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The Diathesis-Stress Model in the First Severe Major Depressive Episode and Psycho-Pharmacotherapeutic Implications

SUMMARY OF THE DOCTORAL THESIS

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Introduction

Major Depressive Disorder (MDD) represents a significant global challenge, affecting millions of people and negatively impacting quality of life and productivity. Although its impact is well known, the causes remain insufficiently understood, involving a combination of genetic, psychological, and environmental factors.

This research focuses on the first severe depressive episode (FSDE), a pivotal moment for intervention and prevention, analyzing the interaction between genetic predispositions, negative life events, and perceived social support. The study explores the role of family history, stressors, and social support in the onset and trajectory of FSDE, using cross-sectional and longitudinal analysis methods.

The research aims to contribute to the development of personalized strategies for the prevention and treatment of MDD. Challenges include the difficulty of separating genetic influences from environmental ones in observational studies, the subjective variability of responses regarding life experiences and social support, and the lack of standardized tools at the national level. Future studies should delve deeper into these interactions and develop personalized interventions tailored to the genetic and psychosocial profiles of patients.

I. General Part

1.The Diathesis-Stress Model

The "diathesis-stress" model explains the onset of psychiatric or organic disorders through the interaction between genetic, biological, or psychological predispositions (diathesis) and exposure to external or internal stressors. Initially developed in the 19th century to understand psychiatric disorders, the model evolved through the "predisposition-excitation" theories, emphasizing the role of heredity and psychological trauma [2]. In the 1960s, the concept was extended to include mental disorders such as schizophrenia and depression, highlighting the interaction between cognitive diatheses and stress [2]. Later, it was adapted to incorporate the role of social support and resilience, acknowledging their importance in modulating the impact of stress [3]. Subsequent studies have demonstrated that social support reduces the negative impact of stressors and enhances an individual's ability to cope with challenges, which is essential in preventing clinical manifestations [4].

The integration of social support and coping strategies into the model has proven effective in alleviating depressive symptoms and improving the quality of life for affected individuals [4].

2. The Genetic Diathesis of Major Depressive Disorder

The vulnerability to developing MDD is determined by a complex combination of factors, with the genetic component playing a central role. These influences include hereditary predispositions and specific genetic variations that can affect how a person responds to stress and antidepressant treatments.

The heritability of MDD has been demonstrated in numerous twin studies, which show that MDD is moderately heritable, with an estimated heritability of about 37% (95% CI = 31-42%) [17]. Thus, approximately one-third of the variance in the risk of developing depression is attributed to genetic factors, with the concordance rate for depression being higher in monozygotic twins (46%) than in dizygotic twins (20%), suggesting a significant genetic influence [16].

Genome-wide association studies (GWAS) have identified numerous genetic loci associated with MDD, highlighting the genetic complexity of this condition. To date, 178 genetic risk loci have been identified, and over 200 candidate genes have been proposed. However, the identified genetic variants explain only a fraction of the estimated heritability, a phenomenon known as "missing heritability." This may be due to the influence of rare and low-frequency genetic variants, as well as complex gene-environment interactions [18].

A family history of depression is an important indirect indicator of genetic risk. Studies have shown that biological relatives of individuals with MDD have a significantly higher risk of developing the condition compared to adoptive relatives, suggesting a strong influence of genetic factors [22]. A longitudinal study showed that the offspring of depressed parents have a threefold higher risk of developing major depression (73.8% compared to 34.1% in the offspring of non-depressed parents) [23].

Among the candidate genes identified in biological theories of depression are those involved in the regulation of monoaminergic neurotransmitters, such as serotonin, dopamine, and norepinephrine, as well as those involved in the synthesis of receptors and

enzymatic systems. The monoaminergic hypothesis suggests that abnormalities in the regulation of these neurotransmitters are crucial for the onset of depression. The 5-HTTLPR polymorphism of the SLC6A4 gene, which encodes the serotonin transporter, has been among the most studied, indicating a link between the short allele (S) and increased stress reactivity [18].

The neurotrophic and neurogenesis theories highlight the role of brain-derived neurotrophic factor (BDNF), which is involved in both neurogenesis and neuronal support [54]. The decreased expression of BDNF in depressed patients and its normalization through antidepressant treatment suggest an important role of BDNF in depression [55]. The stress theory and dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis propose that dysregulation of this system contributes to MDD, with genes such as NR3C1 and FKBP5 modulating stress sensitivity and treatment response [62].

The inflammatory theory of depression suggests that inflammation and immune system dysfunction play a significant role in the pathogenesis of depression, with genes such as IL-6 and TNF-α involved in this process [73]. Dysfunctions of the biological clock, studied in the context of the circadian rhythm theory, and epigenetic mechanisms, such as DNA methylation and histone modifications, are also proposed as factors in the etiopathogenesis of MDD [89].

These genetic and epigenetic perspectives underscore the importance of adopting personalized approaches in diagnosis and treatment, which integrate both genetic predispositions and environmental influences.

3. Major Life Events

Major life events represent significant and well-defined changes that have a considerable impact on mental health, being associated with an increased risk of depression. Typical examples include the death of a loved one, loss of employment, diagnosis of a serious illness, or forced relocation [94]. These events are frequently analyzed in the context of depression to understand their impact on the onset and progression of MDD.

Life events can be classified based on their impact, persistence, controllability, personal influence, affected functional domain, temporal relationship with the onset of

depression, and significance to the individual. Major events are usually associated with a high level of perceived stress and can have significant effects on mental health, particularly in the onset of MDD. Daily hassles, although seemingly minor, can have a significant cumulative effect, especially in recurrent depressive episodes [96].

Acute events are short-term incidents, such as accidents, while chronic stress refers to long-term situations, such as ongoing financial difficulties. Controllable events are those over which the individual has some degree of control, while uncontrollable events, such as natural disasters, are more stressful due to the lack of control [100].

Life events can also be classified based on their dependence on the individual's actions. Independent events, such as the death of a family member, are not hereditary, and environmental influences play a crucial role in their association with depression. In contrast, dependent events, such as interpersonal conflicts, are moderately heritable and may share common genetic factors with depression, having a closer link to its onset [103].

The temporal relationship between life events and the onset of MDD shows that recent events, particularly those within the last six months, have a more direct impact on psychological state. Studies indicate that major stress contributing to the etiology of depression usually occurs within this period, with the greatest impact in the first three months. The effects of these events gradually diminish but can persist in cases of chronic difficulties, affecting long-term mental health [112].

Life events with personal significance, such as the loss of a relationship or a crucial role, significantly increase the likelihood of depression. These events involve feelings of humiliation and entrapment, being important predictors of mental disorders. Studies like the one conducted by Kendler et al. (2003) have shown that life events with high contextual threat, involving significant losses, are strong predictors of major depressive episodes [117].

Gender and age influence the response to stress. Men and women respond differently to stress depending on the stress evaluation and physiological characteristics. For example, women are more sensitive to stressors related to interpersonal relationships. Additionally, the impact and frequency of major events vary depending on the stage of life, with older adults being more affected by events such as health decline or the loss of loved ones, while children are more susceptible to depression following family conflicts [119].

The effect and significance of life events vary significantly depending on the cultural and social context. Cultural identity plays an important role in the relationship between life events and depression, protecting individuals from depressive symptoms through cultural values and social support networks. For example, strong ethnic identity and adaptation to American culture protect Asian-American students from depressive symptoms caused by discrimination [132].

The study of the first severe depressive episode is important for understanding the triggering role of stress. The biological mechanisms involved in the stress response, including HPA axis activation and changes in neuroplasticity, have been proposed as critical factors in the development of depression [143].

Chronic stress affects the inflammatory response, negatively influencing mental health. Inflammation plays an important role in the development of depression through pro-inflammatory cytokines that activate the HPA axis and affect the serotonergic system. Negative psychosocial stimuli, such as major life events, trigger inflammation and contribute to the manifestation of depressive symptoms [152].

The link between major life events and depression is complex, influenced by multiple individual variables, including personality traits and social support. Severe life events before the onset of depression are associated with a poorer response to treatment, highlighting the importance of personalized interventions to improve therapeutic outcomes [201].

4. Social Support and Major Depressive Disorder

The concept of social support has become a topic of interest in medical science due to research that has correlated the absence or deterioration of social connections with the onset of psychiatric disorders.

Social support is defined as the perception or experience of being important to others and being part of a social network of mutual assistance. It can be classified into perceived support and actual support, each having distinct implications for mental and physical health. Informational, instrumental, emotional, and belonging support contribute differently to an individual's well-being. Studies suggest that a high level of perceived

support is associated with positive mental health outcomes and decreased overall mortality [233].

Social support plays a significant role in preventing major depression, acting as a buffer against stress and enhancing psychological resilience. Research indicates that perceived social support can moderate the impact of life events on the development of depression [241].

II. Personal Contributions

5. Working Hypothesis and General Objectives

5.1. Working Hypothesis

The study proposes that there is a significant relationship between the FSDE and psychosocial and genetic factors, including social support, family history of depression, and negative life events. According to the diathesis-stress model, the interaction between genetic predispositions and environmental stressors influences the onset, severity, and treatment response in FSDE.

5.2. Context and Justification

MDD has a high prevalence and a significant impact on individuals and society. The diathesis-stress model suggests that MDD originates from the interaction between genetic predispositions and environmental stress factors. This study aims to investigate how social support, family history of depression, and negative life events contribute to FSDE, filling gaps in current knowledge and providing additional data relevant to the development of therapeutic interventions.

5.3. General Objectives of the Study

Comparison of genetic, psychosocial, and demographic factors between cases and control group: Identifying significant differences and correlations between the clinical and control groups regarding social support, negative life events, demographic factors, and family history of depression.

Evaluation of the influence of psychosocial and genetic factors on the onset of FSDE: Investigating how social support, family history of depression, and negative life

events influence FSDE, aiding in the identification of high-risk individuals and the development of preventive interventions.

Analysis of the impact of negative life events on the severity of depression at onset: Assessing how negative life events contribute to the severity of depression, thereby guiding therapeutic and support strategies.

Investigation of the **influence of negative life events on treatment response:** Analyzing how negative life events affect the treatment response in patients with FSDE, contributing to the personalization of treatments and the improvement of therapeutic outcomes.

6. General Research Methodology

This section describes the general methodology used in the studies included in the thesis, including participant recruitment, inclusion and exclusion criteria, psychometric tools, and statistical analyses applied.

6.1. Internal Pilot Study

An internal pilot study was conducted in the Psychiatry Department of the "Carol Davila" Central Military Emergency Hospital between February and July 2022, with the aim of testing the feasibility of recruitment procedures, the reliability of psychometric tools, and formulating preliminary hypotheses for the main study. A total of 40 participants were included (20 cases with FSDE and 20 controls matched by sex and age), and the results supported the methodological validity [246].

6.2. Study Design

In the first stage, through a case-control design, the study investigated the relationship between FSDE and psychosocial factors (social support, family history of depression, negative life events). In the second stage, the response to SSRI treatment after 6 weeks in patients with FSDE was explored, with a focus on the impact of exposure to life events.

6.3. Participant Recruitment

Between February 2022 and April 2024, 196 patients were recruited, of whom 98 were cases with FSDE and 98 were controls without a history of psychiatric disorders, matched by sex and age (±2 years). The clinical group was recruited from incident cases

presented at the Psychiatry Department of the "Carol Davila" Central Military Emergency Hospital, while the control group was recruited from the general population after a rigorous screening process.

6.4. Inclusion Criteria

Case group:

The primary inclusion criterion was "first severe major depressive episode," without any prior history of psychiatric treatment. The diagnosis was confirmed using the Structured Clinical Interview for DSM IV Disorders (SCID-I). All patients had a score of 24 or higher on the Hamilton Depression Rating Scale (HAM-D17), ensuring the severity of the depressive episode.

Control group:

To be included in the study, participants in the control group had to have a HAM-D17 score ≤ 7, no personal history of psychiatric disorders, and no Axis I diagnosis at the time of the interview.

6.5.Exclusion Criteria

Case group:

Patients with a prior psychiatric history requiring psychotropic treatment, uncontrolled acute or chronic medical conditions, psychotic symptoms, severe suicidal ideation, or evidence of organic causes for depressive symptoms (identified through laboratory or imaging data) were excluded. Patients who required a change in treatment due to worsening symptoms or tolerability, those who had other psychotropic medications introduced (including antipsychotics or mood stabilizers), as well as those who experienced major intercurrent negative life events, were excluded from the 6-week treatment response analysis.

Control group:

Participants with any history of psychiatric disorders or the presence of uncontrolled acute or chronic medical conditions were excluded.

6.6. Psychometric Tools and Evaluation Methods

Demographic data, family history of depression, and negative life events from the previous 6 months (prior to the onset of illness for cases and prior to the initial visit for the control group) were collected through unstructured interviews. The following psychometric scales were used in this study:

- **HAM-D17:** Used to assess the severity of depression, with scores ranging from 0-52; a score ≥24 indicates severe depression.
- **Multidimensional Scale of Perceived Social Support (MSPSS):** Measures perceived social support from family, friends, and other significant people.
- **Hamilton Anxiety Rating Scale (HAM-A):** Assesses the severity of anxiety on a scale from 0 to 56.
- **Global Assessment of Functioning Scale (GAFS):** Measures an individual's psychological, social, and occupational functioning on a scale from 0 to 100.

6.7. Ethical Considerations

The study was approved by the ethics committee of the "Carol Davila" Central Military Emergency Hospital (decision no. 549/10.02.2022). Participants provided informed consent, and data confidentiality was ensured through coding and secure storage.

6.8. Data Analysis

Statistical analyses were performed using R software, version 4.3.2. Normality of scores was assessed with the Shapiro-Wilk test. Student's t-tests, Mann-Whitney U, and Wilcoxon tests were used to compare continuous variables, while chi-square and Fisher's exact tests were applied to categorical data. Linear regression was applied to assess the relationship between depression severity and negative life events. The analysis of changes in clinical scores between the initial visit and the follow-up visit, depending on the number of events, was conducted using analysis of variance (ANOVA) or the Kruskal-Wallis test, depending on data normality. Conditional regression was used to assess the influence on the onset of FSDE, while unconditional regression was applied to analyze treatment response based on exposure to negative life events.

7. Study I: Comparative and Correlational Analysis of Psychosocial, Demographic, and Family History Factors Inter- and Intra-Group

MDD is a severe psychiatric condition that affects the quality of life. This study conducts a comparative and correlational analysis of psychosocial, demographic, and family history factors between individuals with FSDE and a control group, aiming to identify differences and relationships between these variables both at the inter-group and intra-group levels.

7.1. Working Hypothesis

The main hypothesis of the study is that there are significant differences between the FSDE group and the control group in terms of demographic, psychosocial, and family history factors. It is also anticipated that there will be significant intra-group correlations between negative life events and a family history of MDD.

7.2. Specific Objectives

- **Objective 1:** Compare demographic factors (marital status, education, occupation) between the FSDE group and the control group.
- **Objective 2:** Compare levels of psychosocial stress between the FSDE group and the control group.
- **Objective 3:** Compare levels of perceived social support between the FSDE group and the control group.
- **Objective 4:** Evaluate differences in the family history of Major Depressive Disorder among first-degree relatives between the FSDE group and the control group.
- **Objective 5:** Investigate the correlation between negative life events and the family history of Major Depressive Disorder.

7.3. Patients and Method

The study included 196 participants, equally divided between the FSDE group and the control group, matched by gender and ±2 years for age. Data collection was conducted through clinical interviews and self-administered questionnaires. Statistical analysis was performed using the following tests: Mann-Whitney U test, Kruskal-Wallis test, chi-square test, Fisher's exact test, and Spearman's correlation coefficient.

7.4. Results

7.4.1. Objective 1: Comparison of demographic factors (marital status, education, occupation, place of origin) between the FSDE group and the control group

The analysis revealed significant differences between the groups in terms of marital status (Fisher's exact test, $p = 0.0057$), educational level (Fisher's exact test, $p = 0.0022$), and occupation (Fisher's exact test, $p = 0.0247$). The percentage of married individuals was

significantly higher in the control group (61%) compared to the FSDE group (41%). Additionally, 38% of participants in the FSDE group had a low educational level, compared to 19% in the control group. Regarding occupation, 72% of participants in the control group were employed, while only 58% in the FSDE group were employed. No significant differences were observed concerning the place of origin (urban/rural) between the two groups (chi-square test, $p = 0.5203$).

7.4.2. Objective 2: Comparison of psychosocial stress levels between the FSDE group and the control group

The FSDE group reported a significantly higher frequency of negative life events (mean = 0.663 events per participant, SD = 0.731), compared to the control group (mean = 0.286 events, SD = 0.574). The Wilcoxon Rank Sum test indicated that this difference is statistically significant ($p < 0.001$), thus highlighting the importance of psychosocial stress in the development of MDD.

7.4.3. Objective 3: Comparison of perceived social support levels between the FSDE group and the control group

Perceived social support was significantly lower in the FSDE group (mean = 46.2, SD = 16.9) compared to the control group (mean = 53.3, SD = 16.6). The Wilcoxon-Mann-Whitney test indicated a statistically significant difference between the groups ($p = 0.004$), suggesting that a lack of adequate social support contributes to increased vulnerability to depression.

7.4.4. Objective 4: Evaluation of differences in the family history of Major Depressive Disorder among first-degree relatives between the FSDE group and the control group

A family history of MDD was reported by 25.5% of participants in the FSDE group, compared to 11.2% in the control group. The chi-square test indicated that this difference is statistically significant ($\chi^2 = 5.7507$, $p = 0.0165$), highlighting the genetic component in the predisposition to MDD.

7.4.5. Objective 5: Investigation of the correlation between negative life events and the family history of Major Depressive Disorder

A significant negative correlation was observed between the family history of MDD and the number of negative life events in the FSDE group, with a Spearman correlation coefficient of rho = -0.47, $p < 0.001$. In the control group, this correlation was not significant (rho = -0.05, $p = 0.6226$). These results suggest a complex interaction between genetic and environmental factors in the development of depression.

7.5. Discussions

The study results show that marital status, educational level, and occupation are demographic factors with a significant influence on vulnerability to MDD. For example, the study results are consistent with a meta-analysis that indicated an odds ratio (OR) of 1.88 for the association between unemployment and MDD [253]. Additionally, the low levels of social support and increased frequency of negative life events in the FSDE group highlight the role of psychosocial stress in the onset of depression, as documented in previous studies, which have indicated that stressful events are major factors in predicting depression [106, 116]. The negative correlation observed between the family history of MDD and the number of negative life events in the FSDE group suggests that genetic vulnerabilities may influence responses to psychosocial stress. This is similar to the findings of Kendler et al. (rho = -0.47, $p < 0.001$), who showed an interaction between genetic risk and psychosocial stress in the onset of depression [266]. These findings underscore the need for preventive interventions that address both genetic vulnerabilities and environmental factors simultaneously.

7.6. Conclusions

The study highlighted significant differences between individuals with FSDE and the control group in terms of demographic, psychosocial, and family history factors. The results suggest that preventive interventions should consider both genetic vulnerabilities and environmental factors to reduce the risk of developing MDD. Strengthening social support and effective management of psychosocial stress are recommended to reduce the risk of depression.

8. Study II: The Diathesis-Stress Model in the First Severe Major Depressive Episode

8.1. Working Hypothesis

The general hypothesis of the study is that genetic predispositions (family history of major depression) and psychosocial factors (major negative life events, perceived social support) significantly contribute to the onset of the first FSDE. It is also hypothesized that the number of negative life events influences the severity of the inaugural episode. According to the diathesis-stress theory, family history of major depression and negative life events play an essential role in precipitating the onset and severity of MDD, while perceived social support may have a protective effect.

8.2. Specific Objectives

- **Objective 1:** Evaluate the influence of family history of depression on the onset of FSDE.
- **Objective 2:** Examine the impact of negative life events on the onset of FSDE.
- **Objective 3:** Investigate the role of perceived social support as a protective factor.
- **Objective 4:** Explore the interaction between genetic factors, environmental stressors, and perceived social support.
- **Objective 5:** Evaluate the relationship between the number of negative life events and the severity of FSDE.

8.3. Patients and Method

The study included 98 patients diagnosed with FSDE and 98 healthy individuals without a history of psychiatric disorders, matched by gender and age (±2 years). Data were collected through unstructured clinical interviews and self-administered questionnaires, using instruments such as MSPSS, HAM-D 17, and HAM-A.

8.3.1. Data Analysis

Data analysis for objectives 1-4 was conducted using conditional logistic regression to investigate the effects of family history of depression, negative life events, and perceived social support on the onset of FSDE. For objective 5, linear regression models were constructed to explore the relationship between the number of negative life events and depression severity (HAM-D 17).

8.4. Results

8.4.1. Objectives 1-4

- **Initial Model (Model 1):** Conditional logistic regression analysis showed that negative life events (OR = 2.98690, 95% CI: 1.7123 - 5.2102, $p < 0.001$) and family history of major depression (OR = 3.48426, 95% CI: 1.3976 - 8.6865, $p = 0.007$) are significant predictors of FSDE onset. Perceived social support had a modest but significant protective effect (OR = 0.97346, 95% CI: 0.9532 - 0.9942, $p = 0.012$).
- **Model with Demographic Factors (Model 2):** In this model, negative life events and family history of depression remained significant, but the effect of perceived

social support became non-significant (OR = 0.97790, 95% CI: 0.9553 - 1.001, p = 0.062).

- **Models with Interaction Terms:** Adding interaction terms between negative life events and family history of depression or between perceived social support and life events did not show significant interactions. Family history of depression and negative life events remained significant independent factors for FSDE onset.

8.4.2. Objective 5

Exploration of this objective based on a partial data set was the subject of a previously published article [268]. Linear regression analysis showed a significant association between the number of negative life events and depression severity (HAM-D 17), with each additional negative event associated with an average increase of 1.25 points in HAM-D 17 scores. This effect remained robust even after adjusting for demographic and psychosocial variables, although the model explained only a small portion of the variability in depression severity.

8.5. Discussions

8.5.1. Evaluation of the Influence of Family History of Depression on the Onset of FSDE

The study confirms that family history of major depression is a strong predictor of FSDE onset. Individuals with a family history of depression have a significantly higher risk of developing FSDE, highlighting the importance of genetic factors in depression predisposition.

8.5.2. Examination of the Impact of Negative Life Events on the Onset of FSDE

Negative life events are a significant predictor of FSDE onset, supporting the hypothesis that environmental stressors have a direct impact on the triggering of depression. The risk of FSDE increases significantly in the presence of such events.

8.5.3. Investigation of the Role of Perceived Social Support as a Protective Factor

Perceived social support initially showed a protective effect against FSDE onset, but this effect became non-significant when demographic variables were controlled. This suggests that social support may have a protective role, but its influence is complex and may be modulated by other factors.

8.5.4. Exploration of the Interaction Between Genetic Factors, Environmental Stressors, and Social Support

Interactions between family history of depression, negative life events, and perceived social support were not significant. However, the results suggest that social support could moderate the risk associated with family history, indicating the need for further research.

8.5.5. Relationship Between Depression Severity at Onset (Reflected by Clinical Scores) and the Number of Negative Life Events

The relationship between the number of negative life events and depression severity at onset was significant, although the explanatory effect was modest. This indicates that other variables, possibly psychosocial or genetic, may play an important role in determining depression severity.

8.6. Conclusions

The study confirmed that both genetic and psychosocial factors play an essential role in the onset and severity of FSDE, supporting the diathesis-stress theory. Although perceived social support may offer a protective effect, its influence is complex and variable. The results emphasize the need for personalized prevention and intervention strategies that consider the interaction between genetic vulnerabilities and environmental factors.

9. Study III: The Impact of Negative Life Events on the Treatment Response to Selective Serotonin Reuptake Inhibitors (SSRIs) at 6 Weeks

9.1. General Hypothesis

The general hypothesis of the study is that exposure to negative life events may influence the response to SSRI treatment in patients with FSDE after 6 weeks of treatment. This hypothesis is based on previous research suggesting that such events may compromise therapeutic efficacy, although the results in the literature are often contradictory.

9.2. Specific Objective

The specific objective is to evaluate the impact of exposure to negative life events on the treatment response to SSRIs after 6 weeks, adjusting for confounding factors such as age, gender, initial severity of depression, presence of anxiety, and perceived social support.

9.3. Patients and Method

9.3.1. Patients

The study included a subset of 93 patients from an initial clinical cohort of 98 patients diagnosed with severe major depression and treated with SSRIs. Five patients were excluded from the final analysis for specific reasons: two patients did not complete the 6-week follow-up visit, two others required a change in treatment before this visit, and one patient reported a major negative life event before the follow-up visit.

9.3.2. Method

Negative life events were documented through unstructured interviews. To maintain the stability of statistical estimates, the variable "number of events" was coded as binary (0 – no events, 1 – 1 or more events). Treatment response was defined as a reduction of at least 50% in the HAM-D17 score after 6 weeks. The evaluations also included GAFS, MSPSS, and HAM-A scores at the initial and final study time points.

9.3.3. Statistical Analysis

The normality of the distribution of changes in HAM-D17 and GAFS clinical scores was tested using the Shapiro-Wilk test. The distribution of GAFS scores allowed for the use of parametric tests (ANOVA), while the distribution of HAM-D17 scores required non-parametric tests (Kruskal-Wallis). The association between exposure to negative life events and treatment response was assessed using Fisher's exact test and multiple logistic regression, adjusting for confounding factors.

9.4. Results

9.4.1. Evolution of Clinical Scores

HAM-D17 scores significantly decreased from a mean of 29.54 to 13.94 ($p < 0.0001$), and GAFS scores significantly increased from 40.09 to 69.03 ($p < 0.0001$), reflecting significant clinical improvements.

9.4.2. Evaluation of the Impact of Negative Life Events on Changes in Global Functioning and Depression Severity After 6 Weeks of SSRI Treatment

The ANOVA test did not indicate significant differences in the evolution of GAFS scores between groups defined by the number of negative events ($p = 0.727$). The Kruskal-Wallis test showed marginally significant differences between groups defined by the number of events in terms of the evolution of HAM-D17 scores ($p = 0.06097$).

9.4.3. Association Between Exposure to Negative Life Events and Treatment Response

The Chi-square test indicated a significant association between exposure to negative life events and treatment response ($\chi^2 = 6.719$, $p = 0.0095$). The OR for patients exposed to one or more negative events was 0.301, with a 95% confidence interval between 0.128 and 0.707. This OR suggests that exposed patients are significantly less likely to respond favorably to treatment compared to unexposed patients.

9.4.4. Results of Multiple Logistic Regression

Multivariate logistic regression revealed that exposure to negative life events is a significant predictor of poor treatment response ($\beta = -1.2165$, SE = 0.4604, $p = 0.00823$, OR = 0.296, 95% CI: 0.12 - 0.72). It is important to note that the wide confidence interval for the OR (0.12 - 0.72) indicates considerable variability in the effect estimate. This suggests that while exposure to negative events is a significant risk factor, the exact magnitude of this effect may vary significantly depending on other uncontrolled factors or the specific characteristics of the study sample. Therefore, these results underscore the need for further research to clarify and refine the understanding of the impact of these events on therapeutic response. Other variables, such as perceived social support, initial depression severity, gender, and age, did not show significant associations with treatment response, with confidence intervals including the value of 1, suggesting a negligible effect on the likelihood of therapeutic success in the studied context.

9.5. Discussions

This study emphasizes the importance of evaluating the history of negative life events in treatment planning for depression, considering that these events can significantly affect treatment response. However, the wide confidence interval associated with the OR for exposure to negative events suggests high variability, indicating the need to replicate these results in future studies with larger samples and more rigorous control methods. Although other demographic and clinical variables did not show a significant influence on therapeutic outcomes, the complexity of the interactions between these factors and antidepressant treatment warrants further exploration.

10. Conclusions and Personal Contributions

The objective of this research was to investigate various aspects of FSDE, focusing on three main directions: analyzing the psychosocial and genetic factors contributing to the onset of FSDE, applying the diathesis-stress model to understand the mechanisms of onset, and evaluating the influence of negative life events on the response to SSRI treatment.

1. Achievement of Research Objectives

The research achieved its objectives, confirming the initial hypotheses either fully or partially, and contributing to a better understanding of the complexity of the onset and evolution of FSDE. It was demonstrated that a family history of MDD among first-degree relatives is a significant risk factor for the onset of FSDE, highlighting the role of genetic predispositions in the development of the disorder. Additionally, it was shown that negative life events have a significant impact on both the onset of FSDE and the response to treatment, supporting the idea that environmental stressors are important determinants in the disorder's evolution. Although a protective effect of perceived social support was initially observed, this effect became non-significant in extended conditional regression models, suggesting the need for further research to clarify the influence of this factor.

2. Technical and Economic Advantages and Disadvantages

The research provided a deeper understanding of the factors influencing the onset and treatment response in FSDE, contributing to the development of personalized interventions that could reduce costs associated with ineffective treatments and depression recurrence. A major identified disadvantage is the variability of results, particularly in the case of perceived social support, which could not be clearly defined as a protective factor in all models. Additionally, the relatively small number of participants and the specificity of the studied population limit the generalizability of the results, potentially affecting the economic applicability of the conclusions to broader populations. Another limitation is that the possibility of some patients from the initial cohort being later re-diagnosed with bipolar

disorder could introduce confounding factors that might affect the accuracy and interpretation of the study's results.

3. Unresolved Issues

The research highlighted several aspects that require further exploration. The complex interactions between genetic factors, environmental stressors, and social support were not clearly defined, suggesting that the mechanisms by which these factors contribute to the onset and evolution of FSDE are more complex than anticipated. Although a protective effect of perceived social support was initially observed, it became non-significant in more complex models, indicating the need for more detailed research to clarify the role of social support in the prevention and management of FSDE.

4. Future Research Directions

Based on the obtained results, future research should focus on exploring gene-environment interactions, with additional studies needed to clarify how genetic predispositions and environmental stressors interact to influence the onset and evolution of FSDE. Future research should also investigate the context and circumstances in which perceived social support may have a protective effect or how it interacts with other risk factors in FSDE. Given the importance of psychosocial and genetic factors, it is essential to investigate personalized treatment strategies that take these variables into account.

5. Personal Contributions

The contributions of this thesis are significant and are clearly reflected in the three studies presented, each of which explores essential aspects of the diathesis-stress model in relation to the onset and evolution of FSDE.

Study I made a significant contribution by identifying clear differences between individuals who experienced a severe depressive episode and those who did not suffer from depression, within the national context regarding the following factors: negative life events, family history of depression, and perceived social support. It was shown that individuals with FSDE reported a higher number of negative life events compared to the control group, highlighting the role of environmental stressors as risk factors in the onset of severe depression. Additionally, a higher prevalence of family history of major

depressive disorder was found among those with FSDE, suggesting that genetic predispositions are an important contributing factor to the development of the disorder. Individuals with FSDE reported lower levels of perceived social support, suggesting that a lack of social support may be associated with a higher risk of severe depression onset. The study also observed a significant inverse correlation between the reporting of life events and the presence of a family history of depression in the clinical group, but not in the control group, suggesting that in patients with genetic predisposition, other types of psychosocial stress may be important in precipitating FSDE.

These findings contribute to a better understanding of the risk profile for FSDE onset, highlighting the importance of analyzing multiple dimensions—genetic, psychosocial, and environmental—in identifying and preventing severe depression.

Study II explored the applicability of the diathesis-stress model in explaining the onset of FSDE, suggesting that the interactions between genetic predispositions and environmental factors play an important role in the onset of the disorder. The results support the idea that both genetic factors, such as family history, and environmental stressors, such as negative life events, are involved in the occurrence of FSDE. Perceived social support suggests a potential protective effect that requires further investigation in future research. Possible interactions between these factors were identified, which could be explored in future studies.

Study III indicates that exposure to negative life events has a significant impact on the response to SSRI treatment, suggesting the need for personalized treatment based on the patient's psychosocial history. This underscores the importance of treatment strategies that consider not only genetic factors but also patients' life circumstances to optimize the effectiveness of therapeutic interventions. This contribution is relevant to clinical practice, offering a new perspective on how environmental factors can influence treatment outcomes in severe depression.

Each of these contributions is detailed and discussed extensively in the corresponding chapters of the thesis, providing an integrated view of the factors influencing the onset and evolution of FSDE, as well as how these factors can be used to improve treatment and prevention strategies. The work makes an important contribution to current knowledge by thoroughly analyzing the connections between the genetic factors of depression, life events, and perceived social support.

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Scientific Papers Published as Part of the Doctoral Thesis

1. **Andrei Gabriel Mangalagiu**, Sorin Riga, Octavian Vasiliu, Bogdan Mircea Petrescu. "Stress and pathogenesis of major depressive disorder. A narrative review". *International Journal of Medical Dentistry*, Vol 25, Issue 1, 20. Indexare: ISI. https://ijmd.ro/2021/stress-and-pathogenesis-of-major-depressive-disorder-a-narrative-review/ **(Chapter 3, pages 30, 34, 35, 37).**

2. **Andrei Gabriel Mangalagiu,** Sorin Riga, Octavian Vasiliu. "Exploring the Interplay between Family History of Depression, Negative Life Events, and Social Support in First-Episode Major Depression: Insights from a Pilot Case-Control Study". Psychiatry International, Volume 5, Issue 3, 2024. Indexare: ISI. **Factor de impact: 1.2.** https://doi.org/10.3390/psychiatryint5030021 (**Chapter 6, page 61**).

3. **Andrei Gabriel Mangalagiu,** Sorin Riga, Octavian Vasiliu. "The impact of life events on the severity of depressive symptomatology in patients with a first major depressive episode". Psihiatru.ro, Anul XX, Nr. 77 (2), 2024. Indexare: BDI. https://medichub.ro/reviste-de-specialitate/psihiatru-ro/the-impact-of-life-events-on-the-severity-of-depressive-symptomatology-in-patients-with-a-first-major-depressive-episode-id-9743-cmsid-66%C2%A0 (**Chapter 8, page 90**).