of Craiova and assessment of quality of the therapeutic response to antidepressant medication.
2. Identification of risk factors for unfavorable outcome in short term hospital treatment, and in medium – long term outpatients.

METHODOLOGICAL COORDINATES

N = 347 Lot – Retrospective
Based on the inclusion and exclusion criteria the N=347 Lot was formed of patients diagnosed with major depressive disorder or recurrent depressive disorder, hospitalized in 1st Psychiatric Clinic of Craiova between January 1st, 2005 and December 31st 2009.

N1 = 206 Lot – Prospective
Patients in N1 Lot were selected from the patients of N Lot that after discharged, were recorded and monitored in Craiova Mental Health Center until December 31st, 2011. Clinical evaluation was performed in a retrospective-prospective way, between January 1st 2012 and June 30th 2012, the minimal free interval being of 2 years (January 1st 2010 - December 31st 2011). At catamnesis were recorded 180 patients and 26 patients were confirmed dead based on medical documentation from Craiova Mental Health Center and Craiova Institute of Forensic Medicine.

Data sources: observation charts of patients hospitalized in 1st Psychiatry Clinic of Craiova for N Lot, psychological examinations and laboratory results for the N Lot; existing medical
documentation at Craiova Mental Health Center (records and books) for N1 Lot; medical documentation in Craiova Forensic Institute for deceased patients in N1 Lot.

**Indicators for N=347 Lot**: social-demographic (age, educational level, occupation, marital status, social-economic status), clinical (personality type, the presence/absence of psychotrauma in childhood (3-12 years), family history and female specific psychiatric history, pathological personal history, clinical diagnosis, nature of onset, precipitating conditions of onset, onset symptoms, time between real-apparent onset, number of hospitalizations for depressive disorder), indicators of treatment, therapeutic response and evolution of depressive disorder (class of antidepressants used, associated medication, therapeutical compliance, quality of response after first hospitalization, side effects of therapy, somatic disorders arising in the evolution of depressive disorder, HAM-D17 scores obtained at admission and discharge, GAFS and MMSE scores at discharge, quality of evolution).

**Indicators for N1=206 Lot**: class of antidepressants predominantly used (more than 75% of the treatment period), number of antidepressant and association with antipsychotics, adherence to treatment of maintenance, the number of readmissions after the first evaluation, psychiatric and somatic comorbidities occurred after the first evaluation, cognitive impairment – MMSE score, domestic violence, global evolution, survival assessment.

**Working tools**: Hamilton Depression Rating Scale (HAM-D17), Global Assessment of Functioning Scale (GAFS), Mini-Mental Scale Evaluation (MMSE).

**Statistical tools**: Microsoft Excel (Microsoft Corp., Redmond, WA, USA), along with XLSTAT for MS Excel (Addinsoft SARL, Paris, Franţa) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA). The obtained data were stored in Microsoft Excel files, then statistically processed to analyze the relationship between clinical and laboratory data of patients.

**RESULTS**
In the period of assessment, in 1st Psychiatry Clinic of Craiova there were a total of 7799 patients hospitalized, out of which 52% (4076 patients) were male patients and 48% (3723 patients) women. Depressive disorder has a share of 32% (2463 patients) representing one third of all admissions (7799 patients). It shows a significant large number of women (1477 cases – 60%) compared to men (986 cases – 40%), number that maintains the premises of differentiated clinical and therapeutical approach.

**Descriptive statistics of N=347 Lot**
The highest frequency of depression is shown between 40-49 years (53.0%) and 50-59 years (31.7%), in patients with medium educational level (66.9%), unemployed (28 %), working (27.7%) and public servant (24.2%), married (66.5%) with a low (55.0%) or medium economic level (42.7%). Clinical indicators showed depressive type personality predominance (63.4%), presence of psychotrauma in childhood (92.2%), positive family history for depression (75.8%) and female specific psychiatric history: perimenopausal depressive disorder (40.3%), premenstrual depressive disorder (26.5%) and depressive disorders during pregnancy (13.0%). The most common medical
conditions were: endocrine disorders (27.1%), cardiovascular disease (16.7%), diabetes mellitus and obesity (12.1%). Nosological classification of N=347 Lot was: major depressive episode (59.5%), recurrent depressive disorder (40.6%).

Insidious onset of depression was a significant majority (91.4%) with depressive-anxiety symptoms (64.0%), precipitated by psychotrauma during the past year (45.5%). Distance between real and apparent onset was over 3 years (41.8%), the majority of patients had between 2 and 5 admissions (80.1%). The main antidepressants group was the selective serotonin and norepinephrine reuptake inhibitors (SNRIs) (47.8%), followed by selective serotonin reuptake inhibitors (SSRIs) (27.4%). The main drugs associated with antidepressant therapy were the benzodiazepines (37.8%) and mood stabilizers (14.7%), antipsychotics were used only in 13.3% of cases. Good therapeutic compliance was present in 45.0%, results showing a high rate of incomplete remission (83.6%), while the drugs side effects were present in 43.0%. The presence of somatic disorders subsequent to depression diagnosis was recorded in 24.2% of patients.

HAM-D17 scores at admission showed the majority presence of average depressive episode (60.2%), while in hospital, HAM-D17 scores equivalent complete remission (HAM-17 <7) were present in 16.4%, the majority being between 8 and 13. At 69.7% of cases HAM-D17 scores were correlated with GAFS scores, that showed an important social dysfunction (63.1%). The minimum cognitive changes (MMSE) for 69.2% of patients are supporting the unfavorable development of depression in women (68, 3%).

**Descriptive statistics of N1=206 Lot**

In N1 Lot, the main classes of antidepressant substances used were the SSRIs (40.8%) and SNRIs (35.4%). Association between antidepressants and antipsychotics was present in 42.7% of cases. Good compliance of outpatient treatment was present in 36.9%, involving a high rate of treatment discontinuity (65.1%). N1 Lot patients (66.5%) had between 4-6 readmissions between the time of the first evaluation and the catamnesis. The major psychiatric comorbidities are represented by psychotic disorders (36.9%) and MCI (14.1%) while major somatic comorbidities were associated with obesity and cardiovascular diseases (19.9%) and hysterectomy (17.0%).

Evaluation of cognitive status of N1 Lot was done using the MMSE scores, being recorded minimal changes to 58.7% of patients and increased changes in 8.3% of cases. Domestic violence (physical, verbal, emotional) was present in 31.6%. Evaluation of global evolution in N1 Lot which was done under the clinical supervision of physician's from Craiova Mental Health Center and recorded in the source documents showed worsened evolution to 63.1% of patients. The survival rate (87.4%) highlights the major risk of death in the depression in women, due to pathologic causes (stroke, heart attack and cancer) (10.2%) or completed suicide (2, 4%). (Fig. 1)
DISCUSSIONS

Statistical analysis of N=347 Lot

There is a very strong association (chi square p=0.003<0.01, confidence level> 99%) between the positive evolution and the diagnosis of recurrent depressive disorder (TDR) at the expense of major depressive episode (TDM). Recurrence of depression is associated with incomplete remission, low quality treatment and compliance, while major depressive episode has benefits of better quality drug therapy and low rate of incomplete remission. Patients younger than 40 years have a good prognosis and those aged between 40 and 49 years has an unfavorable outcome, the percentage difference being highly significant. \( p=5.28 \times 10^{-11}, p<0.001 \) Psychotraumas in childhood influence the unfavorable evolution, the difference is highly statistically significant \( p=1.64 \times 10^{-08}, p <0.001 \).

Statistical analysis of the relationship between positive family history of psychiatric disorders in and quality of evolution highlights the fact that the majority of patients with unfavorable outcome had close relatives with depressive disorders, while over a third of patients with good prognosis had significant positive family history \( p=1.07 \times 10^{-26}, \text{Chi square} \ p~0 \). In the relationship between evolution and specifically feminine psychiatric history we found a highly significant relation \( p<0.001 \) between good prognosis and lack of such history (40.4%), respectively between unfavorable evolution and premenstrual dysphoric syndrome (31.7%).

Patients with unfavorable outcome of depressive disorder have a 3/1 ratio of hysterectomies and cancer at a rate of almost 8/1 compared to the patients with favorable evolution. The differences are highly statistically significant, the p-value resulting from the chi-square test was well below 0.001 \( p=1.9 \times 10^{-05} \). Complete remission is found almost exclusively in patients with favorable evolution, while patients with incomplete remission have a proportion of about 4/1 unfavorable evolution. \( p=1.40 \times 10^{-22}, \text{Chi square} \ p~0 \) The incomplete remission is associated with multiple recurrent episodes, the occurrence of somatic and psychiatric comorbidities, meanwhile cognitive impairment
was associated with decreased of neuroprotection and reduced compliance and adherence to treatment. [8]

In the N Lot, the high rate of incomplete remission raises the problem of drug therapy quality, pointing out the high frequency of serotonin antidepressants use (75.2%) and association with benzodiazepines (37.8%). During hospitalization, the antipsychotics were used in only 13.3% of patients, in direct correlation with the severity of depressive symptoms or behavioral disorders. Unfavorable evolution is noted mainly in patients receiving therapy with SNRIs, the difference from the patients with the same type of therapy, but with good evolution (58% vs. 24%) being highly statistically significant. We consider this statistical found an extremely important practical standpoint, since almost half of the study lot benefited from this type of medication. \( p = 6.39 \times 10^{-9} \)

**Statistical analysis of N1=206 Lot**

The statistical analysis of N1 Lot was targeted to highlight the risk factors with statistical value for unfavorable evolution in outpatient therapy in the Craiova Mental Health Center, during the free interval between first evaluation and catamnesis. Along ambulatory supervision, in the Craiova Mental Health Center therapeutic decision belonged exclusively to the physician. Evaluation of therapeutic response and remission quality and the presence of any somatic or psychiatric comorbidities were based on observations recorded in medical records belonging physician.

It was noted that patients who presented for treatment in the Craiova Mental Health Center, were mostly patients who received clinical psychiatric assessment with an unfavorable evolution. Thus, 70% of patients with unfavorable initial evolution have returned to Craiova Mental Health Center, as opposed to only 34.6% of patients who initially performed well. Non-responsives to catamnesis (141 patients – 40.6%) can be explained by the good evolution after the first assessment. We found a significant difference between the type of evolution and the number of readmissions after assessment in N Lot. \( \chi^2 = 0.031883 \). The high number of readmissions confirms the low quality of remissions with the presence of residual symptoms [9], favoring therapeutic resistance, and increasing cognitive impairment. [10] The relationship between the compliance and quality of evolution was highly significant \( \chi^2 = 0.001037 \) during outpatient treatment in the Craiova Mental Health Center, conducted after the first evaluation in N Lot.

Patients with associated antidepressant and antipsychotic medication have a trend of much lower quality than patients who had only antidepressant therapy, regardless of the combination of antidepressants used, the difference being highly significant. \( \chi^2 = 5.02 \times 10^{-6} \) There is a highly significant difference on overall evolution according to presence or absence of psychiatric comorbidities. If psychiatric comorbidities are present, then prognosis is worse for behavioral suicidal manifestations and cognitive dysfunction like MCI or Alzheimer’s Disease. The prognosis does not improve significantly in the case of psychotic disorders, including bipolar disorder. [11] \( \chi^2 = 1.5 \times 10^{-16} \)
We found significant differences in terms of the global evolution through somatic comorbidities, the negative prognosis being associated with stroke (100% negative) or metabolic syndrome (77.8%). *(Chi square p=0.045831)* Patients with important cognitive changes have evolved significantly below the minimal changes, the differences are also highly significant. *(Chi square p=0.0005)* The presence of domestic violence or suicide along close relatives is significantly associated with an unfavorable evolution of depressive disorder in women. *(Chi square p=0.007891)*

**Statistical correlations of N1=206 Lot**

The correlation between MMSE and GAFS scores *(r=0.490, p<0.001, GAFS=1.46xMMSE+2.99)* indicates that GAFS values tend to be higher with higher MMSE values, emphasizing that good social functioning is associated with preservation of cognitive function. Analysis of correlation between HAM-D17 and GAFS scores *(r=0.141, p<0.01, HAM-D17=0.028xGAFS+14.26)* indicates that HAM-D17 scores tend to be higher for lower GAFS scores. This phenomenon may be related to the quality of treatment administered in accordance to the severity of the depressive episode. Correlation between MMSE and HAM-D17 scores *(r=0.082, p>0.05)* does not indicate a significant direct link between the scores of the two working tools.

Highlighting the correlations between the therapeutic effect of various antidepressants and quality of cognition was realized by comparing averages MMSE scores from N1=206 Lot to the classes of antidepressant. *(ANOVA F=4.081, ANOVA p=0.00037, p<0.01)*. Procognitive effects showed by mirtazapine and novel antidepressants, that are listed in the *Other* category in the methodology (agomelatine, tianeptine), while SSRIs, SNRIs and trazodone had discognitive effects.

Statistical correlations between GAFS average scores and psychiatric comorbidities in N1 Lot revealed a high statistical significance *(ANOVA F=8.2636, p<0.001)*. GAFS high scores were strongly correlated with the absence of psychiatric comorbidities, while GAFS average scores between 23 and 29 could be correlated with the presence of suicidal behavior and psychotic and bipolar disorders.

**Comparison statistical elements between N and N1 lots**

We found a significant difference in terms of treatment followed by patients with depressive disorder [12] between the first evaluation and catamnësis, a finding that may be responsible for the high rate of somatic comorbidities and unfavorable global evolution. The differences between the two lots show the great variability of antidepressants by low compliance and limited effectiveness, clinical elements that diminish the quality of remission and increase the number of relapses and readmissions. Both incomplete remissions and frequent readmissions are risk factors for somatic and psychiatric comorbidities, and cognitive impairment. (Fig. 2)
It is noted a highly significant association among antipsychotic therapy and obesity with or without diabetes mellitus (DM) and cardiovascular disease (CV), confirming the risks of using these drugs in the treatment of depression. [13] Women patients without antipsychotic treatment have less frequent somatic comorbidities. Transient ischemic attack and stroke has an incidence of 6.8% in patients with antipsychotic treatment, severe side effects of this association is recognized by recent studies. (chi square p=0.003787) (Fig. 3)

Women's vulnerability to depression is significantly higher for somatic comorbidities, that lead to an unfavorable evolution while the depressive symptoms persist, requiring changes in the therapeutical strategies and augmenting antidepressant therapy with antipsychotic drugs.

Fig. 3 Association between antipsychotic medication and the risk of somatic in the two lots.
CONCLUSIONS

1. During 2005-2009, patients admitted with depressive disorder accounted for 32.0% of total admissions, respectively 24.2% men and 39.7% women.

2. Specific psychiatric history for depression in women were: perimenopausal depression (40.3%), premenstrual depression (26.5%), depression during pregnancy (13.0%). Out of the medical history, the more common were endocrine disorders (27.1%), cardiovascular diseases (16.7%) and diabetes mellitus (12.1%).

3. The main factors associated with hospitalization for depression in women were: psychotrauma in childhood (92.2%), insidious onset (91.4%), positive family history for depressive disorder (75.8%), average educational level (69, 9%), depressive and anxiety symptoms (64.0%), premorbid depressive personality (63.4%), married (62.5%), low social-economic level (55.0%) and the age between 40 and 49 years (53.0%).

4. The main classes of drugs used in hospital treatment were SNRIs - 47.8% SSRIs - 27.4%, in combination with benzodiazepines - 37.8 % and antipsychotics - 13.3%.

5. The main ambulatory treatments were SSRIs - 40.8% and SNRIs - 35.4%, associated with antipsychotics - 42.7%.

6. There is a significant difference (p<0.001) between the structure of the clinic and outpatient therapy.

7. Compliance to treatment was low, 55.0% in hospital and 38.9% in the outpatient, mainly due to the side effects of therapy.

8. Significantly associated factors with unfavorable short-term evolution (N=347 Lot) were: positive family history for psychiatric disorders (p~0), the presence of somatic comorbidities (p~0), the distance of less than three years between the real and apparent onset (p~0), incomplete remission (p=0), ages between 40 and 49 years (p<0.001), the presence of psychotrauma in childhood (p<0.001), psychiatric history specific to women (p<0.001), insidious onset (p<0.001), major psychotrauma during the last 12 months (p<0.001), more than 5 admissions from the first assessment (p<0.001), SNRIs antidepressant therapy (p<0.001), SSRIs and SNRIs associations (p<0.001) and correlation between HAM-D17 and GAFS at discharge (gamma coefficient= 0.663847, the maximum being 1).

9. Significantly associated factors with unfavorable medium and long term evolution (N1=206 Lot), highlighted the death rate (12.6% out of which 2.4% committed suicide) were: low quality compliance (p<0.001), discontinuation of treatment (p<0.001), the association of antipsychotic medication (p<0.001), the occurrence of psychiatric comorbidities (p<0.001), minimal changes in cognition (p<0.001), presence of domestic violence (p<0.01) and somatic comorbidities (p<0.05).
10. The relationship between GAFS (social functioning) and MMSE (cognitive impairment) scores is a significant indicator for prediction of unfavorable evolution ($p<0.001$).

11. The association between GAFS low scores and psychiatric comorbidities constitute a significant predictive indicator for cognitive impairment and suicide ($p<0.001$).

12. Given the fact that 70% of patients had an unfavorable evolution during the study, we believe that there are neurobiological, clinical and epidemiological arguments for a differentiated approach to depression in women, leading to specific therapeutical strategies, with beneficial effects on the evolution and prognosis of this disorder.

SELECTIVE REFERENCES