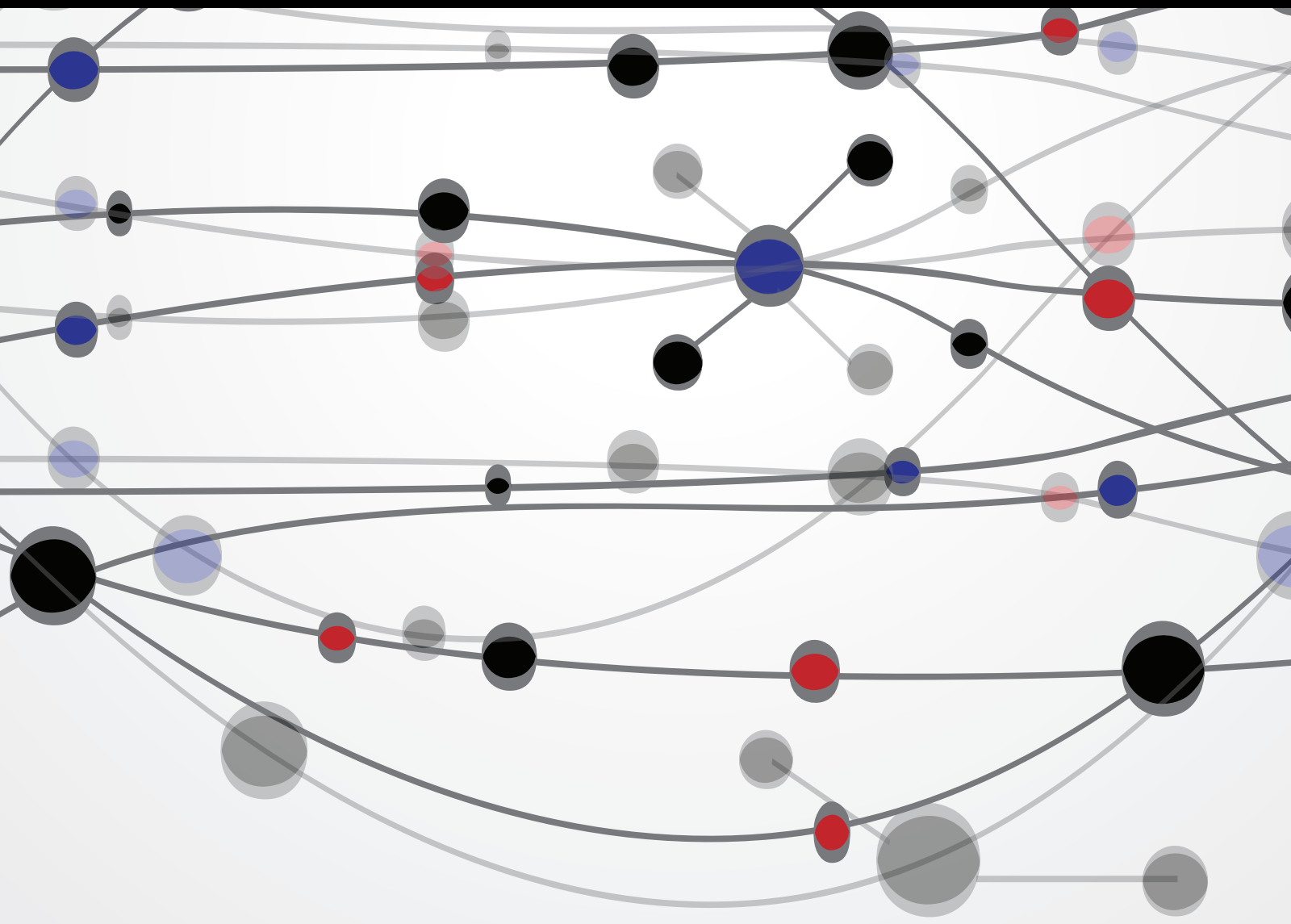
The Scientific World Journal

Mood Disorders: From Psychopathogenesis to Treatment

Guest Editors: Ru-Band Lu, Barry J. Hoffer, Hsien-Yuan Lane, Yen-Kuang Yang, San-Yuan Huang, and Yuan-Hwa Chou



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Editorial

Mood Disorders: From Psychopathogenesis to Treatment

Ru-Band Lu[1,2,3,4,5]

[1]*Department of Psychiatry, College of Medicine and Hospital, National Cheng Kung University, Tainan, Taiwan*
[2]*Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[3]*Institute of Allied Health Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[4]*Addiction Research Center, National Cheng Kung University, Tainan, Taiwan*
[5]*Center for Neuropsychiatric Research, National Health Research Institutes, Miaoli, Taiwan*

Correspondence should be addressed to Ru-Band Lu; rblu@mail.ncku.edu.tw

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Mood disorder is a group of diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification system where a disturbance in the person's mood is hypothesized to be the main underlying feature. In the most recent surveys, mood disorders have the highest lifetime prevalence rate and suicide risk of any psychiatric disorders. We invite investigators to contribute original research articles as well as review articles that will stimulate the continuing efforts to understand mood disorder. Preference is given to articles with a clear empirical component, whether including hypotheses testing, treatment model building, or a review of empirical work. Theoretical and speculative articles are welcomed as well for their contribution to the forming of empirically testable hypotheses. We are particularly interested in articles focusing on the novel concept of psychopathology and treatment in mood disorders.

This journal may include several hot topics: (1) "The State of the Art of the DSM-5 "with Mixed Features" Specifier"; (2) "Risk Factors for Depression in Children and Adolescents with High Functioning Autism Spectrum Disorders"; (3) "Multivariate Statistical Analysis as a Supplementary Tool for Interpretation of Variations in Salivary Cortisol Level in Women with Major Depressive Disorder"; (4) "The Pathogenesis and Treatment of Emotion Dysregulation in Borderline Personality Disorder"; (5) "Social Anxiety among Chinese People"; (6) "One-Year Follow-Up of the Effectiveness of Cognitive Behavioral Group Therapy for Patients' Depression: A Randomized, Single-Blinded, Controlled Study"; (7) "Evaluation of the Effectiveness of a Psychoeducational Intervention in Treatment-Naïve Patients with Antidepressant Medication in Primary Care: A Randomized Controlled Trial."

In 1999, Arkiskal et al. discussed bipolar disorders in "Consensus of Bipolar Subtypes in Barcelona." They suggest that psychiatrists and specialists should be highly concerned about the mixed features specific to bipolar disorders. In bipolar disorders, one can hope that future research will be conducted with these bipolar spectrum definitions, further validating or invalidating them, and provide better data for future clinicians to be able to use these concepts, if validated, for better clinical outcomes. One of the articles demonstrated that mixed features in bipolar disorder are frequently arguable for clinicians. The authors proposed that a diagnostic category should be preferred to a specifier and mixed states should be better as a concept of spectrum of states in DSM-5, based on their literature review.

Higher prevalence rate of comorbidity with depression in adolescents with autistic spectrum disorder was noted as well. Another article conducted very well literature review in the following domain: prevalence, explicative hypotheses and vulnerability, risk of suicide, and depressive symptoms in the comorbidity issue between depression and higher functioning autistic spectrum disorder. Therefore, in further clinical and research studies, researches would make more in-depth research possible on incidence and risk groups, symptomatological expression, differential diagnosis, duration, and prognosis and treatment of depression, as well as prevention of suicide, in the individuals with autism spectrum disorder.

It is quite complicated to analyze the relationship between treatment response and different diagnostic variables of laboratory. The linear and nonlinear statistical tools of multivariate statistical analysis could be used. Another article suggested that hierarchical cluster analysis (HCA) and principal component analysis (PCA) are useful as complementary tools for interpretation of the results obtained by laboratory diagnostic methods, using cortisol variations in major depressive disorder as a model. However, from more than thousands of review articles, there were many factors that may influence cortisol level, such as age, gender, stress, hospitalization, life cycle, menstruation cycle, and drugs. The clinician and researchers will be well controlling those confounding factors in the clinical and research use.

The generic term "emotion dysregulation" is often used to characterize a range of behavioral phenomena that are paramount in borderline personality disorder (BPD). Following a critical review of the current theories, one of the articles tries to propose a psychodynamic theory that aspires to explain all peculiarities in the course of BPD-specific emotional dyscontrol. The authors argue that the proposed theory explains the symptoms of BPD more thoroughly and inspires a parsimonious interpretation of brain imaging findings. The author draws clinical implications of the proposed theory and, accordingly, cites an efficacy study for treatment of emotion dysregulation. A very interesting item, in DSM-5 disruptive mood dysregulation disorder, belongs to major depressive disorder and episodes duration in children and adolescents. But few studies know what is going on when they become adults. Is it BPD, emotion dysregulation phenomena as a symptom of BPD, major depression, or bipolar disorders?

Social anxiety could be influenced by education and culture. It has been well studied in Western culture but unclear in others. Another article studied the relative factors in developing social anxiety, such as attachment, parenting behavioral activation, and cultural factors in Han Chinese people. The containment of social anxiety shows difference between Han Chinese and Western populations, especially in attachment, parenting, behavioral inhibition/activation, and the collectivist cultural factor-attitude toward group. The authors suggest more culturally sensitive assessment tool of social anxiety among the Han Chinese.

Cognitive behavior group therapy (CBGT) might be effective in depressive patients. Another article demonstrated a 12-session CBGT on those patients. In a single-blind randomized controlled study with a 2-arm parallel group design, eighty-one subjects were randomly assigned to intervention group (CBGT) or control group and 62 completed the study. The primary outcome was Beck Depression Inventory and Hamilton Rating Scale for Depression. The secondary outcome was automatic thoughts measured by automatic thoughts questionnaire. Both groups were evaluated at the pretest (2 weeks before), posttest (after 12 therapy sessions), and short-term (3 months), medium-term (6 months), and long-term (12 months) follow-up. All the assessments were maintained for 1 year. The results showed that CBT is effective in depression symptoms, alternative thinking, reconstructive thoughts, automatic negative thoughts, and cognitive errors.

Antidepressant (AD) with psychoeducation (PE) had been the approved treatment of choice for patients with major depressive disorder. Although psychoeducation was suggested to be effective in treating depressed patients using a randomized controlled trial design in primary care, researchers and clinicians should be more cautious about using psychoeducation as an effective treatment in depression, such as the background of leading therapist and the dynamics between therapists and members. Consequently, researchers and clinicians are suggested to renew information about mood disorders from various aspects.

Acknowledgments

I would like to thank our guest editors, Professors Barry, J. Hoffer, Yun Wang, Hsien-Yuan Lane, Yen Kuang Yang, San-Yuan Huang, and Yuan-Hwa Chou. I would also like to thank the following professionals: Dr. Yun-Hsuan Chang, Sheng-Yu Lee, and Shiou-Lan Chen for their assistance in this special issue.

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Clinical Study

One-Year Follow-Up of the Effectiveness of Cognitive Behavioral Group Therapy for Patients' Depression: A Randomized, Single-Blinded, Controlled Study

Kai-Jo Chiang,[1,2] Tsai-Hui Chen,[1,2] Hsiu-Tsu Hsieh,[1,2] Jui-Chen Tsai,[3] Keng-Liang Ou,[4,5,6,7] and Kuei-Ru Chou[1,3,8]

[1]*Graduate Institute of Nursing, College of Nursing, Taipei Medical University, No. 250 Wu-Hsing Street, Taipei 11031, Taiwan*
[2]*Department of Nursing, Tri-Service General Hospital, National Defense Medical Center, Sec. 2, No. 325 Chenggong Road, Taipei City 11490, Taiwan*
[3]*Department of Nursing, Taipei Medical University Shuang-Ho Hospital, No. 291 Zhongzheng Road, New Taipei City 23561, Taiwan*
[4]*Graduate Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, No. 250 Wu-Hsing Street, Taipei 11031, Taiwan*
[5]*Research Center for Biomedical Devices and Prototyping Production, Taipei Medical University, No. 250 Wu-Hsing Street, Taipei 11031, Taiwan*
[6]*Research Center for Biomedical Implants and Microsurgery Devices, Taipei Medical University, No. 250 Wu-Hsing Street, Taipei 11031, Taiwan*
[7]*Department of Dentistry, Taipei Medical University Shuang-Ho Hospital, No. 291 Zhongzheng Road, New Taipei City 23561, Taiwan*
[8]*Psychiatric Research Center, Taipei Medical University Hospital, No. 250 Wu-Hsing Street, Taipei 11031, Taiwan*

Correspondence should be addressed to Kuei-Ru Chou; kueiru@tmu.edu.tw

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The aim of the study was to investigate the long-term (one year) effectiveness of a 12-session weekly cognitive behavior group therapy (CBGT) on patients with depression. This was a single-blind randomized controlled study with a 2-arm parallel group design. Eighty-one subjects were randomly assigned to 12 sessions intervention group (CBGT) or control group (usual outpatient psychiatric care group) and 62 completed the study. The primary outcome was depression measured with Beck Depression Inventory (BDI-II) and Hamilton Rating Scale for Depression (HRSD). The secondary outcomes were automatic thoughts measured by automatic thoughts questionnaire (ATQ). Both groups were evaluated at the pretest (before 2 weeks), posttest (after 12 therapy sessions), and short- (3 months), medium- (6 months), and long-term (12 months) follow-up. After receiving CBGT, the experimental group had a statistically significant reduction in the BDI-II from 40.30 at baseline to 17.82 points at session eight and to 10.17 points at postintervention ($P < 0.001$). Similar effects were seen on the HRSD. ATQ significantly decreased at the 12th session, 6 months after sessions, and 1 year after the sessions ended ($P < 0.001$). We concluded that CBGT is effective for reducing depression and continued to be effective at 1 year of follow-up.

1. Introduction

Depression is a chronic relapsing condition, with relapse rates of 50%–80%. Another concern is that chronic depression increases the risk of suicidal behavior [1]. The proportion of people suffering from depression increases each year, and about 13%~20% of adults have depression-related symptoms during their lives. The average age of onset is between 20 and 40 years. The risk factors are a female gender, low socioeconomic status, unemployment, and divorce or separation. Psychosocial factors include personality traits and family and physical and environmental factors. If depressed patients receive appropriate treatment, about 50% can be completely cured, 30% have partial symptom relief, and 20%

remain chronically depressed. Over a patient's lifetime, 5 depressive episodes may occur every 4~6 years [2].

Medication is commonly used for depressed patients in outpatient clinics, and the level of depression affects the regularity of medication use and the rate of symptom improvement [3–6]. Several studies had demonstrated that cognitive behavioral therapy (CBT) was effective for reducing depression symptoms in patients with depression [7–10]. Previous studies found that cognitive behavioral group therapy (CBGT) results in a lower depression recurrence rate than care-as-usual alone [11–15]. CBGT primarily corrects patients' distorted and negative cognition. Through a change in automatic thoughts and dysfunctional attitudes, psychological problems caused by incorrect cognition can be improved, behavioral activation can be increased, and residual depression can be reduced. Through the guidance of a cognitive behavioral therapist, patients are able to understand that different situations or stimulus events can cause the same incorrect beliefs. Patient's early automatic thoughts can be corrected to avoid dysfunctional attitudes. With a change in dysfunctional attitudes, depression can be reduced [6, 12–16].

Several meta-analyses evaluated CBGT as a treatment for depression. Measuring instruments included the Beck Depression Inventory (BDI-II), Hamilton Rating Scale for Depression (HRSD), 20-Item Symptom Checklist (SCL-20), and Geriatric Depression Scale (GDS). A meta-analysis by Gloaguen et al. [17] reviewed 48 studies and found that CBGT was significantly better than waiting-list, antidepressants ($P < 0.0001$), and a group of miscellaneous therapies ($P < 0.01$), but CBGT was equal to behavioral therapy ($P = 0.95$), and the effect size was −0.05 to −0.82 (95% confidence interval (CI) = −0.83, −0.02). Another meta-analysis of 57 studies comparing CBGT with other support groups showed that CBGT better maintained its effectiveness compared to other support groups at 1.5 years of follow-up. Results of two recent meta-analyses showed that CBGT made a significant difference in depression, with the effect size of 0.93 (95% CI = 0.14~1.73, $P < 0.05$) and 0.72 (95% CI = 0.59~0.85), respectively [18, 19]. However, some previous studies adapted CBGT in patients with depression without using rigorous allocation concealment, randomization, or blinding. This study is a more rigorous design and provides evidence for the effectiveness of CBGT in patients with depression in Eastern culture [12, 13]. The study was to investigate the effectiveness of the cognitive behavior group therapy (CBGT) on depression patients over 12 months of follow-up.

2. Materials and Methods

2.1. Study Design. This was a single-blind randomized controlled study with a 2-arm parallel group design. Eighty-one subjects were randomly assigned into 12 sessions intervention group (CBGT) or control group (usual outpatient psychiatric care group). Eighty-one participants were recruited for this study. Forty-one participants were randomized to the experimental group and forty participants to the control group.

2.2. Study Participants. Study participants were depressed patients in the psychiatric outpatient clinic of a medical center in northern Taiwan. Standard inclusion criteria were (1) depression diagnosed by a psychiatrist and meeting the diagnostic definition of DSM-IV-TR; (2) age older than 18 years; (3) willingness to fully participate in a 12-week CBGT study, for 2 hours a week; (4) a total score on the BDI-II of ≥17; and (5) a score on the Mini-Mental Status Examination (MMSE) of at least 24 points. Exclusion criteria were (1) patients with schizophrenia, organic brain syndrome, obsessive-compulsive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar disorder, mental retardation, alcohol dependence or abuse, drug dependence or abuse, personality disorder, or anxiety or panic attacks; (2) patients receiving other psychotherapies; and (3) patients with other serious medical conditions (such as epilepsy, lung disease, hypertension, heart disease, diabetes mellitus, gout, and cancer).

2.3. Sample Size. The sample size was estimated using G-Power. G-Power is an application which performs a power analysis. This study used an alpha value of 0.05, a power of 0.80, an effect size of 0.53 (based on a previous meta-analysis) [20], and 3 repeated measures (including at 3, 6, and 12 months); the required number for a valid sample was determined to be 43. Dropout was considered, and eighty-one participants were recruited for this study. Forty-one participants were randomized to the experimental group and forty participants to the control group. Eleven and eight participants withdrew from the experimental and control group, respectively, due to lack of interest or hospitalization (dropout rates 27% and 20%, resp.). This left thirty participants in the experimental group and thirty-two participants in the control group (Figure 1).

All patients agreed to have a face-to-face interview before entering the group. This allowed them to understand their current disease condition, and the researcher also explained the purpose of CBGT. Times for the CBGT groups were determined by participant's availability for participation. The venue for CBGT was a group therapy room in the psychiatric department of the hospital. CBGT was implemented for 12 weeks in the experimental group; the control group was given care-as-usual. All medications were selective serotonin-reuptake inhibitors prescribed by psychiatrists in the outpatient clinic. Before the group therapy began, both groups completed the pretest. The pretest included a demographic table, the BDI-II, HRSD, and ATQ. The experimental group completed the BDI-II and HRSD each week after their group therapy session. After the twelfth session, both groups completed the posttest. Posttest scales included the BDI-II, HRSD, and ATQ. Short- (3 months), medium- (6 months) and long-term (12 months) follow-ups were conducted. Assessors collected the follow-up questionnaires in person.

2.4. Randomization and Allocation Concealment. Randomization assignment was used to randomize participants into the experimental group or care-as-usual control group. Randomization is determined using a computer program (Research Randomizer) which generates a list of random

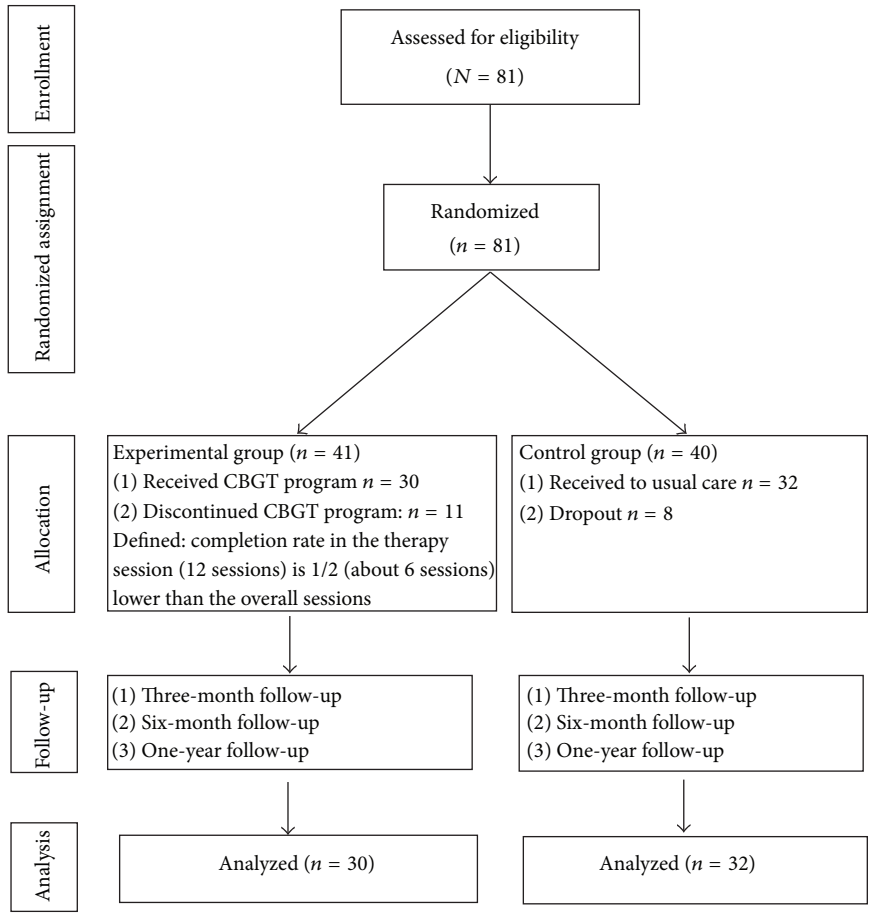

Figure 1: Participant flow at each step after randomization.

numbers and allocation to one of two conditions. Study participants were patients with depression in the psychiatric outpatient clinic of a medical center in Northern Taiwan. Eighty-one subjects were randomly assigned into 12 sessions intervention group (CBGT) or control group (usual outpatient psychiatric care group). There were 41 participants in the experimental group and 40 participants in the control group. The allocation sequence was generated prior to the recruitment of participants by a computer program and concealed in sequentially numbered and sealed opaque envelopes, which were opened when participants were ready for allocation. The control group received their usual outpatient psychiatric care.

2.5. Blinding. This was a single-blind study, where only the assessors were masked to the nature of the treatment given to the participants. The assessors instructed patients not to talk about their treatment during the assessment. Participants were informed about their treatment allocation by the therapist but not by the raters. Raters and therapists were not allowed to have a discussion about study participants [21]. Participants and administering clinicians were blinded to the results of randomization until the beginning of the study, when they were informed of the treatment allocation by a member of the research team who was not involved in the outcome assessment. Study participants and the therapist involved in recruitment and assessment were blinded to the treatment allocation throughout the study.

2.6. Group Therapist. The group therapist was a doctoral student with 8 years' experience in cognitive therapy and group therapy. The group leader followed the manual, Handbook of Cognitive Behavioral Therapies [22]. Group leader adherence was monitored by two senior external experts in group dynamics who were independent of the program component of the system. They rated compliance with the fundamental principles of cognitive behavioral therapy and adherence to modules and interventions specified in the treatment manual. The control group received their usual outpatient psychiatric care and was asked to complete the assessment instruments during the same weeks that the treatment groups were tested.

2.7. Assessors. During the study, assessors were closely monitored to avoid their interfering with treatment. They could not discuss any study information related to the subjects with the therapists. At the beginning of each observation phase, the assessors reminded the subjects not to disclose their group assignment or discuss the details of their therapy with anyone. Assessors only collected data during the study.

2.8. Study Procedures. The CBGT was manualized and involved 12 weekly 2-hour group sessions. In CBGT sessions

1~4, the initial phase, an "overview of cognitive behavioral therapy," was introduced. A "feeling of great difference" allowed group members to understand the linkage of cognition-emotion-behavior and to discover their "automatic thoughts" and monitor the contents. "Exploration of the vertical arrow" allowed members to understand their core beliefs and define and adjust those beliefs. Sessions 5~8 were the middle phase. The "extended arrow" allowed members to ask three questions: "what does it mean to me?"; "if this is real, why does it make me so sad?"; and "if it happens, will it be that bad?" This allowed them to further understand that different situations often have a core belief. "Suspension of beliefs" allowed members to learn that the vertical arrow was composed of sequential beliefs. If they practiced stopping the first few beliefs, then the series of negative thoughts would not emerge. After understanding their beliefs, "role playing" was used to practice different strategies. Members then identified their innate characters and composed a "schema map." They drew in their major positive and negative memories. Sessions 9~12 were the late phase where "redrawing the schema map" was used to change the proportions of positive and negative memories on the schema map. Alternative thoughts were used to counter negative thoughts and avoid an extension of those negative thoughts. "Problem-solving" was presented to allow members to brainstorm various solutions and understand the advantages and disadvantages of each solution before selecting an appropriate one. "Blessings be with you" managed the separation anxiety of members who were about to face termination of the group. Finally, members were asked to give feedback to the group and indicate the contributions of each member to the group.

2.9. Study Instruments

2.9.1. Participant Demographics. After the participants were randomly assigned to the experimental group and the control group, baseline assessment was started two weeks before the CBGT. Baseline data included the patients' name, age, gender, educational level, marital status, occupation, religion, source of family support, number of episodes of depression, regularity of medication use, major physical diseases, and MMSE score.

2.9.2. Beck Depression Inventory (BDI-II). The Chinese version of the BDI-II was approved by Beck et al. and translated and revised by Professor Hui-Chen Ko based on the 1978 version of the BDI-II. It is a 21-question, self-reported questionnaire. The total score ranges from 0 to 63, with a higher total score indicating more severe depression. Guidelines published in 1993 define a score of 17~29 points as moderate depression and 30~63 points as severe depression. From a receiver operating characteristic curve, the best cutoff point on the Chinese version of the BDI-II was consistent with foreign studies. The results of a reliability and validity study on the Taiwanese version showed that the internal consistency reliability α value was 0.87 and the Spearman-Brown split-half reliability was 0.94 [23]. This scale was self-reported by the participants; the pretest was completed two weeks before the CBGT.

2.9.3. Hamilton Rating Scale for Depression (HRSD). The HRSD used a 21-item rating scale, measures the severity of symptoms of depressed patients, and takes 15~20 minutes to complete. The scale defined moderate depression as 18~24 points and severe depression as ≥25 points [24]. The interrater reliability was 0.84. The interrater reliability of training estimation was 0.76 [25, 26]. This scale was measured by the assessor; the pretest was completed two weeks before the CBGT.

2.9.4. Automatic Thoughts Questionnaire (ATQ). Hollon and Kendall developed the ATQ. The 30-item ATQ was established to measure the frequency of occurrence of automatic negative thoughts associated with depression [27]. The total score ranges 30~150 points, with a higher score indicating more automatic negative thoughts. Reliability measures for the depressed patients revealed a coefficient alpha of .94. The ATQ was cross-validated and found to significantly discriminate psychometrically depressed from nondepressed criterion groups.

2.10. Statistical Methods. This study used the statistical package program SPSS version 18 for archiving data and statistical analyses. Chi-square tests (categorical data) and t-tests (continuous data) were used with patient demographics to analyze differences between the experimental and control groups. Generalized estimating equations (GEEs) were used to analyze differences in categorical data of extraneous variables (gender, educational level, occupation, marital status, religion, family support, regularity of medication use, number of episodes of depression, and major physical diseases) between the experimental and control groups. GEEs were also used to explore the effectiveness of the CBGT intervention and to test levels of depression as indicators of the effect of repeated measurements. Trends and changes in the experimental and control groups were compared. This study used an ITT analysis to retain the essence of randomization and allow for the study results to represent the original design. Subjects whose completion rate in the therapy session (12 sessions) was 1/2 (about 6 sessions) lower than the overall sessions were not included in the ITT analysis. For missing data, we used the last observation carried forward to impute an estimate.

2.11. Therapeutic Adherence and Monitoring of Adverse Events. To maintain the consistency of the intervention in this study, investigators explained the recruitment and training procedures to the therapist and provided a standardized therapeutic manual. Onsite clinical psychiatrists monitored all participants from pretreatment through follow-up for signs and symptoms of adverse events (AEs) such as suicide attempts and changes in clinical severity status. Safety and tolerability were assessed by clinical and/or statistical review of AEs. All randomized patients were included in the AE analysis. None of the patients reported adverse symptoms during the study.

2.12. Ethical Considerations. The study was approved by the Institutional Review Board of Tri-Service General Hospital. The benefits and risks of participation in the study were fully

explained to each patient. The informed consent can only be recognized when participants scored at least 24 points on the Mini-Mental Status Examination (MMSE) to confirm that their cognitive abilities were good. During the study, if a subject decided to withdraw due to any discomfort, the investigator fully respected that decision and guaranteed that the decision to withdraw from the study would not affect other treatments. Study subjects were informed that data were deidentified, kept confidential, and used for academic research purposes only. The individual in this paper has given written informed consent to publish these case details.

3. Results

3.1. Participant Demographics. We recruited 81 participants and randomly assigned them into the experimental and control groups. Forty-one participants were assigned into 12 sessions intervention group (CBGT) and forty participants in the control group (usual outpatient psychiatric care group). A total of 62 participants completed the study, 30 in the experimental group and 32 in the control group. Figure 1 provides a detailed chart of the flow of participants through the study.

Demographic data are shown in Table 1. There were 39 female participants (62.9%) and 23 male participants (37.1%). Twenty-four participants (38.7%) were high school/vocational high school (and below) graduates, and 29 participants (46.8%) were junior college/college graduates. The average age of 30 participants in the experimental group was 45.43 (standard deviation, SD = 10.88) years, and the average age of 32 participants in the control group was 46.81 (SD = 10.38) years. The average MMSE score for the experimental group was 29.07 (SD = 1.20) points and for the control group was 29.28 (SD = 0.89) points.

Twenty-nine participants (46.8%) had regular medication use, while 33 (53.2%) were using medications irregularly. There was no statistical difference in medication adherence between the two groups at pretest or at the 1-year follow-up ($P = 0.46$). Twenty-nine participants (46.8%) had two episodes of depression, and 22 participants (35.5%) had one. There were 14 participants (22.6%) with no major physical diseases; 48 participants (77.4%) had major diseases such as hypertension, heart disease, gout, and diabetes mellitus. No difference between the groups reached statistical significance ($P = 0.17$).

The average BDI-II score for the control group was 37.59 (SD = 10.24) points and that of the experimental group was 40.30 (SD = 9.09) points. The average HRSD score for the control group and experimental group was 37.66 (SD = 7.09) and 40.37 (SD = 9.46) points, respectively. The average ATQ score for the control group was 129.50 (SD = 7.61) points and that of the experimental group was 131.53 (SD = 9.78) points. There was no statistically significant difference between the two groups at baseline ($P > 0.05$).

3.2. Changes in the Level of Depression at Follow-Up after Participating in CBGT. Table 2 presents average values of the HRSD and BDI-II scores. After CBGT, the average BDI-II score of the experimental group was reduced from 40.30 (SD = 9.09) points at the pretest to 10.17 (SD = 4.33) points at the posttest. The average score at the 1-month follow-up was 9.09 (SD = 3.39) points, 11.47 (SD = 3.73) points at the 3-month follow-up, 12.87 (SD = 4.34) points at the 6-month follow-up, and 12.10 (SD = 4.64) points at the 12-month follow-up. After CBGT, the average weekly BDI-II score for the experimental group was significantly reduced at week four to 24.18 points; at week eight it was 17.82 points, and the effectiveness was maintained for 1 year (Figure 2). Before the group intervention, the average HRSD score for the experimental group was 40.37 (SD = 9.46) points; after the group intervention, the average score on the posttest was 8.77 (SD = 3.99) points. The average score on the 1-month follow-up test was 10.03 (SD = 3.19) points, 11.73 (SD = 3.61) points on the 3-month follow-up test, 13.27 (SD = 4.06) points on the 6-month follow-up test, and 12.90 (SD = 3.75) points on the 12-month follow-up test (Table 2). Figure 3 shows that, after CBGT, the average weekly HRSD score for the experimental group was significantly reduced at week four to 26.14 points and at week eight to 17.64 points, and the effectiveness was maintained for 1 year. Effect size for the difference between the intervention and control conditions at 12 month follow-up is 0.55.

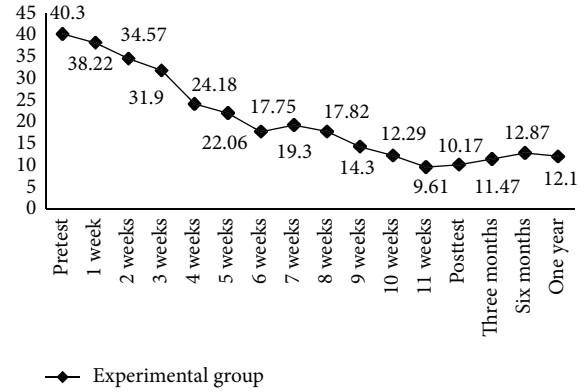

Figure 2: Changes in BDI-II scores at the various follow-up assessments.

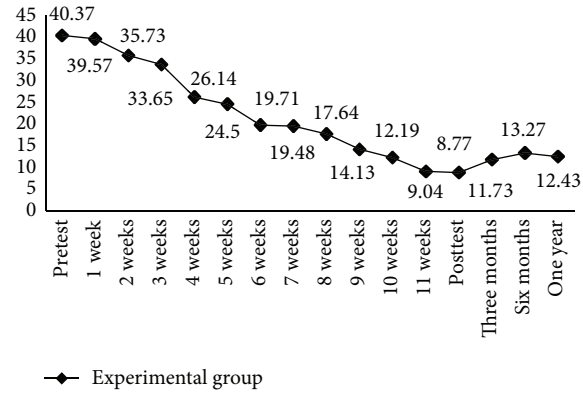

Figure 3: Changes in HRSD scores at the various follow-up assessments.

Table 1: Patient demographics ($N = 62$).

Variable (category)	Experimental group ($n = 30$)		Control group ($n = 32$)		Total ($N = 62$)		P value
	Number	(%)	Number	(%)	Number	(%)	
Gender							
Male	10	37.1	13	40.6	23	37.1	0.55
Female	20	62.9	19	59.4	39	62.9	
Educational level							
Junior high school and below	7	23.3	3	9.4	10	16.1	0.29
High school	5	16.7	9	28.1	14	22.6	
Junior college/college	15	50.0	14	43.8	29	46.8	
Masters and above	3	10.0	6	18.7	9	14.5	
Occupation							
Employed	11	36.7	11	34.4	22	35.5	0.65
Unemployed	10	33.3	14	43.8	24	38.7	
Housekeeper	9	30.0	7	21.8	16	25.8	
Marital status							
Married	17	56.7	16	50.0	33	53.2	0.46
Single	1	3.3	0	0.0	1	1.7	
Separated/divorced/widowed	12	40.0	16	50.0	28	45.1	
Religion							
Folk beliefs	19	63.3	19	59.4	38	61.3	0.99
Christianity	6	20.0	9	28.1	15	24.2	
Buddhism and Taoism	5	16.7	4	12.5	9	14.5	
Support							
Family support	13	43.3	11	34.4	24	38.7	0.47
No support	17	56.7	21	65.6	38	61.3	
Medication adherence							
Regular	16	53.3	13	40.6	29	46.8	0.46
Irregular	14	46.7	19	59.3	33	53.2	
Number of episodes							
One	10	33.3	12	37.5	22	35.5	0.74
Two	16	53.4	13	40.6	29	46.8	
Three	3	10.0	5	15.6	8	12.9	
Four	1	3.0	2	6.3	3	4.8	
Major diseases							
Yes	21	70.0	27	84.4	48	77.4	0.17
No	9	30.0	5	15.6	14	22.6	
Age (years)		45.43 ± 10.88		46.81 ± 10.38			0.65
MMSE score		29.07 ± 1.20		29.28 ± 0.89			0.61
BDI-II score		40.30 ± 9.09		37.59 ± 10.24			0.27
HRSD score		40.37 ± 9.46		37.66 ± 7.09			0.21

MMSE, Mini-Mental Status Examination; BDI-II, Beck Depression Inventory; HRSD, Hamilton Rating Scale for Depression.

The evaluation results of BDI-II scores for the two groups using GEEs showed that a higher score indicated a higher level of depression. For the variables of the interaction of group and time period (Table 3), when the posttest was compared to the pretest, the average BDI-II score of the experimental group was 30.3 points lower than that of the control group. At the 3-month follow-up test compared to the pretest, the average score for the experimental group was 29.9 points lower than that of the control group; at the 6-month follow-up test compared to the pretest, the average score of the experimental group was 28.2 points lower than that of the control group; at the 12-month follow-up test compared to the pretest, the average score for the experimental group was 28.4 points lower than that of the control group. All of the above changes in BDI-II scores reached statistical significance ($P < 0.001$) (Table 3). This indicated that, after CBGT, there was greater improvement of depression in the experimental group than the control group.

The evaluation results of HRSD scores of the two groups using GEEs showed that a higher score indicated a higher

Table 2: Average values on the BDI-II, HRSD, and ATQ.

Variable	Pretest		Posttest		3-month follow-up test		6-month follow-up test		12-month follow-up test	
	M	SD	M	SD	M	SD	M	SD	M	SD
BDI-II										
Experimental group ($n = 30$)	40.30	9.09	10.17	4.33	11.47	3.73	12.87	4.34	12.10	4.64
Control group ($n = 32$)	37.59	10.24	37.75	9.66	38.69	7.63	38.34	7.13	37.97	5.85
Total ($N = 62$)	39.90	9.72	24.40	15.80	25.52	14.98	26.02	14.13	25.53	13.87
HRSD										
Experimental group ($n = 30$)	40.37	9.46	8.77	3.99	11.73	3.61	13.27	4.06	12.90	3.75
Control group ($n = 32$)	37.66	7.09	37.28	7.15	39.22	4.24	39.72	4.45	45.94	7.87
Total ($N = 62$)	38.97	8.37	23.48	15.49	25.92	14.39	26.92	13.98	29.95	17.76
ATQ										
Experimental group ($n = 30$)	131.53	9.7	44.10	7.73	44.30	4.98	46.20	5.67	46.37	4.94
Control group ($n = 32$)	129.50	7.61	130.00	5.77	129.38	3.90	128.97	2.86	129.50	3.28
Total ($N = 62$)	130.48	8.72	88.44	43.80	88.21	43.09	88.92	41.93	89.27	42.09

BDI-II, Beck Depression Inventory, a higher score indicating a higher depression level; HRSD, Hamilton Rating Scale for Depression, a higher score indicating a higher depression level; ATQ, Automatic Thoughts Questionnaire, a higher score indicating more automatic negative thoughts.
Pretest, 2 weeks before cognitive behavioral group therapy (CBGT); posttest, tested after 12 CBGT sessions; 1-month follow-up test, 3-month follow-up test, 3-month follow-up after CBGT; 6-month follow-up test, 6-month follow-up after CBGT; 12-month follow-up test, 12-month follow-up after CBGT.
M, mean; SD, standard error difference.

Table 3: GEE analysis of BDI-II results.

Variable	B	SE	Wald X^2	P value
Group (EXP)[§]	2.621	1.7139	2.338	0.126
Time (2nd)[⊕]	0.156	0.7566	0.043	0.836
Time (3rd)[⊕]	1.094	0.7659	2.039	0.153
Time (4th)[⊕]	0.750	0.9723	0.595	0.440
Time (5th)[⊕]	0.375	1.6816	0.050	0.824
Interactions				
Group (EXP) × time (2nd)[#]	−30.3	1.6582	333.662	$P < 0.001^*$
Group (EXP) × time (3rd)[#]	−29.9	1.7056	307.878	$P < 0.001^*$
Group (EXP) × time (4th)[#]	−28.2	2.0456	189.815	$P < 0.001^*$
Group (EXP) × time (5th)[#]	−28.4	2.4239	137.359	$P < 0.001^*$

BDI-II, Beck Depression Inventory; GEE, generalized estimating equation; EXP, experimental group; CON, control group.
[*] $P < 0.001$.
[§]Reference group, the control group.
[⊕]Reference group, time (1st).
[#]Reference group, group (CON) × time (1st).
"2nd": the measurement at the end of therapy.
"3rd": the measurement 3 months after group therapy.
"4th": the measurement 6 months after group therapy.
"5th": the measurement 12 months after group therapy.

level of depression. For the variables of the interaction of group and time period (Table 4), when the posttest was compared to the pretest, the average HRSD score of the experimental group was 31.2 points lower than that of the control group. When the 3-month follow-up test was compared to the pretest, the average score of the experimental group was 30.2 points lower than that of the control group; when the 6-month follow-up test was compared to the pretest, the average score of the experimental group was 29.2 points lower than that of the control group; when the 12-month follow-up test was compared to the pretest, the average score of the experimental group was 35.7 points lower than that of the control group. This indicated that, after CBGT, the HRSD score of the experimental group showed greater improvement than the control group, and the effects lasted through the 12-month follow-up.

3.3. Changes in the Automatic Thoughts at Follow-Up after Participating in CBGT. Table 2 presents average values of the ATQ scores. After CBGT, the average ATQ score of the experimental group was reduced from 131.53 (SD = 9.70) points at the pretest to 44.10 (SD = 7.73) points at the posttest.

Table 4: GEE analysis of HRSD results.

Variable	B	SE	Wald X^2	P value
Group (EXP)[§]	2.707	1.9923	1.846	0.174
Time (2nd)[⊕]	−0.375	0.8487	0.195	0.659
Time (3rd)[⊕]	1.563	1.0743	2.115	0.146
Time (4th)[⊕]	2.063	1.2476	2.733	0.098
Time (5th)[⊕]	8.281	1.9381	18.257	$P < 0.001^*$
Interactions				
Group (EXP) × time (2nd)[#]	−31.2	1.8316	290.621	$P < 0.001^*$
Group (EXP) × time (3rd)[#]	−30.2	1.9646	236.233	$P < 0.001^*$
Group (EXP) × time (4th)[#]	−29.2	2.2523	167.648	$P < 0.001^*$
Group (EXP) × time (5th)[#]	−35.7	2.7467	169.381	$P < 0.001^*$

HRSD, Hamilton Rating Scale of Depression; GEE, generalized estimating equation; EXP, the experimental group; CON, the control group.
[*] $P < 0.001$.
[§]Reference group, the control group.
[⊕]Reference group, time (1st).
[#]Reference group, group (CON) × time (1st).
"2nd": the measurement at the end of therapy.
"3rd": the measurement 3 months after group therapy.
"4th": the measurement 6 months after group therapy.
"5th": the measurement 12 months after group therapy.

Table 5: GEE analysis of ATQ results.

Variable	B	SE	Wald X^2	P value
Group (EXP)[§]	1.938	2.1764	0.793	0.373
Time (2nd)[⊕]	0.500	1.8361	0.074	0.785
Time (3rd)[⊕]	1.094	1.6022	0.466	0.495
Time (4th)[⊕]	−0.125	1.2981	0.009	0.923
Time (5th)[⊕]	−0.531	1.5506	0.117	0.732
Interactions				
Group (EXP) × time (2nd)[#]	−87.933	3.0076	854.778	$P < 0.001^*$
Group (EXP) × time (3rd)[#]	−87.108	2.4175	1298.323	$P < 0.001^*$
Group (EXP) × time (4th)[#]	−84.802	2.8230	902.370	$P < 0.001^*$
Group (EXP) × time (5th)[#]	−85.167	2.1862	1517.552	$P < 0.001^*$

ATQ, Automatic Thoughts Questionnaire; GEE, generalized estimating equation; EXP, experimental group; CON, control group.
[*] $P < 0.001$.
[§]Reference group, the control group.
[⊕]Reference group, time (1st).
[#]Reference group, group (CON) × time (1st).
"2nd": the measurement at the end of therapy.
"3rd": the measurement 3 months after group therapy.
"4th": the measurement 6 months after group therapy.
"5th": the measurement 12 months after group therapy.

The average score at the 1-month follow-up was 42.07 (SD = 6.71) points, 44.30 (SD = 4.98) points at the 3-month follow-up, 46.20 (SD = 5.67) points at the 6-month follow-up, and 46.37 (SD = 4.94) points at the 12-month follow-up.

The evaluation results of ATQ scores of the two groups using GEEs showed that a higher score indicated a higher level of depression. For the variables of the interaction of group and time period (Table 5), when the posttest was compared to the pretest, the average ATQ score of the experimental group was 87.9 points lower than that of the control group. When the 12-month follow-up test was compared to the pretest, the average score of the experimental group was 85.2 points lower than that of the control group. This indicated that, after CBGT, the ATQ score of the experimental group showed greater improvement than the control group, and the effectiveness was maintained throughout the 12-month follow-up.

4. Discussion

The finding of current study implies that CBGT is indeed beneficial for patients with depression. In terms of immediate post intervention, it was found that CBGT lowered the level of depression and reduced the automatic negative thoughts, which was consistent with the results of past meta-analyses [19, 28, 29]. Beck found that vulnerability of the

individual was a paramount cause of depression. At an early stage of life, a vulnerable individual captures certain assumptions or attitudes and these continue into adulthood and become characteristics in their lives. In the cognitive model, vulnerability results in automatic negative thoughts. Automatic thoughts extend downward to core beliefs when certain events occur. The most common core beliefs are "I am a loser" and "I am useless." When these core beliefs emerge, patients become depressed. According to this theory, reducing distorted attitudes and automatic thoughts can reduce depression.

Our results showed that CBGT significantly improved the level of depression in patients at follow-up, and this was maintained for 1 year. The average BDI-II score of 40.3 points was reduced to 12.9 and 12.3 points at the 6- and 12-month follow-up assessments after the cognitive group intervention. This result is consistent with findings of Embling [30] that BDI-II scores at the 6- and 12-month follow-ups were reduced from 31.7 to 19.8 and 15.2 points, respectively. Depressed patients in the experimental group were less susceptible to recurrent depression because they were taught how to escape from automatic negative thoughts that emerge from their minds by understanding the cognition-emotion-behavior sequence of automatic thinking in the first four CBGT sessions. At the beginning of CBGT, patients are led to understand relationships between automatic thoughts, emotions, and behaviors. They have to record situations, thoughts, and emotions, and the contents of these records include the time, situation, and logical deviation. During the treatment process, patients discover their cognitive distortions through discussion of their homework assignments. Through exploration and discussion, patients are assisted in finding other ways to identify and correct distorted thoughts and elicit positive emotions, behaviors, and thoughts using cognitive strategies. Common cognitive strategies include (1) cognitive restructuring, for which patients learn to understand their distortions of core beliefs and how to replace nonlogical cognitions with logical analysis, so that negative distorted thoughts can be corrected; (2) reattribution, for which patients easily attribute failure to themselves because of an unrealistic sense of responsibility which causes remorse and guilt, where therapists point out the unrealistic assumptions and let patients see their unrealistic thinking and make an objective attribution of failure; (3) decentering or distancing, for which patients disengage from their thoughts or explanations and look at them with more-realistic attitudes and this technique allows patients to understand and forgive others without being excessively harsh and mean to them; (4) examining the evidence, for which patients correct automatic thoughts by viewing evidence for and against them; (5) defining vocabulary, for which patients give themselves inappropriate labels such as "I am a weak person" or "I am a stupid person" and therapists then ask patients to define "weak" and "stupid"; and (6) alternative thinking, for which patients are guided to think about multiple possible perspectives and behaviors in the current situation.

In the middle phase of CBGT, focus was placed on core beliefs which deeply affect their thinking. These beliefs are entrenched, but patients practiced viewing them from others' perspectives and correcting their distorted automatic thoughts and logic. This phase required other members to assist in finding evidence to strengthen positive thinking. The latter phase allowed patients to find suitable alternative thoughts, behaviors, and techniques. It also allowed them to think about their sustained solutions, that they were the leading actors at this moment and that they should take full control of themselves. It allowed patients to change their automatic thoughts and deviated/distorted attitudes such as dichotomous thinking. It allowed patients to think about possible gray areas in a view of things instead of having only positive and negative perceptions. At the same time, the link between negative thoughts and emotions was changed. When negative thoughts emerged, the connections to these negative thoughts were identified. When patients encountered different stressful life events, they consciously switched to alternative thoughts. When their thoughts changed, their emotional responses to an event were less dramatic. Long-term effects of CBGT might be to educate patients in using different techniques to change their own thoughts when they are faced with future stressors, change the link between distorted thoughts and feelings to correct those thoughts or beliefs, educate themselves about medication compliance, recognize early signs of recurrence including depressive emotional changes, and provide effective communication.

The strength of this study is that it has rigorous study design, and it has provided robust evidence that CBGT is an effective treatment in reducing depressive symptoms. Previously, one-year long-term follow-up study on CBGT is limited. This study has provided the long-term follow-up evidence. According to the result of this study, we have established the evidence base in mental health care for depression patients in Chinese population.

5. Conclusions

According to BDI-II, HSRS, and ATQ scores, CBGT effectively reduced the level of depression and automatic negative thoughts were maintained for 1 year. The effect of therapy showed a tendency to decrease depression and the techniques learned by the patients can provide patients with alternative thinking and reconstructive thoughts and correct their automatic negative thoughts and cognitive errors.

The study has several limitations which may hinder the final conclusions: the generalizability is limited by the exclusion of individual participants; other limitations include a relatively small sample size and the fact that this is an exploratory study. Moreover, the long-term follow-up allowed for collection of a number of events and outcomes that increased the longitudinal power. Despite these limitations, our results support CBGT for depressed patients continuing to be effective at the 1-year follow-up.

Conflict of Interests

The authors declare that no competing interests exist.

Authors' Contribution

Kai-Jo Chiang, Tsai-Hui Chen, Hsiu-Tsu Hsieh, Jui-Chen Tsai, Keng-Liang Ou, and Kuei-Ru Chou conceived and designed the study. Kai-Jo Chiang, Tsai-Hui Chen, Hsiu-Tsu Hsieh, and Kuei-Ru Chou performed the data collection. Kai-Jo Chiang, Hsiu-Tsu Hsieh, and Kuei-Ru Chou analyzed the data. Kai-Jo Chiang, Tsai-Hui Chen, Hsiu-Tsu Hsieh, Jui-Chen Tsai, Keng-Liang Ou, and Kuei-Ru Chou contributed reagents/materials/analytical tools. Kai-Jo Chiang, Tsai-Hui Chen, Hsiu-Tsu Hsieh, and Kuei-Ru Chou wrote the paper.

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Review Article

The Pathogenesis and Treatment of Emotion Dysregulation in Borderline Personality Disorder

Andreas Laddis[1,2,3]

[1]*Private Practice, Framingham, MA 01545, USA*
[2]*School of Public Health, Boston University, Boston, MA 02118, USA*
[3]*International Society for the Study of Trauma and Dissociation, McLean, VA 22102, USA*

Correspondence should be addressed to Andreas Laddis; aladdis@gmail.com

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Uncontrollable emotional lability and impulsivity are a paramount phenomenon of Borderline Personality Disorder (BPD). This paper aims to review theories that entertain emotion dysregulation as the core deficit of BPD and a key factor in the etiology of BPD, in order, then, to propose the author's own theory, which arguably transcends certain limitations of the earlier ones. The author asserts that his psychodynamic theory explains the symptoms of BPD more thoroughly and it inspires a more parsimonious interpretation of brain imaging findings. In closing, the author draws implications of the proposed theory for clinical practice. He reports an efficacy study for treatment of emotion dysregulation based on that theory.

1. Introduction

The generic term "emotion dysregulation" is used often to characterize a range of behavioral phenomena that are paramount in Borderline Personality Disorder (BPD). These phenomena consist of various negative emotions, a succession of fear, anger, anxiety, depression, guilt, and shame, with uncontrollable intensity and duration. Sufferers report feeble will to contain these emotions or to engage with others' interventions to that end [1]. Dysregulation of negative emotions occurs in the larger context of mood lability, that is, shifting abruptly between negative and positive moods, although negative moods still dominate [1, 2].

The term "emotion dysregulation" is also used for etiological constructs, explanations for this uncontrollability of emotions. Mostly, etiological theories are biological. They postulate an innate limbic abnormality and, with less certainty, a corollary abnormality in the prefrontal cortex [3–7]. They are inspired by the unresponsiveness of emotion dysregulation in BPD to psychotherapeutic interventions and by the resemblance to emotion dysregulation in certain neurological syndromes. The most accepted variant among them [3] proposes that limbic abnormality is not sufficient to explain the pathogenesis of emotion dysregulation. It adds the qualification that, differently from other neurological abnormalities, it is possible to learn skills to modulate the BPD kind of abnormal limbic excitation, just as it is for normal excitation. A severe limitation of biological theories is failure to explain how a limbic abnormality can be object-specific. In contrast to neurological syndromes, emotion dysregulation in BPD occurs only with negative emotions evoked strictly during adversity in a relationship, like threat of betrayal or abandonment [2, 8]. Even so, it does not occur in every instance of such adversity [1, 7]. More ambitiously, psychodynamic theories about the nature of emotion dysregulation in BPD aim to transcend that limitation of biological theories.

This paper begins with review of factor analyses of BPD symptoms, which strongly indicate that emotion dysregulation is a cardinal feature of BPD. Next, it reviews studies in the neuropsychology and neurobiology of normal emotion regulation and its developmental roots in attachment theory. The next two sections review biological and psychodynamic theories of emotion dysregulation in BPD. That review concludes with presentation of the author's own psychodynamic theory that is composed of well-researched concepts from cognitive psychology. The proposed theory features a very specific core psychological shortcoming born of errant, sometimes

exploitative, caretaking practices in BPD patients' childhood. The paper proceeds with description of clinical concepts and techniques that implement the proposed theory's advantages and with a preliminary study of such interventions' efficacy.

2. Descriptive Psychopathology and Factor Analyses

Exploratory and confirmatory factor analyses of diagnostic criteria for BPD support the hypothesis that emotion dysregulation is the core mechanism [9–14]. These factor analyses used diagnostic criteria from the American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders*, *4th Edition* (DSM-IV) [2]. (The criteria remain unchanged in the current edition, DSM-5.) The analyses conclude in favor of either a one-factor or a three-factor model. Emotion dysregulation pertains to eight of nine diagnostic criteria (exception: chronic feelings of emptiness) [2, p. 654]. They are rephrased below to highlight the strict correlation of emotional excess and lability with very specific adversity, namely, threat of betrayal or abandonment:

(i) Frantic efforts to avoid real or imagined abandonment in a valuable relationship.

(ii) Lability, that is, sudden and dramatic shifts in the sufferer's view of oneself and of others, alternating between idealization and devaluation.

(iii) Affective instability, marked reactivity of mood, mainly irritability and anxiety.

(iv) Potentially self-damaging impulsivity, for example, reckless sex or driving, drug use.

(v) Inappropriate and intense, uncontrollable anger.

(vi) Recurrent threats to commit suicide or self-mutilation.

(vii) Transient, stress-related paranoia and dissociative experiences.

Several studies revealed a unidimensional structure for BPD [10, 11, 14]. Among them, Fossati et al. [10] as well as Johansen et al. [14] found high diagnostic efficiency of "unstable relationships," which highlights the object-specificity of emotion dysregulation in BPD. Others [9, 12, 13] found support for multidimensional models. One exploratory factor analysis [9] revealed three factors, disturbed identity and interpersonal relationships, affective dysregulation, and impulsivity. Sanislow and colleagues [12] submitted this model to confirmatory factor analysis. They found DSM-IV criteria to comprise a statistically coherent construct, along three dimensions, now named disturbed relatedness, affective dysregulation, and behavioral dysregulation. Putnam and Silk [7] assert that the results from Sanislow et al. can also be interpreted as representing a single factor because those three factors pertain to a single event. Factor analyses with adolescent cohorts [11] showed a small, disputable departure from the construct of BPD for adults.

Findings from studies of the neurobiology of BPD are pertinent to those from factor analyses. Hypotheses for brain imaging studies in BPD are based on findings for normal emotion regulation. As expected, they focus on the prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, and amygdala and their connections [7, 15]. A thoughtful review concludes that "structural, resting functional, and task-related functional neuroimaging in BPD implicate a network consisting of disrupted amygdala and PFC function, in particular regions in the ACC … and ventral medial PFC" [7, p. 915]. Occasionally, findings for the PFC were negative [16, 17]. Some authors considered their findings to be characteristic of BPD, compared with brain imaging for other disorders with emotion dysregulation. Tebartz van Elst et al. [18] thought so of the specific combination of reduced volume in the amygdala, hippocampus, right ACC, and left orbitofrontal cortex. Others made a similar claim more precisely for reduced activity in the subgenual anterior cingulate cortex [19]. Alternative interpretations for such neurobiological findings in BPD will be discussed in a later section.

3. Normal Emotion Regulation and Its Development

3.1. Neuropsychology and Cognitive Psychology. The study of emotion regulation is one facet of studying the relation between cognition and emotion. It has attained well-researched concepts about the function and nature of emotion regulation [20–24].

The function of emotion regulation is to "stop and think" [25]. It is to stop pursuit of one's current goal or to suspend one's mood, that is, one's lingering emotional preference for the current goal, as the means to resetting one's priorities. The initiative to reset priorities is carried out more or less deliberately, as a priority of its own value, driven by preference for it. Such preference for resetting priorities is born of (a) reasoning about problems with the current goal (unforeseen costliness, neglect of emergent, competing needs, etc.) and (b) reasoning about alternative priorities becoming valuable and feasible [24, 26]. The *power* to reason about alternative priorities takes leaps with stages of brain maturation. The *will* to rethink one's priorities, on the other hand, is acquired with individual experience of its benefit, that is, the benefit of searching for new possibilities before one can know that they will be found. Infants are introduced to that benefit by caretakers who help them regulate their emotions and guide their attention about possibilities in reality that the children themselves cannot discern. Section 3.3 will describe progress in the study of attachment and development of emotion regulation in some detail.

Normally, emotions mostly end spontaneously, without the person's awareness of priority when an initiative of changing priorities or when an initiative of different emotional value and higher priority is born in response to developments in reality or in the mind. That entails a physiological representation of the hierarchy of these priorities from old learning. Implicit preferences derive from success with old, once-conscious choices [23, 24]. For similar reasons, the preference to rethink an ongoing commitment itself may take over spontaneously. But shifting emotions spontaneously should not be called "emotion regulation." The term "emotion

regulation" should be reserved for intentional manipulation of (a) triggers of unwanted emotions and of (b) the course of the triggered emotion. Intention to stop and think, in turn, requires finding reasons to do so under the current conditions or adopting a trusted other's reasons.

Similar to the implicit mechanism that resets priorities spontaneously, there is an implicit mechanism that resists changing priorities; it grants force and tenacity to the emotion that drives the current priority [21–23]. This mechanism, too, derives from a once-conscious determination for the importance and urgency of the current goal. Commitment to a goal automatically primes the person's attention selectively for developments, in reality or in the mind, that are pertinent to the completion of this goal, developments conducive or adverse to it. Furthermore, that preference becomes stronger as the person approaches timely completion. Intentional emotion regulation may be initiated on top of these spontaneous adjustments of priority and force, whether to enhance them or counter them.

It is important to cite here yet another implicit psychological influence because it pertains to the review of emotion dysregulation in BPD later. Sometimes emotion seems to be generated and to endure independently from driving a goal, purposelessly. It seems that it starts with no reason, no intended outcome in relation to desired or feared objects, whether in reality or in the mind. That is why clinicians and factor analyses often distinguish between behavior dysregulation and emotion dysregulation. Sometimes, patients feel unable to stop pursuit of a failing goal in order to think of adjustments to its course or to think of priorities to replace it altogether. At other times, patients feel unable to end a seemingly purposeless emotion. They want to modulate it because it colors their current preferences, counter to their conscious reasoning, and it persists irrationally. There are two kinds of such lingering, seemingly purposeless moods. One is a mood of worry and irritability that coincides with rumination about lingering concerns, whose unintended contemplation intrudes recurrently. The second kind is a mood of vigilant anticipation of mistreatment in every relationship. Research in cognitive psychology has shown that such persistent and pervasive moods are initiated by conscious determination of priority to ascertain a current threat of betrayal. Then, they linger and prime attention selectively for negative aspects of unrelated priorities [21].

3.2. Neurobiology. The prefrontal cortex (PFC) is unanimously considered the locus of self-organization and self-direction [7, 26, 27]. Miller and Cohen describe the PFC function in concise and insightful terms: It is to "orchestrate thought and action in accordance with internal goals" [26, p. 167]. It consists of "active maintenance of patterns of activity that represent goals and the means to achieve them. They provide bias signals throughout much of the rest of the brain, affecting ... sensory modalities, as well as systems responsible for response execution, memory retrieval, emotional evaluation, etc." [26, p. 171]. The authors properly avoid saying that "it," the PFC, modulates, inhibits, primes, and so forth the function of other brain organs, because the patterns that the PFC relays to those organs represent the operations and commitments to one or another goal by the activity of the brain as a whole. A special property of the PFC perhaps pertains to the fact that goals gain immunity from interference as they approach completion. The PFC neurons retain the representation of the intent to complete the goal despite processing intervening inputs for other possibilities of initiative [26]. Furthermore, these authors hypothesize, progression to completion strengthens the interaction between neural representations of the effective behavior and neural representations of the transformations in the object. With reiteration of the process for similar goals, memory of successful behavior is encoded as a single skill with subtle and substitutable variations [26]. Miller and Cohen cite evidence that success-related emotions induce connectivity and structural development with neuromodulatory signals from the tegmentum to the PFC.

The insight that the experience of success may correlate with the size of brain organs that organize and encode learning will be revisited while entertaining interpretations of structural brain imaging findings in BPD. It has inspired a similar well-founded hypothesis about the size of the ACC in particular [28]. As mentioned earlier, some consider hypofunction of ACC's subgenual part or small size of the right ACC to be corollary of emotion dysregulation in BPD. The function of the ACC is commonly characterized as "conflict monitoring" because the ACC becomes active during experimental tasks that require a very exact order of steps despite constant cues to follow a more familiar but erroneous order [28]. That creates the subjective experience of vigilance and effort in order to inhibit responding to the familiar cues. How the ACC contributes to success remains in dispute. Certainly, the task requires some form of effortful, repetitive reappraisal and regulation of the familiar preference. Remarkably, this experimental task resembles having to ascertain threat of betrayal, disregarding someone's seductive cues of benevolence that obscure cues of betrayal.

3.3. Attachment and Development of Emotion Regulation. The essential social-psychological task of raising children is to develop their ability to reason about their priorities and to know when such reasoning itself becomes a priority. Biologically, that means (a) maturation of working memory, that is, the brain's capacity to manipulate and compare a range of options, including untested possibilities, and (b) the ability to inhibit urges deriving from old preferences. Socially, it means learning to collaborate with others (a) for possibilities of individual initiatives beyond one's own imagination and (b) for ends that can be pursued well only jointly. This section will present briefly the foundation of such development in childhood with an emphasis on emotion regulation.

The physiology of fundamental emotions itself is not fully mature at birth [29]. The complement of characteristics (facial expression, body posture, hormonal, autonomic, etc.) of fundamental emotions is innately given and invariable. Some of them, for example, distress from physical discomfort and disgust at certain smells and tastes, are mature even in preterm babies. Unmistakable expression of anger, on the other hand, seems to coincide with the advent of locomotion.

Critical among fundamental emotions are surprise and interest for novelty. Infants' distress from fear manifests differently from distress due to frustration of interest and play [27].

The physiology of comparing a range of options and inhibiting old preferences (frontal and cingulate cortex, hippocampus) matures very slowly, into late adolescence or beyond [30]. Its maturation seems to progress in pace with the growth of the parietal and temporal cortex and certain subcortical and cerebellar regions [29, 31]. That physiological fact is manifested in behavioral progress. Six-month-old infants are already able to inhibit distraction when invited to learn something new [29]. But the capacity for speed, accuracy, and complexity of those operations grows later by means of utilizing information from those concurrently growing regions. The size and functionality of the ACC, especially on the right side, seem to take the largest leap in toddlers [27, 28].

Infants' mature fundamental emotions are the medium for induction of growth by caretakers. Infants spontaneously engage in novelty, but their interest propels them to exploration only to a point. Their motivation must be sustained by caretakers who structure and demonstrate the possibilities for the next step [32], a process aptly called motivational scaffolding [33]. That begins with attunement with the caretaker's facial expression of interest, desire, fear, or whatever, in reference to objects and events. Eventually, children learn to initiate this kind of "social referencing," looking at the caretaker's face and posture as a guide about what matters around them [29]. Infants become able to disregard interfering temptation, fear, or discomfort, more or less spontaneously, while the caretaker's eyes and gestures direct their interest to an object [33]. If necessary, caretakers may manipulate distracting objects and the infant's attention and posture to create opportune conditions for the child's commitment to the goal. Staging lessons collaboratively in that manner is for children the source of learning the value and the skills for willful, effortful emotion self-regulation.

From the regularity of parents' response to their distress, infants learn to expect being picked up for comfort. One-month-old infants soothe themselves while the caretaker is still approaching [34]. At four months, infants cry more loudly if the caretaker is unresponsive. Beginning at that age, the distress probably is not from physical discomfort but from wanting company for play and exploration [29, 32]. Children, then, may endure frustration in play because "affection/faith in the caretaker is a more important motive than [solitary] pursuit of the goal" [29, p. 519]. Perhaps surprisingly, it seems that before age of six months infants will take comfort from any responder, whereas later they learn to expect it from a preferred caretaker [35].

4. Biological Theories and the Neurobiology of BPD

There are two variants of biological explanations of emotion dysregulation in BPD:

(1) The first variant is about biological abnormality of limbic excitation, alone or combined with abnormality of the prefrontal regulating cortex. The prototypical, comprehensive developmental theory by Linehan tends to attribute such abnormality to genetics. Others, mainly from the domain of Complex Posttraumatic Stress Disorder (Complex PTSD), an entity related to BPD, with very similar pattern of emotion dysregulation, attribute such abnormality to toxic influences from the physiology of recurrent traumatic distress in childhood [36].

(2) The second variant also comes from the domain of Complex PTSD [37]. It postulates that the physiological representation of failed, trauma-related coping is endowed with extraordinary force. When triggered later by reminders of such trauma, the person reflexively resumes the old commitment to successful coping with force and tenacity, unable to stop and reappraise the current triggering event for its true value.

This section will summarize variants of Linehan's theory in particular, because it has provided the rationale for hypotheses in brain imaging studies. Then, it will discuss interpretations of findings from those studies.

4.1. Biosocial Developmental Theories. Linehan [3] took note of how unresponsive to psychotherapeutic intervention the *phenomenon* of emotion dysregulation in BPD patients is and she attributed it to a "fundamental" psychological *mechanism* of emotion dysregulation. She conceived the creation of that mechanism in "biosocial" terms, that is, as the outcome of a "biological irregularity ... combined with certain dysfunctional environments," in the manner of neglect or exploitation by the child's caretakers [3, p. 42]. The biological vulnerability consists of extraordinary limbic excitability for danger that shows as quick and intense arousal and slow return to emotional baseline. Based on research available at the time, Linehan attributed this biological vulnerability to innate temperament; however, she allowed for intrauterine and postnatal influences. She entertained that the mechanism of that uncontrollable excitability resembles that of partial complex epileptic seizures or other neurologically based limbic dysfunction. On the other hand, she explained the BPD patients' insufficient modulation of limbic "irregularity" as failure to develop modulation skills through experience, not due to a biological shortcoming. Therefore, such skills could be learned belatedly in psychotherapy; they consist of (a) suppressing one's somatic experiences of emotion and the urge to act defensively and (b) turning attention away from the threat and committing to a fear-free priority.

Linehan attributes BPD patients' failure to acquire modulation skills to invalidating environments of their childhood. Invalidating caretakers do not recognize the extraordinary intensity and duration of emotion as an innate irregularity, which they must modulate with extraordinary patience and effort. Instead, they respond to the child's excitability with erratic, inappropriate, and extreme ways, punishing it or trivializing it, as if the child exaggerated it for other reasons. Children, in turn, are left feeling blamed or disbelieved about the genuineness of their emotions. Linehan founded this

theory of invalidating environments and insufficient development of emotion modulation on earlier literature about (a) the harmfulness of a family's "expressed emotion" for a member with mental disorder and (b) disregard for certain temperamental expressions of discontent in early infancy because they contradict cultural ideals of femininity. This interpersonal mechanism of emotional invalidation greatly resembles the mechanism of emotional abuse and neglect described later in the context of attachment theory.

Curiously, Linehan does not address the *psychodynamics of emotion dysregulation* in BPD, that is, how patients appraise *reasons to persist with the emotion and defensive action and reasons to regulate it* and, then, how they choose which to enact. Having skills is only part of that determination. On closer look, the course of emotion dysregulation in BPD suggests that patients labor to reason whether to sustain their emotion or regulate it. BPD patients report becoming recurrently aware of the need to contain their fear and defensive action, but also becoming recurrently driven to persist urgently, before they could find sufficient reasons to enact containment [1]. They fail to stop and think because their reasons to will doing so are still insufficient, not despite having intended so with certainty. The section about attachment theory described how children learn the benefit of containing their emotions, which then, under similar conditions, becomes their reason to will containing their emotions later. The last section of this paper demonstrates the clinical importance of understanding the mechanism of BPD patients' emotion dysregulation in psychodynamic terms. There, the author describes an experimentally tested crisis intervention by means of giving the sufferer reasons to stop and think, nonetheless, while still engaged with the object of fear.

Several authors have adopted Linehan's etiological paradigm of developmental failure to compensate for innate limbic hyperexcitability [4–7]. Some [4] coined the name "hyperbolic temperament" for it. A theory by Gratz and colleagues [5] is notable because it began to amend the construct of innate limbic hyperexcitability, without abandoning it altogether, in order to accommodate the multitude of BPD phenomena that contradict it. One such discrepant phenomenon, in articles cited above, is that fear and commitment to defensive actions during episodes of disorder fluctuate, apparently due to current reappraisals of the danger and one's coping options. Gratz and colleagues themselves focus on another example of phenomena that contradict innate limbic irregularity: preadolescent children with BPD traits often take risks without much vigilance for pain and damage.

Furthermore, along with others [7], Gratz and colleagues noticed that adult BPD patients shift between risk-taking and risk-avoidance. Innate tolerance for risk enhances a person's willingness to endure threat as the means to attaining a desired outcome [38]; in BPD patients, it implies ability to regulate limbic excitability for danger in selected contexts. Indeed, between episodes of disorder, BPD patients choose to expose themselves to danger in two qualitatively different ways that could be aptly described as sensation-seeking and risk-taking [1]. In the instance of sensation-seeking, they periodically expose themselves to harm and exploitation for immediate petty satisfactions, recklessly, with genuine indifference for the long term, therefore, with little fear and little need to contain it. On the other hand, they periodically reinvest in lasting relationships for their long-term needs; then, they mind the risk of betrayal and abandonment constantly. In the latter context, the patients' appraisals of risk of betrayal shift abruptly, which, in turn, determines striking shifts in the patients' threshold of limbic excitability for distress and sacrifices that they must endure.

To explain why the supposedly innate limbic excitability for danger prevails only in certain contexts, Gratz et al. [5] postulate a second innate trait, "disinhibition," which consists of several "dimensions," like sensation-seeking and risk-taking. Accordingly, BPD symptoms result from a "synergistic influence" of the two traits. The authors properly cite evidence that a measure of tolerance versus aversion for risk is a heritable trait, with obvious advantages for each preference [38]. But they acknowledge that the correlation between *innate* proclivity for risk-taking and BPD in adulthood is far from established. Finally, they offer no theory for the hypothesized mechanism of "synergy" between innate limbic excitability and innate risk-taking.

4.2. The Neurobiology of BPD. Structural, resting functional, and task-related functional neuroimaging in BPD found aberrations in activation or volume in a network that consists of particular regions of the PFC (especially the dorsolateral PFC, DLPFC), the ACC, and the amygdala [7, 39–41]. This restates an earlier summary from reviews of findings from brain imaging to set the stage for expansion to subtler data and, next, for discussion of whether the data support the biosocial theories above. A small hippocampus is another consistent finding, but it is not accompanied by functional neuroimaging data and it is a finding for various mental disorders [7, 39, 40]. One review included hyperactivation of the insula and sparse connectivity between the insula and the ACC as a marker of emotion dysregulation in BPD in particular [42]. Other reviews entertained unilaterally low volume in the left OFP and right ACC as typical of BPD, compared with other disorders with much anxiety and depression [40, 41]. This summary uses "aberration" to avoid terms like alteration, dysfunction, disruption, impairment, and so forth, which imply brain damage or cessation of development. The literature is replete with this kind of implicit interpretation of neuroimaging data as damage and maldevelopment. The paragraphs below will gather evidence and reasons for alternative interpretations.

Various findings are discrepant with the initial summary in various ways. For example, some studies showed no structural or functional aberration from imaging of the prefrontal cortex of BPD patients [16, 17]. In another kind of discrepancy, opposite to expectation, the amygdala showed greater activation in response to effortful regulation of emotion, the latter being evident as prefrontal activation. One very common finding raises doubts about the innateness of limbic excitability in BPD and about the interpretation of brain imaging variations as damage: several brain imaging manifestations of emotion dysregulation in BPD are present also

during emotion dysregulation in persons with various mental disorders or no mental disorder, for example, in violent offenders, aggressive psychiatric patients, and uncontrollably anxious or depressed persons with unspecified diagnoses [40]. Finally, clinical remission of such uncontrollable anxiety and depression is consistently accompanied by reversal of the functional neuroimaging variations that those patients share with BPD patients at times of dysregulation [41]. That effect follows treatment with either medication or psychotherapy, but it seems to last longer after psychotherapy. It makes a powerful argument against the prevailing interpretation of neuroimaging findings as evidence of damage or stunted development.

Crocker and colleagues give good reasons for alternative interpretations [40]. Neuroplasticity could be a sufficient explanation for most findings, given the role of all these brain parts in consecutive physiological embodiments of learning. A related principle to remember while interpreting these findings is that neurogenesis, new connections among neurons and myelinization, which result in volume changes, ensue only from behavior that comes to successful closure [24]. Very insightfully, Bush and colleagues hypothesized that "success of [behavioral] regulation ... might be correlated with cingulate size" [28, p. 215]. It is reasonable to conclude that the physiology of success is what makes treatment with antidepressants or psychotherapy "neurotrophic," promoting brain growth and maturation, not the office visit or the antidepressant chemical itself [41]. In that light, this paper proposes the following interpretation of neuroimaging data: brain systems which mediate appraisal of possibilities for goals and timely completion of chosen goals vary in activation and size depending on their history of having done so successfully. Small size of those structures reflects repeated failure to learn how to choose *and then complete* the most compelling among everyday goals, like coping with conflict and betrayal of expectations in important relationships. Such is indeed BPD patients' predicament.

5. Psychodynamic Theories of Emotion Dysregulation in BPD

In contrast to biological theories, the psychodynamic ones have conceptually the potential to explain all phenomena of emotion regulation in BPD. They aspire to doing so parsimoniously, by postulating a single mechanism, namely, conflict among reasons for or against regulating the emotion, all generated concurrently in the present [1]. For example, psychodynamic theories promise to postulate and prove *reasons and motives* why patients with BPD sometimes regulate inklings of mistrust and fear very easily, as they do in a phase of infatuation with someone. They similarly promise to explain why in other phases of the same relationship patients must exert much effort to regulate such emotions and they occasionally succeed. For psychodynamic theories, forming the intention to regulate an emotion (if biologically able to do so) is separate from the biological ability to enact it. Normal fluctuations or anomalies in the biology of self-control are one among several reasons to contemplate before making the commitment to do so. People who misjudge their biological *ability* to enact their *intention* to self-regulate discover their attention and effort failing their intention. Even persons with biological shortcomings of emotion regulation are able to do so, if only to a point, with much effort and with help from trusted others. Mental disorder is different from repeatedly failing to control decidedly unwanted behavior. It consists of certain behavior becoming more compelling and concurrently more perilous, unwanted.

The main challenge for psychodynamic theories is to discern *reasons and motives* for such *disorder* of emotion regulation. Indeed, BPD patients experience emotion dysregulation as having reasons to persist despite concurrently having reasons to fear persisting. The challenge for psychodynamic theories is in the fact that some of the reasons and ensuing motives are active implicitly, outside the person's awareness. Psychoanalytical and cognitive-psychological theories have different explanations for the generation of implicit influences in psychodynamic conflict. The author proposes a theory to explain emotion dysregulation in BPD that is composed of well-tested cognitive-psychological concepts about the relation between explicit and implicit motives.

5.1. The Psychoanalytical Theory. While studying Linehan's theory, Selby and Joiner Jr. determined that it was necessary to augment it with a decidedly psychodynamic dimension [6]. They determined that disorder was about the purposefulness of emotion, the linkage between emotion dysregulation and behavior dysregulation [41]. They thought that, whatever the person's innate temperament might be, *emotion gains strength from the person's reasons to persist with a current goal* that the emotion propels. In emotion dysregulation of BPD, that goal is invariably to ascertain a threat of betrayal. Tying the strength of emotion to the value of a goal implies that emotion becomes uncontrollable if the person's commitment to that goal becomes compelling and urgent. Selby and Joiner Jr. explain that BPD patients ruminate and catastrophize unnecessarily about failing to manage a threat of betrayal. Thus, they kindle their fear and defensive actions repetitively with "pernicious" results in the manner of a "cascade of emotions." These authors' insight about the psychodynamics of circularity to the end of mastery is very valuable. Still, the limitation of this theory is that it does not address *reasons* why BPD patients catastrophize about a particular instance of betrayal in a particular relationship.

Patients' unstoppable rumination typically is about making sense of catastrophic betrayal in the past. Alternatively, it is about perceived betrayal in the present, however, over a trivial want or in an insignificant relationship. Psychoanalytical theory explains the urgency with which such rumination intrudes with various unconscious motives, that is, motives which patients do not recognize as active in them presently. One unconscious motive that theory attributes to patients is to urgently master old traumatic betrayal, either retrospectively, in their memory, or by asserting themselves over trivial wants in the present. Such interpretations do not explain why mastering old betrayal in memory and fighting over trivial unfairness become urgent in the particular instance, let alone why without the sufferer's awareness. At other times,

BPD patients are mostly oblivious to everyday unfairness and can usually end reminiscing of old trauma at will. To remedy that psychoanalytical limitation, the psychodynamic theory proposed in this paper attributes to patients a motive to ascertain a current threat of grave betrayal in a life-defining relationship. Preoccupation with lesser unfairness and with old trauma derives force *from the need to urgently make sense of the threat that matters singularly in the present*. That urgent need lingers latently and influences conscious priorities implicitly, but patients can be helped to remember having made that linkage consciously. They can remember appraising ways to cope with the current threat as futile because of numerous shortcomings; drawing lessons from old trauma engages the sufferers' attention most because it is the one shortcoming that seems in the sufferer's control to remediate.

It is instructive to note how psychoanalytical theory has attempted to explain patients' unawareness of reasons to pursue mastery of old trauma in memory so relentlessly. It has resorted to a biological, instinct-like mechanism called "completion principle" [37]. Accordingly, learning to finish old failed tasks is physiologically branded in memory as of some priority and once triggered later, it automatically displaces the person's consciously preferred priorities. In fact, this explanation was born in the study of PTSD, where uncontrollable reminiscing of a particular traumatic event is a paramount feature. The empirically testable laws of learning theory contradict the notion of such a completion principle. New lessons are physiologically encoded to be remembered only if successful [20, 24]. Unfinished lessons, too, are similarly encoded if the need for their completion is anticipated consciously [21]. Furthermore, once triggered later, the drive to finish an old lesson is instantly subject to reappraisal and modulation, just like any other motive evoked reflexively. The drive to finish learning how to cope with betrayal takes priority only if it is triggered in the context of consciously needing that lesson urgently.

Some psychoanalytical authors explain emotion dysregulation in BPD with yet another unconscious motive. They describe the patient's relentless, though self-damaging, behavior as "repetition compulsion." They attribute to patients an unconscious motive to replicate being loved for being inadequate, needy, and submissive, as in earlier mistrusted caretaking relationships. That theory says that survivors of childhood abuse make an "introject" of an abusive caretaking relationship as a preferred outcome to be recreated in later relationships. Then, unbeknownst to themselves, they enact the subordinate's part one-sidedly, repeatedly, to induce the other into the dominant role [42, 43].

Findings from social psychology [44, 45] provide an explanation for how regressive motives may be attributed falsely to a person. In other words, a person's actions may appear to serve a latent motive against one's interests (e.g., to be loved for being exploitable), even opposite to one's declared goal otherwise (to test the other's trustworthiness). Curtis [44] critiques psychoanalytic theories that attribute regressive, no longer wanted behavior to "enduring personality dispositions" which prevail *automatically*, that is, by force unrelated to appraisal of current developments. He believes that such theories show "lack of attention to the influence of current situational variables . . . on maintaining the current self-organization of behavior" [44, p. ix]. In other words, such theories are blind to interpersonal developments that trigger habitual, unwanted behavior faster than they stimulate the person's reasoning to modulate it. Studies in social psychology [46, 47] have demonstrated how a person's honest intent to change old personality traits may be derailed. People committed to learning new social rules still borrow components from their old behavior, which others then misinterpret as a true, though unspoken, intent to deceive and they treat it accordingly. For those who honestly deny such an unspoken intent to deceive, some in the psychoanalytic tradition would still postulate an unconscious motive to regress.

5.2. The Proposed Psychodynamic Theory

5.2.1. The Core Deficit and Pathogenesis. Indeed, the outcome of BPD patients' actions during emotion dysregulation is often exploitation by others, as the outcome of the purported unconscious motive to replicate old abuse would be. However, on closer look, the patients' singular motive that drives their self-defeating behavior is the opposite; it is to ascertain threat of betrayal urgently, so as to avert it [48]. Having had an inkling of betrayal, patients become urgently motivated to prove it. With stealth, hiding their true motive, patients stage hypothetical situations that justify making excessive demands and sacrifices, the kind of events that others misinterpret as intended to replicate being loved for their submissiveness and neediness. The proposed theory explains why patients fail to stop and think [49]. Why do they repeat that testing method relentlessly, despite becoming aware that it defeats their true purpose?

That method is born as the only way that children can test the trustworthiness of caretakers who manipulate the child's operations in order to make their own trustworthiness untestable. Caretakers who want to keep their caretaking prerogatives despite failing their function, for whatever reason (exploitation, inadequacy, etc.), give false reasons for failing and then manipulate the child's ability to prove those reasons false. They manipulate the evidence for their reasons and the evidence that alternative caretakers are trustworthy or the child is worthy of them. If their deception is discovered, they shift the criteria of proof of their fidelity and earn the child's patience with bribes and threats of punishment.

Putting the burden of proving their deception on the child perverts the rules of intimacy [1]. To explain the gravity of that, it is necessary to briefly define the function of intimacy and its rules. Partners in intimate relationships (e.g., parents and their children, siblings, lovers, and life mates) make a commitment to collaborate for the satisfaction of each other's needs in the long term, despite any foreseeable adversity. They commit to taking care of each other's needs before they can know them, even after one partner may become unable to contribute. By the rules of intimacy, a partner who fails promises made and expectations fostered has the burden of proving reasons to fail, including temptations and selfishness. The aggrieved partner, on the other hand, has the burden

to make up for the failing partner's legitimate shortcomings and to help correct them, without exploitative tradeoffs and punishments. The rules of intimacy serve to invite partners to reveal their weaknesses and get help, without danger of exploitation or abandonment. Loving partners strive to prove themselves trustworthy, instead of requiring the other partner to catch them dishonest.

Staging hypothetical situations suddenly is the only power that a child has to test caretakers before they could create false appearances of good reasons to fail. At the same time, for children trapped in untrustworthy relationships, that becomes the limit of their imagination about how trust can be measured and tested. Upon having an inkling of betrayal, BPD patients presume that others will necessarily manipulate them. The author proposes that this belief is the core deficit in BPD.

5.2.2. The Testing Method

Regressive Social Learning [48, 49]. Having had an inkling of betrayal, BPD patients urgently assume the burden to prove it. With stealth, they stage hypothetical situations that justify making excessive demands and sacrifices. Continually shifting moods of suspicion, vengeance, cajoling, self-blame, and expiation all occur in the context of such testing. According to the author's clinical experience and research cited below, vehement reminiscing and testing lesser relationships occur only in the context of a crisis of trust in a single relationship that matters. Others usually mistake the patient's purpose as manipulation for trivial or inappropriate wants. Some partners take advantage with bad tradeoffs and punishments. The better ones become wary and set harsh limits. For the patient, these painful responses become new triggers of apprehension and any justifications offered by the partner become new obscure reasons to sort out as true or false. The patients' own testing activity renders them less certain than before, one way or the other.

5.2.3. The Theory of Disorder in BPD. The author's theory of mental disorder hinges on a cybernetic concept. In cybernetic terms, disorder consists of derangement of a system's self-correcting mechanism, or "governor" [20, 28]. In human behavior, the governor is stopping to think. It consists of taking a step back to correct errors in the pursuit of a goal or ending the troubled goal unfinished to replace it with a more opportune one. Mental disorder, in turn, consists of errors in the governor's activity itself, which then results in failure to correct the troubled goal as well as failure to replace it. Rethinking the importance and urgency of ascertaining catastrophic betrayal could become a laborious goal of its own priority. The will to stop the troubled goal and think is constructed gradually with reasoning about intervening pains, costs, and competing needs gone unattended. BPD patients' experience is indeed of insufficient reasons, insufficient determination to stop their self-defeating behavior, whereas each round of failure generates new urgency to try again, before the sufferer could stop and think.

6. Implications for Treatment of Emotion Dysregulation in BPD

The author has developed a psychotherapy model for BPD and complex posttraumatic disorders. It is the Role Reconstruction Therapy (RRT) model, formerly presented as the Cape Cod Model [50]. It is based on the theory that the patients' regressive testing, commonly recognized as repetition compulsion, is the core deficit or core source of uncontrollable errors in episodes of disorder. The treatment is designed to engage the patient in learning the rules of intimacy. Patients and a partner in a particular troubled relationship, for example, a parent, brother, or lover, stage a few daily commitments to fulfill goals where one or the other anticipates betrayal. Betrayal, in turn, is defined as breaking promises made for bad reasons, namely, (a) for self-serving priorities or (b) because of shortcomings, like deficient skill, forgetfulness, anxiety, and so forth, which the failing person could remediate with others' help. The object of therapy is to demonstrate that it is possible to test another's trustworthiness with some certainty by the rules of intimacy. That entails requiring the failing partner to prove good reasons for the failure, instead of requiring the aggrieved partner to prove hidden bad reasons. This section will describe the crisis intervention according to the RRT and will present results from a study of its efficacy [49].

According to the RRT crisis intervention [49], the therapist first discerns the trigger of hyperarousal, that is, the threat of betrayal in a current relationship of singular importance. Then, the therapist engages the patient in ascertaining that partner's trustworthiness in an effective and timely manner, to replace repetition compulsion. The expected outcome is that the disorder will subside promptly upon engagement in coaching about the rules of intimacy and that the remission will last as long as the patient remains engaged. Patients will not relapse to disorder even if they discover betrayal in the particular instance, because their disorder is about their goal to attain certainty, one way or another.

The crisis intervention provides a technique to sidestep all symptoms (repetitive reliving of old trauma and disputes over trivial conflict in the present) in order to engage the patient about the underlying crisis of trust and repetition compulsion in the single relationship that matters urgently. The clinicians demonstrate how intimacy can be made safe: partners become transparent about reasons to fear and to mistrust, as well as reasons to fail the other's trust, if both parties respond in good will, without recrimination or rejection. This is a method that patients cannot envision on their own, to replace repetition compulsion, the mechanism of disorder and the source of all symptoms. With each crisis intervention, patients internalize a measure of competence in ascertaining threats of betrayal on their own. Beyond containment of symptoms, crises are treated as opportunities for reparative therapy in their own right.

The author tested the efficacy of this crisis intervention [49]. The study measured reduction of symptoms in the experimental and control groups treated separately, at comparable crisis intervention centers (run by the same authority, treating similar populations, and using the same

admission criteria). The control group received treatment as usual (TAU, which included elements of DBT and much more medication).

Ordinarily, the experimental intervention takes place for an hour or two initially and then in several shorter sessions over a period of the next day or two. Typically, patients arrive loudly preoccupied with desire, mistrust, worthlessness, and powerlessness in various relationships, including trivial or hallucinated ones. The therapist stimulates that preoccupation by listening empathically and inquisitively, in hope of eliciting associations with the relationship that matters the most, for example, with one's mother, brother, son, or lover. The therapist discerns that object of the patient's rising need and fear and speaks to those emotions with empathy and a hint of hope, for example, saying "it must be insufferable to live with such fear of someone that you need so much. There is a way to become more certain whether your fear is justified." Invariably, patients respond with a sudden lull in their unstoppable, irrational activity. In that lull, the therapist proposes that there is indeed a better method to become sure of the mistrusted partner's intentions, one way or the other; it can work for one failed commitment at a time, but certainty about the other's overall trustworthiness can accumulate in measurable increments. Engagement in that proposition replaces the patient's frantic regressive testing and symptoms cease for the duration of that engagement.

Modulation of particular symptoms with medication, grounding, and so forth is useful to facilitate engagement and reengagement in the therapeutic proposition. But such measures become unnecessary for hours or days at a time, as long as the patient invites the partner to ascertain each other's trustworthiness by the rules of intimacy: the patient and the partner assume the burden to reveal their true shortcomings for failing promises made and expectations fostered; then, they commit to a reasonable plan to remove those shortcomings jointly, with the aggrieved party's help.

The efficacy study found significant reduction of symptoms within 8–24 hours after initiation of this intervention, primarily as measured with the *Brief Psychiatric Rating Scale (BPRS)*. The BPRS consists of eighteen items and five subscales. There was significant improvement in the total BPRS score for the experimental group. Among the five subscales (thought disorder, withdrawal/retardation, anxiety/depression, hostility/suspiciousness, and activation), improvement was most significant for the four mood-related ones.

The Cochrane Collaboration reviewed studies of efficacy of crisis interventions for patients with BPD and recognized this study as one among 15 studies that "merited closer inspection," out of 1958 studies screened [51]. Compared to this rapid recovery of thoughtfulness and ability to regulate emotions, other selected "crisis interventions" lasted much longer, up to one month.

7. Conclusion

This paper reviewed the literature pertaining to the pathogenesis of emotion dysregulation in BPD and then it proposed a psychodynamic theory that the author argues remedies certain limitations of earlier theories. The author also presented the principles for a psychotherapy model according to the proposed theory.

The strength of this theory, compared to biological ones, is that it explains why limbic hyperexcitability in BPD is only episodic and strictly object-specific; it pertains only to danger of grave betrayal. In that sense it validates the collection of criteria in the DSM as a coherent entity. Compared to psychoanalytical explanations, in turn, the proposed theory has the advantage that it postulates implicit mechanisms and forces which can be verified as psychological facts. There is preliminary evidence that those conceptual advantages are of clinical value, measured as efficacy of treatment. The main limitation of the proposed theory is its status as largely untested. The efficacy of crisis intervention itself could be tested more rigorously, by isolating the effects of the singular RRT intervention (engagement in ascertainment of threat by the rules of intimacy) from other incidental treatment variables more methodically. There has been no investigation of efficacy for the long-term treatment with the RRT.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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Research Article

Multivariate Statistical Analysis as a Supplementary Tool for Interpretation of Variations in Salivary Cortisol Level in Women with Major Depressive Disorder

Ewelina Dziurkowska and Marek Wesolowski

Department of Analytical Chemistry, Medical University of Gdansk, Gen. J. Hallera 107, 80-416 Gdansk, Poland

Correspondence should be addressed to Marek Wesolowski; marwes@gumed.edu.pl

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Multivariate statistical analysis is widely used in medical studies as a profitable tool facilitating diagnosis of some diseases, for instance, cancer, allergy, pneumonia, or Alzheimer's and psychiatric diseases. Taking this in consideration, the aim of this study was to use two multivariate techniques, hierarchical cluster analysis (HCA) and principal component analysis (PCA), to disclose the relationship between the drugs used in the therapy of major depressive disorder and the salivary cortisol level and the period of hospitalization. The cortisol contents in saliva of depressed women were quantified by HPLC with UV detection day-to-day during the whole period of hospitalization. A data set with 16 variables (e.g., the patients' age, multiplicity and period of hospitalization, initial and final cortisol level, highest and lowest hormone level, mean contents, and medians) characterizing 97 subjects was used for HCA and PCA calculations. Multivariate statistical analysis reveals that various groups of antidepressants affect at the varying degree the salivary cortisol level. The SSRIs, SNRIs, and the polypragmasy reduce most effectively the hormone secretion. Thus, both unsupervised pattern recognition methods, HCA and PCA, can be used as complementary tools for interpretation of the results obtained by laboratory diagnostic methods.

1. Introduction

An efficient and accurate diagnosis is of primary importance for clinical care. A wide range of laboratory diagnostic methods has been developed to support strategies of disease control. Proper evaluation of large matrices of the data acquired with the aid of modern laboratory diagnostic techniques involves the use of advanced statistical methods. Multivariate statistical analysis is one that seems to be very useful to solve that problem. They enable us to explain the meaning of the multidimensional data in the mathematic and statistic way and to enable extraction of the most useful information from the complicated data sets.

Multivariate statistics includes both linear and nonlinear statistical tools that can be used in order to understand the relationships between variables and their relevance to the problem being studied [1–4]. There are many different multivariate models, each with its own type of analysis, for instance, multivariate analysis of variance (MANOVA), principal component analysis (PCA), discrimination analysis (DA), partial least squares (PLS) and their variants, cluster analysis (CA), and various types of artificial neural networks. These methods are very helpful in bioprocess data analysis [1, 4].

In multivariate statistics a data matrix is created in two dimensions, where the samples in the rows are described by variables in columns [2, 3]. PCA enables reduction of the number of possibly correlated variables into the smaller value of orthogonal ones. It is one of the most popular multivariate data analysis tools that can be applied to find correlation between variables and to observe changes in them. PLS allows us to find the latent relations between variables and is useful as a discrimination tool. In that way PLS is similar to PCA, while CA enables us to measure the similarities and dissimilarities between the samples and to classify them into

groups. In that way CA simply discovers structures in the multidimensional data without explaining why they exist.

PCA is widely used in medical studies. As claimed in the literature, this method has been used as supplementary tool facilitating diagnosis of some diseases, for instance, cancer [5–8], allergy [9, 10], pneumonia [11], or Alzheimer's disease [12]. The study of changes in cancer tissues by inspection of relationships between levels of trace elements (Pb, Al, Zn, Cd, Cu, Ni, and Co) in laryngeal cancer and healthy tissues suggests that PCA can differentiate the cancer and healthy tissues [7]. This method was also used to expose differences in the levels of various essential elements in serum and arterial wall of patients with atherosclerosis obliterans and the control group [13] and to discriminate between the levels of metabolites, such as amino acids and alcohols in serum of patients with oral cancer and healthy subjects [8]. Moreover, PCA was found to be an effective tool for grouping patients with the fourth stage of breast cancer and healthy ones into separate clusters based on the blood levels of hydroxylated phospholine lipids [6]. For better interpretation of the data, PCA is frequently combined with CA. This combination was used as a supplementary tool for diagnosis of Alzheimer's disease based on the serum concentration of multivalent cations [12]. The results show that both techniques can be useful for early detection of Alzheimer's disease enabling efficient therapy.

Multivariate statistics is also applied in psychiatry for solving problems due to interpretation of the data acquired for patients with major depressive disorder (MDD) [14] and bipolar disorder (BP) [15]. PLS has shown that the proton nuclear magnetic resonance (NMR) spectra of blood plasma of the depressed patients differ significantly from those of the control group [14]. Thus, NMR spectroscopy could be considered as a useful tool for the diagnosis of depression. The NMR spectroscopy was also used to study the blood serum metabolic profiles of patients with BP under different treatments [15]. Taking into account the levels of lipids, lipoproteins, and amino acids in blood serum of these patients, PCA and PLS suggest that the changes in metabolic profile of blood serum can be associated with the treatment. Gas chromatography/mass spectrometry coupled with multivariate data analysis tools has shown that the metabolic profiles of blood plasma can also be used as a novel laboratory-based test for diagnosis MDD and its subtypes (early life stress/MDD and nonearly life stress/MDD) [16]. Furthermore, hierarchical cluster analysis (HCA) was found to be a profitable tool for classifying personality profiles in women with perinatal depression [17].

The above literature screening shows that multivariate statistical analysis is a beneficial tool in the medical sciences for solving the complex relations between objects and variables in the multivariate databases. Therefore, the aim of this study was to use two unsupervised pattern recognition techniques, hierarchical cluster analysis (HCA) and principal component analysis (PCA), to seek the relationship between the antidepressants used in the therapy and the cortisol level and hospitalization periods of subjects with major depressive disorder (MDD). For this reason, the levels of the hormone were determined in saliva obtained from depressed women during their hospitalization, and the acquired matrix of the data was examined by advanced multivariate statistical methods, HCA and PCA.

2. Experimental Part

2.1. Participants. Women with MDD defined according to the International Classification of Diseases (ICD-10) were recruited into the study at the Hospital for Nervous and Mental Diseases in Starogard Gdanski (Poland). The enrolment was based on the clinical interview with psychiatrist. The subject was informed about the aim of the study and was asked for their written consent to participate in the study. They were also informed that they can refrain from participating in the study at any time if desired. The participants were excluded if they did not understand the meaning of the study or when participating in the study could be detrimental to their well-being. Pregnancy and breastfeeding were also excluding factors. Finally, 97 women with MDD were included in this study. The mean age of the participants was 48 (±10) years and mean period of hospitalization was 42 (±24) days. Multiplicity of hospitalization was 3 (±2) times. The study had been approved by the ethical committee of the Medical University of Gdansk, Poland.

2.2. Materials. Saliva obtained from depressed women treated with different antidepressants was used in this study. Because the hormone is secreted in the diurnal cycle and its highest level occurs in the morning, the samples were collected without any stimulation into plastic tube, every day about 10 a.m., during the whole period of hospitalization. The subjects were instructed to rinse the mouth with water and not to eat or drink about half an hour before the collection. After collection saliva samples were transported to the Medical University of Gdansk, where they were frozen until the analysis.

2.3. Hormone Assay. To quantify the salivary cortisol a HPLC procedure with UV detection was developed [18]. A mixture of acetonitrile and water (30 : 70; v/v) was taken as a mobile phase and a chromatographic column with C_{18} packing was a stationary phase. For calibration an internal standard, carbamazepine, was applied. The hormone was isolated from saliva by liquid-liquid extraction with dichloromethane.

2.4. Statistical Methods. All statistical calculations were carried out using Statistica 10 (StatSoft, Cracow, Poland) software. The level of statistical significance was set at $p < 0.05$. The Wilcoxon test was used for assessment of impact of the antidepressant therapy on the mean cortisol level during three periods of hospitalization. This test is an equivalent to Student's t-test. As a nonparametric statistical pattern it can be used for comparing two sets of samples or repeated measurements on a single sample. ANOVA test (one-way analysis of variance) was applied for evaluation of the impact of antidepressants on the hospitalization period as well as the mean and final levels of cortisol. This test is used for comparing the mean values of three or more sets of samples. Moreover, for assessment of statistically significant

differences among four HCA clusters, ANOVA test with the NIR test as a *post hoc* analysis was used.

To establish a relationship between the antidepressants as well as the cortisol level and hospitalization period due to MDD, HCA and PCA were used. For both multivariate techniques, a matrix with 16 variables characterizing 97 patients was created. The matrix included the patients' age, multiplicity and period of hospitalization, initial and final cortisol levels, its highest and lowest concentrations, and also the difference between them. Furthermore, mean concentrations and medians determined during the whole period of hospitalization as well as the mean levels of hormone in different hospitalization phases were also used. The best results were obtained using Ward's hierarchical agglomeration with Euclidean distance measure in HCA and strategy without the rotation of factors in PCA.

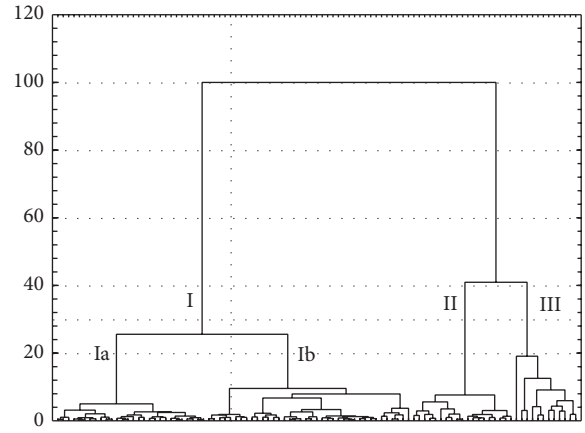

Figure 1: HCA dendrogram illustrating the clustering of ninety seven patients under antidepressant therapy.

3. Results

97 patients participated in this study who are hospitalized at the Hospital for Nervous and Mental Diseases in Starogard Gdanski (Poland). About 2700 saliva samples were collected from patients into plastic tube every morning during the whole period of hospitalization. The mean age of the patients was 48 years and the mean period of hospitalization was 41 days. As shown in Table 1, for the treatment of depression, antidepressants with different mechanism of action and defined daily dosage were used during the whole period of hospitalization. In some cases either combination treatment or neuroleptics, like olanzapine or perazine, were applied.

ANOVA test demonstrates that antidepressants used for the treatment did not have a significant impact on the hospitalization period ($p = 0.1160$, $F = 1.6416$). Moreover, this test also shows that the therapy has no influence on either the mean salivary level of the hormone ($p = 0.6263$, $F = 0.7899$) or the final cortisol level ($p = 0.8190$, $F = 0.5690$). The Wilcoxon test was carried out to indicate statistical differences among the mean cortisol levels in different hospitalization periods. This test has shown that there is a statistical difference between the mean concentrations in 30% and 60% of the hospitalization periods. The most significant differences were found during the treatment with TCAs (tricyclic antidepressants) ($p = 0.0229$, $Z = 2.2749$), SSRIs (selective serotonin reuptake inhibitors) ($p = 0.0003$, $Z = 3.6434$), SNRIs (serotonin and norepinephrine reuptake inhibitors) (0.0008, $Z = 3.3510$), SSAs (specific serotonin antidepressants) ($p = 0.0280$, $Z = 2.1974$), polypragmasy ($p = 0.0004$, $Z = 3.5162$), and neuroleptics ($p = 0.0058$, $Z = 2.7562$). However, there were no differences between the mean cortisol levels in 60% and 90% of hospitalization periods. In the case of the mean levels of cortisol in 30% and 90% of the hospitalization period, there were the differences when the patients were treated with SSRIs ($p = 0.0031$, $Z = 2.9603$), SNRIs ($p = 0.0012$, $Z = 3.2374$), polypragmasy ($p = 0.0006$, $Z = 3.4128$), and neuroleptics ($p = 0.0044$, $Z = 2.8451$).

The data set acquired in this study was subjected to hierarchical cluster analysis (HCA) and principal component analysis (PCA) to establish the relationships among subjects under antidepressant therapy with different active pharmaceutical ingredients. The results of HCA are presented in Figure 1. There are three clusters at a level of 1/3 of the maximum distance. The majority of the patients are grouped in cluster I, which is divided into two subclusters (Ia and Ib) at the level of 1/4 of the maximum distance. Patients with the low mean cortisol concentration when the highest hormone level was lower than 31 ng/mL are grouped in cluster Ia. Furthermore, in all cases the final cortisol concentrations were lower than 10 ng/mL. SSRIs and TCAs are the most commonly used drugs in the antidepressant therapy.

Cluster Ib is formed by subjects with the mean cortisol concentrations between 3 and 24 ng/mL. Also the mean level of cortisol in different periods of hospitalization was higher and was in the range from 1 to 45 ng/mL. In some cases the final cortisol concentration was above the reference value, and the highest one amounted to 42 ng/mL. In this cluster 11 patients were treated with combination therapy mainly with SSRIs and SNRIs or SSAs.

Clusters II and III are joined with cluster I at the maximum distance. Cluster II is created by patients with the mean cortisol level higher than the reference value. The level of the hormone was in the range between 10 and 31 ng/mL. Also the final concentration was higher (mostly a dozen or so ng/mL), but in some cases it was the several dozen ng/mL. The mean level of hormone determined in the different periods was between 4 and 83 ng/mL. In this group only SSRIs and SNRIs antidepressants were applied. There were no neuroleptics and the polypragmasy was used only in three cases. The majority of patients who formed cluster II were hospitalized between 29 and 82 days.

The last cluster is formed by patients with very high final and mean levels of the hormone determined during the 30%, 60%, and 90% of the hospitalization period. In all the cases the hospitalization was longer than 29 days.

The selected characteristic features of the patients created four clusters in Figure 1 are compiled in Table 2. The ANOVA test shows that the patients' age, multiplicity of hospitalization, lowest cortisol concentration, and median determined during the whole period of hospitalization did not have

Table 1: Average levels of cortisol in saliva of patients under antidepressant therapy.

Antidepressant	Active substance (dose, mg/day)	Monotherapy					Polypragmasy				
		Number of patients	Mean concentration of salivary cortisol, ng/mL				Number of patients	Mean concentration of salivary cortisol, ng/mL			
			Initial	Final	Highest	Lowest		Initial	Final	Highest	Lowest
TCAs	Amitriptyline (100 mg)	7	53.03	18.84	161.25	1.25	—				
	Clomipramine (100 mg)	3	16.46	13.08	55.00	2.50	1	72.00	5.50	72.00	2.62
	Opipramol (100 mg)	1	33.75	13.75	33.75	2.50	—				
	Doxepin (100 mg)	1	87.72	5.62	87.72	1.62	1	13.50	2.00	13.50	2.00
SSRIs	Sertraline (50 mg)	10	39.44	32.51	190.00	0.25	5	39.60	5.10	95.00	1.25
	Citalopram (40 mg)	7	59.46	6.89	93.25	0.62	3	52.42	8.42	72.00	1.75
	Escitalopram (20 mg)	5	47.46	4.77	98.50	1.25	4	39.45	5.06	61.00	1.25
	Fluvoxamine (100 mg)	3	43.54	20.75	49.75	2.50	—				
	Fluoxetine (20 mg)	1	2.50	3.75	3.75	2.50	—				
	Paroxetine (20 mg)	2	68.25	98.94	195.00	2.50	—				
SNRIs	Venlafaxine (75 mg)	14	88.32	9.13	372.5	0.25	5	41.55	5.45	95.00	2.50
SSAs	Mianserin (90 mg)	7	63.75	26.05	195.00	1.25	5	33.27	6.90	46.25	1.25
NaSSAs	Mirtazapine (45 mg)	1	33.00	8.62	33.00	6.25	1	31.25	2.75	31.25	2.50
SARIs	Trazodone (300 mg)	3	79.17	6.46	182.50	1.25	8	32.91	4.03	45.75	1.50
SSREs	Tianeptine (37.5 mg)	3	40.50	16.62	52.00	1.75	—				
RIMA	Moclobemid (600 mg)	1	37.50	5.62	37.50	1.25	—				
Others psychoactive drugs		10	44.51	12.22	133.50	1.25	1	42.50	25.00	42.50	2.50

TCAs: tricyclic antidepressants, SSRIs: selective serotonin reuptake inhibitors, SNRIs: serotonin-noradrenalin reuptake inhibitors, SSAs: specific serotonin antidepressants, NaSSAs: noradrenergic and selective serotoninergic antidepressants, SARIs: serotonin antagonist and reuptake inhibitors, SSREs: selective serotonin reuptake enhancers, and RIMA: reversible inhibitors of monoaminooxidase-A.

Table 2: Characteristic features of four groups of patients under antidepressant therapy displayed by HCA dendrogram.

HCA cluster	Antidepressant	Number of patients	Age of patients, years	Multiplicity of hospitalization	Hospitalization period, days	Initial and final cortisol levels, ng/mL	Highest and lowest cortisol levels, ng/mL	Mean cortisol level, ng/mL	Median for cortisol level, ng/mL
Cluster Ia	TCAs	5	51	3	29	16.57–9.67	1.25–26.25	10.80	8.44
	SSRIs	9	49	2	63	17.33–4.83	2.00–31.50	8.51	6.94
	SNRIs	2	44	1	59	15.00–5.53	1.25–24.75	8.50	7.53
	SSAs	3	39	2	66	20.58–5.21	1.25–24.25	9.30	8.75
	NaSSAs	1	63	1	21	33.00–8.62	6.25–33.00	17.50	8.62
	SSREs	1	28	7	46	27.50–9.25	1.75–27.50	8.62	7.62
	Others psychoactive drugs	4	44	3	25	12.56–7.92	1.37–21.25	7.59	6.69
	Polypragmasy	3	50	2	40	11.79–2.42	1.25–15.62	5.48	6.00
Cluster Ib	TCAs	4	55	1	71	31.06–11.59	1.25–55.00	12.98	9.15
	SSRIs	7	46	2	48	32.99–11.05	1.25–49.75	11.78	7.50
	SNRIs	5	45	2	63	33.80–12.57	1.25–62.50	9.31	4.00
	SSAs	1	57	2	46	29.50–2.87	1.25–29.50	6.34	4.62
	SARIs	2	42	5	80	27.50–7.19	1.25–37.50	9.13	7.34
	SSREs	2	47	2	21	47.00–20.31	1.75–52.00	16.24	10.69
	RIMA	1	50	5	23	37.50–5.62	1.25–37.50	10.41	6.12
	Others psychoactive drugs	4	42	3	31	34.75–7.70	1.25–38.75	11.84	6.25
	Polypragmasy	9	48	3	39	38.46–5.10	1.25–46.25	9.15	7.53
Cluster II	TCAs	2	60	1	28	86.86–6.62	1.62–87.70	22.26	10.53
	SSRIs	6	49	3	46	77.59–15.71	1.25–95.00	14.19	7.62
	SNRIs	5	45	1	38	82.25–7.85	2.50–91.00	20.97	10.00
	SSAs	2	58	1	53	58.00–6.31	1.37–102.00	12.47	7.87
	Polypragmasy	2	62	5	45	76.00–9.54	2.50–95.00	20.62	8.34
Cluster III	TCAs	1	31	3	32	161.25–83.75	8.75–161.25	50.57	30.62
	SSRIs	4	48	3	35	87.44–105.00	0.25–195.00	19.55	9.06
	SNRIs	3	44	2	51	234.96–7.72	0.25–3.75	30.03	5.94
	SSAs	1	53	6	29	195.00–151.25	5.00–195.00	26.03	11.25
	SARIs	1	51	4	76	182.50–5.00	1.25–182.50	26.73	13.00
	Others psychoactive drugs	2	45	2	33	366.27–41.25	1.25–133.50	16.97	7.28

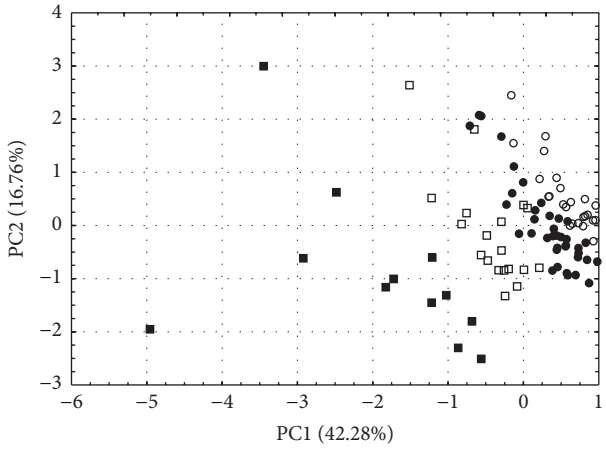

Figure 2: PCA scores plot illustrating the grouping of ninety-seven patients under antidepressant therapy. ○: cluster Ia, ●: cluster Ib, □: cluster II, and ■: cluster III.

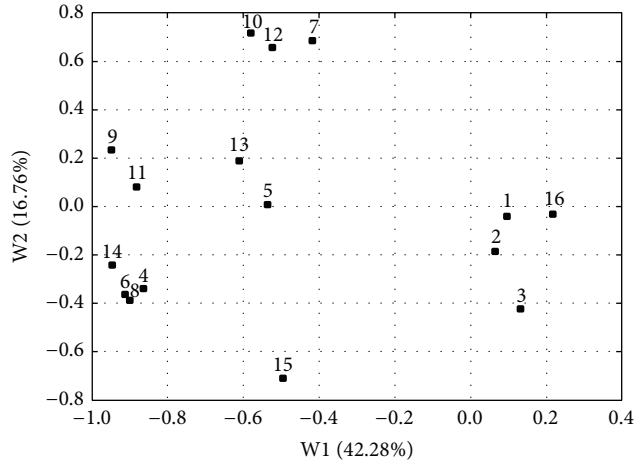

Figure 3: PCA loadings plot illustrating the impact of fourteen raw variables on the scattering of ninety-seven patients under antidepressant therapy. The Arabic digits denote the raw variables as follows: 1: patients age, 2: multiplicity of hospitalization, 3: period of hospitalization, 4: initial cortisol level, 5: final cortisol level, 6: the highest cortisol concentration, 7: the lowest cortisol concentration, 8: difference between the highest and lowest cortisol concentration, 9: mean concentration, 10: median determined during the whole period of hospitalization, 11: mean level of hormone during the 30% of the hospitalization period, 12: mean level of hormone during the 60% of the hospitalization period, 13: mean level of hormone during the 90% of the hospitalization period, 14: standard deviation of the mean concentration, 15: relative standard deviation of the mean concentration, and 16: antidepressant.

a significant impact on grouping the subjects into four clusters. However, the statistically significant differences between these clusters were found in the case of the highest cortisol concentration and the difference between highest and lowest cortisol concentration as well as standard deviation and relative standard deviation of mean cortisol concentration. This test also showed that there is a statistical difference between cluster III and remaining clusters taking into account the final cortisol level and mean level of hormone during the 90% of the hospitalization period.

The second multivariate approach, PCA, creates two first principal components (PC1 and PC2) that explain more than 59% of the data variability. Figure 2 illustrates a PCA score plot in the form of a two-dimensional plane. It confirms the results obtained by HCA. In both cases, patients formed three groups. The first one is created by subjects with initial cortisol concentration lower than 40 ng/mL. In the majority of cases the hormone level falls in the range of a dozen or so ng/mL. Also the mean level was dozen of ng/mL and the highest one the most often is the initial one. On the other hand, patients with a very high initial cortisol level and at the same time the high mean level of the hormone in the first period of hospitalization (30%) are grouped in cluster III. The same women formed the third cluster in HCA (Figure 1).

Figure 3 shows the PCA loadings, that is, the relationship between the raw variables and calculated principal components. The raw variables, which located the subjects according to the PC1 axis, were the mean, initial, and the highest salivary cortisol levels, the difference between highest and lowest cortisol concentration, the mean level of hormone during the 30% of hospitalization period, and the standard deviation of mean cortisol concentration. The most significant impact on the characteristic scattering of the subjects according to PC2 axis had the median, the lowest, and the mean levels of cortisol during the 60% of hospitalization as well as the relative standard deviation of mean cortisol concentration, which is negatively correlated with this axis.

4. Discussion

To disclose the relationship between the drugs used in the therapy of MDD and the salivary cortisol level as well as the period of hospitalization, 97 patients were treated with various groups of antidepressants. The largest group of the patients was treated with SSRIs that are the first-line drugs in the treatment of depression. These drugs have lower side effects in comparison with older TCAs. In this study 28 patients received SSRIs in monotherapy whereas 11 subjects were treated with SSRIs in polypragmasy. The second group of the most commonly used antidepressants was SNRIs. Venlafaxine, which was used by 14 patients in monotherapy, is only the one active pharmaceutical ingredient from this group that is applied in the therapy of depression in Poland. SNRIs are a new group of drug substances that act as inhibitors of serotonin and norepinephrine, and also by low increase in the dopamine concentration. The latter effect was found to be helpful in the treatment, especially for patient with decreased activity. Both patients with severe depression and patients of advanced age with any kind of depression are treated with TCAs. In this study 12 women were treated with tricyclic antidepressants in monotherapy, despite their numerous side effects [19].

Inspection of the data listed in Table 1 shows that the mean final level of cortisol was lower in almost all the therapies. Only in the case of paroxetine the mean initial hormone level was lower than the final one. Furthermore,

the majority of therapies decrease the cortisol concentration to the reference values. As reported in the literature, the salivary cortisol level of a healthy person in the morning should fall within the concentration range between 1 and 8 ng/mL [20]. Moreover, antidepressants used in polypragmasy much more strongly affected cortisol secretion and in all cases the reduction in hormone concentration was observed.

ANOVA test indicates that any of treatments do not affect the hospitalization period or the mean cortisol concentration. However, the Wilcoxon test revealed that some of the therapies enabled a better control of the hormone secretion. Among the ten different therapies used for the treatment of depression, four of these were the most effective. The therapies with SSRIs, SNRIs, polypragmasy, and neuroleptics decrease the cortisol level in the first fraction of hospitalization (significant differences between 30% and 60% of the hospitalization period). At the same time there were no differences in the cortisol levels between 60% and 90% of hospitalization, when these groups of drugs were used. The fluctuation of cortisol secretion did not increase in the third period of hospitalization as demonstrated by significant differences between 30% and 90% of hospitalization and no statistical differences between the second and third one were found.

In the case of TCAs and SSAs, the Wilcoxon test did not show significant differences between the mean concentrations of cortisol quantified in the same hospitalization period. These results can be due to fluctuation of the hormone level. On the one hand, in the first fraction of hospitalization the cortisol secretion decreased and at the end of the treatment (about 30th day) its level increased and the mean concentration was elevated. On the other hand, the cortisol secretion was raised at the beginning by only a few ng/mL and in second and third fraction of cure the level fell to the referential values. The differences between the absolute values were of the order of a few ng/mL, but at the same time they were a few times higher. Examples of this type of cortisol secretion are patients treated with TCAs.

Statistically significant differences between four clusters of the patients are due to concentration of cortisol, especially the initial and highest one but also the difference between highest and lowest cortisol concentration. It is difficult to identify which class of the drugs has the strongest power to reduce the secretion of hormone, because in all clusters all types of drugs are included. That is why it can be stated that this is individual differences in response to treatment, though some trends exist. In the first cluster 25% of the patients were treated with SSRIs (above 50% of all treated with SSRI) and 19% with polypragmasy (more than 26% of all treated this way), 14% with TCAs and almost 13% with others psychoactive drugs (80% treated with neuroleptics). In this cluster the fluctuation of the cortisol concentration during the whole period of hospitalization was the lowest. Also there were no significant differences between subclusters Ia and Ib in mean level of the hormone and the mean concentration of cortisol in the 30% of hospitalization, but there were the differences between these subclusters and two remaining. Moreover, the mean concentration of cortisol in the 30% of hospitalization was different in this cluster than in clusters II and III.

To sum up, multivariate statistical analysis has shown that there are no explicit results demonstrating which of the antidepressants had the greatest impact on the hospitalization period. In some cases it can be stated that there is a tendency to grouping the patients based on the influence of the treatment on the cortisol secretion. Both multivariate techniques have shown that in the first cluster there are the majority of the patients treated with TCAs, SSRIs, SNRIs, polypragmasy, and neuroleptics. This group is characterized by a small fluctuation of the hormone secretion. The best results of decreasing the cortisol concentration were achieved in the case of SSRI and polypragmasy treatment. The substantial group of patients treated with these antidepressants is grouped in cluster Ia, where the fluctuation of cortisol secretion during the whole period of hospitalization is the lowest.

The results obtained by HCA and PCA were confirmed by Wilcoxon test, which revealed that antidepressants, such as TCAs, SSRIs, SNRIs, SSAs, or polypragmasy, but also neuroleptics, reduced to the highest degree the cortisol secretion in the first 30% of the hospitalization period. In the case of SSRIs, SNRIs, and polypragmasy, the reduction of the hormone secretion was also retained to up the end of the hospitalization. It can thus be concluded that the inhibition of the secretion is stable.

Almost all patients treated with polypragmasy are grouped in clusters Ib and II, both in the HCA dendrogram and the PCA score plot. It is known that combined treatment is only used, when a patient does not respond to the treatment with one drug. In this case the cortisol secretion is inhibited by two or even three drugs with different mechanisms of action.

HCA and PCA have also demonstrated that neuroleptics, which are also used for the treatment of depression, did not create a separate cluster. In this case, almost all the patients treated with antipsychotic drugs are grouped in cluster I. This suggests that neuroleptics affected cortisol secretion similarly as did antidepressants.

5. Conclusions

This study has shown that various groups of antidepressants affect in the varying degree the cortisol level. SSRIs and SNRIs, but also polypragmasy most effectively suppress the hormone secretion. The results of this study were confirmed by HCA and PCA. Both multivariate statistical techniques can be used as complementary tools for interpretation of the results obtained with the aid of laboratory diagnostic methods.

These analyses suggest that the determination of cortisol level at the beginning of the hospitalization and its decreasing during a few first days of the treatment can be helpful in prognosis of the effectiveness of therapy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Social Anxiety among Chinese People

Qianqian Fan[1] and Weining C. Chang[2]

[1]*Division of Psychology, School of Humanities and Social Sciences, Nanyang Technological University, 14 Nanyang Drive, Singapore 637332*
[2]*Department of Clinical Sciences, Graduate School of Medicine, Duke-National University of Singapore, 8 College Road, Singapore 169857*

Correspondence should be addressed to Qianqian Fan; qfan002@e.ntu.edu.sg

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The experience of social anxiety has largely been investigated among Western populations; much less is known about social anxiety in other cultures. Unlike the Western culture, the Chinese emphasize interdependence and harmony with social others. In addition, it is unclear if Western constructed instruments adequately capture culturally conditioned conceptualizations and manifestations of social anxiety that might be specific to the Chinese. The present study employed a sequence of qualitative and quantitative approaches to examine the assessment of social anxiety among the Chinese people. Interviews and focus group discussions with Chinese participants revealed that some items containing the experience of social anxiety among the Chinese are not present in existing Western measures. Factor analysis was employed to examine the factor structure of the more comprehensive scale. This approach revealed an "other concerned anxiety" factor that appears to be specific to the Chinese. Subsequent analysis found that the new factor—other concerned anxiety—functioned the same as other social anxiety factors in their association with risk factors of social anxiety, such as attachment, parenting, behavioral inhibition/activation, and attitude toward group. The implications of these findings for a more culturally sensitive assessment tool of social anxiety among the Chinese were discussed.

1. Introduction

Social anxiety is marked by emotional discomfort, fear, apprehension, or worry about social situations, interactions with others, and being evaluated or scrutinized by other people [1]. Individuals' experience of social anxiety may vary in frequency or severity and may involve various social situations [2]. Experience of severe levels of social anxiety is accompanied by intense negative emotional reactions that would lead to avoidance and escape from interactions with significant others, acting-out, and other inappropriate coping strategies [3, 4]. Because social interaction is required in people's daily life, severe social anxiety is a debilitating condition that interferes with one's ability to enjoy a healthy social life. In addition, people with extreme social anxiety symptoms may even have higher risk for other physical or psychological comorbidities, such as substance abuse, and major depressive disorder [5, 6].

Given that social anxiety could significantly impede people's psychological wellbeing and mental health development, there is increasing empirical research on diagnosis, development, and treatment of social anxiety (e.g., [7]). Though social anxiety is recognized as a universal human condition, it might have different meanings, experiences, and manifestations in different cultures. Researchers have conducted cross-cultural studies on social anxiety to better understand specific characteristics of social anxiety in different cultures. For example, it was found that Asian Americans reported significantly more social anxiety than White Americans for both adults and adolescents [8, 9]. One study suggested that differences in prevalence rates of social anxiety across cultures might be due to differences in self-efficacy about initiating social relationships and perceived social status [10]. Another study showed that presentation and interpretation of social anxiety symptoms also vary across cultures [11].

Even though prior studies have found cross-cultural differences in social anxiety and looked into the mechanisms that might help understand these differences, some limitations of existing research need to be addressed before any firm conclusion can be drawn. First, in some of the studies [9, 12, 13], the participants were Asian Americans living in North America. Asians growing up in Western cultures as an ethnic minority in a non-Asian environment might have certain aspects different from Asian people living in Asia, where Asians are the majority. Moreover, the generic term of "Asian" could not represent the Chinese people or any single Asian ethnic group, who might have unique experiences and expressions of social anxiety. Secondly, many researchers often study Asian social anxiety from the perspective of the Westerners [14]. Therefore, their conclusions might be generated from the perspective of Westerners. For example, some cross-cultural studies directly used social anxiety scales developed in Western cultures without modifications. The results and implications might not be accurate or informative considering the fact that not only behavioral manifestations but also the linguistic expressions of social anxiety might be different across different groups. Thirdly, these studies often failed to suggest how these observed differences originated and what factors might account for them. One weakness of these studies is that they were basing their comparisons on prescribed cultural groups (demographic designation). Observed cultural differences were often interpreted as a result of distal and broad social, cultural, or contextual factors without these factors being directly examined [15]. Hence, conclusions and implications of many previous studies could only be regarded as heuristic, inspiring new hypotheses being hypothetical and tentative.

As a collective community, the Chinese emphasize interdependence with social others and the importance of maintaining social harmony [16]. Accordingly, social anxiety among the Chinese may emerge largely as a function of focused attention on how individual behaviors and performance impact others. The Chinese experience social anxiety not only in terms of the subjective experiences of the individual, but also as a concern for others. They focus their attention on how their own individual performance might impact or reflected on social others. It is important for the Chinese to take the perspective of the others in addition to that of the self to maintain a smooth coordinated existence in social situations [17]. Therefore, compared to the Westerners, the Chinese are likely to experience social anxiety with different phenomenological experiences in both the meaningful content and the magnitude. In addition, there might be specific dimensions of social anxiety showing the effect of others in the Chinese culture [18]. Hence, we would like to explore if the meanings, experiences, and manifestations of social anxiety in the Chinese might have some characteristics that are unique to the culture. We would also like to investigate whether there exist culture-specific constructs or dimensions underlying the Chinese social anxiety experiences and whether these dimensions function the same as the known factors/constructs present in the Western cultures.

In the present study, attempts have been made to address limitations of previous research to better understand social anxiety in the Chinese. First, the subjects were all Chinese. Therefore, in contrast to previous studies, where the samples were made of a mixture of Chinese and other ethnic groups, the present study was conducted on a culturally homogeneous Chinese sample in a society where the dominant culture is the Chinese culture. Secondly, all the measurements in the present study were either developed among the Chinese population or carefully reviewed and modified if necessary for those developed in the Western cultures. Therefore, unique underlying mechanisms of social anxiety conditioned in the Chinese culture are more likely to be detected with locally developed measurements [14]. Thirdly, universal and cultural specific risk factors contributing to social anxiety in Chinese population were investigated with the effect of gender controlled. Previous research has found that the lifetime prevalence rate of social anxiety disorder is 15.5% in women and 11.1% in men [19]. Females reported more severe social anxiety in more social situations than males, which is indicated by higher scores on social anxiety instruments for women [20]. Therefore, after controlling for gender, we could determine the contribution of these risk factors to social anxiety. It is helpful to understand the mechanisms of social anxiety in the Chinese culture and to further assist diagnosis, prevention, intervention, and treatment of social anxiety in the Chinese community population as well as clinical population.

Research has suggested that social anxiety is a developmental outcome of a series of risk factors, including genetic risk factors, insecure attachment experiences, inappropriate parenting styles, information processing biases, temperamental factors, and more broad contextual forces such as ethnicity and culture [21]. Previous empirical research has provided evidence on the relationships between social anxiety and these risk factors [22–24]. The current study further investigated relationships between social anxiety and four of these factors: attachment, parenting styles, BIS/BAS as the temperamental factor, and a cultural factor, patterns of interdependence. The objective was to explore the validity of the revised social anxiety scale by testing whether social anxiety could be predicted by these factors as expected.

Prior studies have indicated individuals with an avoidance attachment style tend to deny their own emotional needs for attachment and perceive others as untrustworthy, so it is difficult for them to develop intimate relationships with significant others. Individuals with anxious attachment styles may underestimate themselves and overestimate others in interpersonal relationships and further worry about abandonment and rejection [25]. Therefore, avoidance attachment would limit opportunities for intimate relationships, and anxious attachment would lead to a maladaptive pattern of thoughts and behaviors in interpersonal situations. It was hypothesized that attachment-related anxiety could predict social anxiety in a positive manner, relative to attachment-related avoidance.

Attachment theory also posits that the development of attachment styles is affected by the relationship between the individual and his caregiver. Children who have unreliable,

unavailable, untrustworthy parents may have a maladaptive approach to future interpersonal relationship and cause either avoidance behaviors or demanding behaviors that may further create a chronic state of anxiety in various social situations [26]. Specifically, children are more likely to have high social anxiety if their parents are demanding and directive and value child obedience but are not responsive or supportive. Therefore, parenting characterized by low levels of warmth and high levels of control is associated with children's social anxiety. The current study hypothesized that parenting control might positively predict social anxiety, and parenting warmth might negatively predict social anxiety.

Temperamental characteristic of behavioral avoidance overlaps with shyness and social withdrawal. Previous research found that behavioral inhibition to an unfamiliar person, object, feeling, or situation is an antecedence of social anxiety [27]. Behavioral avoidance has been also shown to be associated with the development of social anxiety in people of both normal and anxious parents [28]. Therefore, the current study hypothesized that behavioral inhibition could positively predict social anxiety.

A Chinese social group is considered a vertical collective, where hierarchy is emphasized and people may sacrifice their own interests for the group [29]. Previous research has suggested that the individual is more likely to have social anxiety if he values his status, role, and interpersonal relationship in his group more than his own wellbeing [30]. Chang and Koh [31] suggested that a group may serve three functions for its individual members: meeting the functional/survival needs; meeting the affective/emotional needs; and meeting the need of having a frame of reference for defining the self. In a traditional Chinese group, people may not feel an affective interdependence to the same extent as institutional interdependence. More affective interdependence and less institutional interdependence could provide more emotional support to individuals in the group and then help them to fight with negative affect. Therefore, it was predicted that institutional interdependence and collective-self could positively predict social anxiety, and affective interdependence could negatively predict social anxiety.

Therefore, the present study aimed to investigate social anxiety among the Chinese people using a cultural psychology framework. A sequential use of qualitative and quantitative approaches was employed. The first study explored into the meaning and manifestation of social anxiety among Singaporean Chinese through interviews and focus group discussions. The second study, as a validation study, tested the relationships between risk factors and social anxiety using culturally appropriate measures. One objective was to examine whether these relationships between the newly identified dimensions converge with the existing known dimensions to form a coherent construct of social anxiety. The other objective was to test whether factors of social anxiety functioned the same in the development of social anxiety being predicted by risk factors. Finally, a measure of the cultural dimension collectivism, attitude toward group [31], was employed to examine the relationship between social anxiety and patterns of interdependence.

2. Method

2.1. Study 1

2.1.1. Participants. Sixty-one unselected Chinese participants (74% male) were recruited from undergraduate courses at a large public university in Singapore in exchange for research participation credit. Among the sixty-one participants, twenty-five were interviewed individually. They ranged in age from 19 to 24 years (M = 21.00, SD = 1.98). The sample consisted of 72.0% male and 28.0% female. The remaining thirty-six participants participated in focus group discussion. They ranged in age from 20 to 33 years (M = 22.33, SD = 2.43). The sample consisted of 75.0% male and 25.0% female.

2.1.2. Measures. The *Social Interaction Anxiety Scale* (SIAS; [32]) and the *Social Phobia Scale* (SPS; [32]) are both 20-item questionnaires assessing fears of social interaction or scrutiny by others. The SIAS tapped a single construct of social interaction fear. There are three factors in the SPS, including a general scrutiny concern of being observed or attracting attention in a variety of public places, specific fears, and fears of being viewed as sick, ill, odd, or having lost control in front of others.

SIAS and SPS have been translated into Chinese, and the psychometric properties have been examined in a large Chinese sample. It was suggested that the reliability coefficient was .874 for SIAS and .904 for SPS [33]. Convergent validity was also supported by a high correlation between SIAS (.514), SPS (.479), and Fear of Negative Evaluation Scale (FNE; [34]). Therefore, it was recommended that SIAS and SPS have good psychometric quality in Chinese population and could be employed to understand Chinese social anxiety.

2.1.3. Procedure. Study 1 and Study 2 procedures were reviewed and approved by the Institutional Review Board (IRB) at Nanyang Technological University, Singapore (IRB number: 15-1-10-1). After signing consent forms, twenty-five participants were interviewed for half an hour. Participants were asked to speak freely and to express and clarify their experiences when they felt anxious, nervous, or awkward in social situations, such as giving a public speech and talking to strangers. If they did have such anxious experiences, they were then asked to describe their behaviors, reactions, feelings, emotions, thoughts, and anything related to their experiences. In order to gather enough information, the questions were mostly open-ended questions such as "Can you tell me more"; "Can you explain that"; "What you mean". During this interview, participants' answers were recorded. After interviewing all the 25 people, an item pool was generated for the local expressions of social anxiety. The item pool was then compared with the items in the SIAS and the SPS. 10 new items of people's behaviors, feelings, and thoughts when they were anxious which are not in the SIAS and the SPS were generated.

The second step was to conduct focus group discussions to evaluate the new items. Seven groups were organized, and each one consisted of four to seven participants. Participants were asked to read all of the items, including 40 items in

the SIAS and the SPS, and the 10 new items. Afterwards, they could ask any questions about any item, for instance, if they could understand the meanings, if they considered all of the items were related to their socially anxious behaviors, feelings, or thoughts, and so forth. Their responses were recorded. Based on the discussion of these items, some modifications were made to the 10 new items.

During the interview and focus group discussion, the communication between the interviewer and interviewees was in Chinese and English. The new items were not only represented in Chinese but also translated with back-translation method. First, the original items were translated into English by two native English speakers who have the intimate knowledge and personal experiences of both the Chinese- and English-mediated cultures. Then, the English translations were back-translated into Chinese by a native Chinese speaker. Then, the original items were compared with the back-translations, and translators made corrections to the final English translations. No items were eliminated or significantly changed during the translation process.

2.2. Study 2

2.2.1. Participants. Two hundred and ninety-six unselected Chinese participants (32% female) were recruited from undergraduate courses at a large public university in Singapore in exchange for research participation credit. Participants ranged in age from 18 to 29 years (M = 20.78, SD = 1.73).

2.2.2. Measures. The SIAS and the SPS [32], each of which consists of twenty items, plus the ten new items developed in Study 1, are to assess fears of social interaction and anxious symptoms in social situations. The whole questionnaire had an alpha coefficient of .94 in the present study. Alpha coefficients were .77 for factor 1, social interaction anxiety, .83 for factor 2, other concerned anxiety, .79 for factor 3, specific anxiety, and .90 for factor 4, being observed by others. All of the alpha coefficients are within acceptable range.

The *Experiences in Close Relationships Scale-Revised* (ECR-R; [35]) is a 36-item questionnaire to assess individual differences with respect to attachment-related anxiety and attachment-related avoidance. Attachment-related anxiety refers to an excessive need for approval from others and the fear of interpersonal rejection or abandonment, whereas attachment-related avoidance refers to an excessive need for self-reliance and fear of interpersonal intimacy or dependence. The ECR-R had an alpha coefficient of .76 in the present study.

The *Singapore Chinese Parenting Scale-short form* (Children's version) (SCPS; [36]) is a 23-item scale to measure perceived parenting. The scale was developed upon Chinese parenting dimensions, strictness (such as imposing restrictions on the child), and warmth (such as hugging, kissing, and physical nurturance). The SCPS had an alpha coefficient of .84 in the present study.

The *Behavioral Inhibition System and Behavioral Approach System Scale* (BIS/BAS; [37]) is a 24-item questionnaire to assess individual differences in the sensitivity of behavioral inhibition system and behavioral approach system. The BIS measures the sensitivity to signals of punishment, nonreward, and novelty. It functions to inhibit behaviors that may lead to negative or painful outcomes [38]. The BAS is responsible for the experience of positive feelings such as hope, elation, and happiness and sensitive to positive outcomes; behaviorally, it promotes goal-directed activities toward potential rewards [38]. The present study used the short version of BIS/BAS revised in Singapore [39]. In this 14-item revised scale, BIS/BAS included original items as well as new items developed in Singapore. The revised scale had an alpha coefficient of .73 in the present study.

The *Attitude toward Group Scale*-short version (AGS; [31]) is a 15-item scale to assess three dimensions of attitude toward group. The institutional interdependence subscale measures the degree to which the individual perceived his functional relationship with the group. The affective interdependence subscale measures the degree to which the individual sees his group as a source of and a referent for his emotions. The collective-self identification subscale measures the degree to which the individual assumes the identity of the group. The AGS had an alpha coefficient of .87 for the entire scale in the present study.

2.2.3. Procedure. After participants signed an informed consent, they completed the self-report measures described above.

3. Results

3.1. Study 1. 10 new items which are not in the SIAS and the SPS were shown in Table 1. All the items from the SIAS and the SPS and the 10 new items were then combined and submitted to Exploratory Factor Analysis (EFA). For the whole data, the Kaiser-Meyer-Olkin measure of the sample adequacy was .93, with Bartlett's test of sphericity significant ($P < 0.001$), indicating sufficient correlations among the variables to proceed for factor analysis. Principal Components Analysis (PCA) with promax rotation was conducted to identify underlying factors in the 50-item social anxiety scale. According to the scree plot, four-factor solution was recommended. The total variance explained by the four-factor solution was 45.40%, and by the five-factor solution it was 48.18%. In addition, the four-factor solution had more items with communities smaller than .30, so the five-factor solution was preferred. Parallel analysis was also conducted and suggested a five-factor solution because the eigenvalues of the first five factors from the current data were bigger than the 95th of the distribution of eigenvalues derived from random data. Therefore, based on the results of scree plot, parallel analysis, communalities, variance explained by factors, and rotated factor loadings by promax method, a five-factor solution was preferred.

Confirmatory factor analysis was then used to evaluate whether this five-factor model adequately fit the data [40]. Analysis of Moment Structure (AMOS) [41] was applied to test this five-factor model with all the items from the SIAS and the SPS, as well as the 10 new items. The Root Mean Square

Table 1: 10 new items of social anxiety scale.

1	I am afraid of being singled out to deal with difficulties.
2	I am worried people will laugh at my anxious behaviors.
3	I am afraid of making others uncomfortable if I do not know them well.
4	I am afraid of being seen as a person with no proper upbringing.
5	I am worried that I could not always maintain a good image.
6	I am afraid of losing my friends if I behave in a wrong way.
7	I feel that I need to take a deep breath when I am with others.
8	I am afraid my inappropriate behaviors may cause stress in my friends.
9	I stutter when I make a public speech.
10	I am afraid of being misunderstood as a loner.

Table 2: Mean difference between women and men on social anxiety and its 4 factors.

	Men			Women			F	P
	n	M	SD	n	M	SD		
Social anxiety	128	3.36	.91	228	3.57	.78	5.13	0.02*
F1	128	3.59	1.09	228	3.68	.85	.77	0.38
F2	128	3.59	1.10	228	3.92	.99	8.35	0.00**
F3	128	2.49	.87	228	2.44	.90	.17	0.68
F4	128	3.39	1.04	228	3.73	.94	10.28	0.00**

Note: $^{*}P < 0.05$, $^{**}P < 0.01$. F1 = social interaction anxiety; F2 = other concerned anxiety; F3 = specific anxiety; F4 = being observed by others.

Error of Approximation (RMSEA) was .06; Comparative Fit Index (CFI) was .81. These indices indicated that a five-factor solution did not adequately fit the data [42].

Among these five factors, factor 2 and factor 5 were highly correlated ($r = .70$, $P < 0.01$). The alpha coefficients for factor 2 and factor 5 were .87 and .83, respectively, and the alpha coefficient for the combination of the two factors was .91. Therefore, the two factors seemed to measure similar aspects of social anxiety and could be combined as one factor in the final four-factor solution. Following EFA, confirmatory factor analysis was conducted to evaluate whether this four-factor model adequately fit the data [40]. The Root Mean Square Error of Approximation (RMSEA) was .07; Comparative Fit Index (CFI) was .92. These indices indicated that this four-factor solution was simpler and better than a five-factor model.

In the final four-factor solution, factor 1 included 15 items from the SIAS and one new item. According to the content of the items, factor 1 was labeled as social interaction anxiety. Factor 2 included six new items, two items from the SIAS, and one item from the SPS. Factor 2 was labeled as other concerned anxiety. Factor 3 included six items from the SPS and one new item. Factor 3 was labeled as specific anxiety. Factor 4 included three items from the SIAS, 13 items from the SPS, and two new items. Factor 4 was labeled as being observed by others.

3.2. Study 2

3.2.1. Gender Difference in Social Anxiety. Analyses of variances were conducted to examine differences between men and women (see Table 2). Women scored higher than men on the whole social anxiety scale ($F = 5.13$, $P < 0.05$), on factor 2, other concerned anxiety ($F = 8.35$, $P < 0.01$), and on factor 4, being observed by others ($F = 10.28$, $P < 0.01$). Women and men showed no significant differences on factor 1, social interaction anxiety ($F < 1$), and factor 3, specific anxiety ($F < 1$).

3.2.2. Relationships between Attachment and Social Anxiety. A series of hierarchical regression analyses were conducted to examine the specific contribution of attachment to social anxiety and its four factors. Predictor variables were entered in two steps. In the first step, gender was entered as a predictor. In the second step, attachment-related anxiety and attachment-related avoidance were simultaneously entered as predictors. This analysis provided a stringent test of the incremental validity of attachment.

The results of these analyses were presented in Table 3. In the hierarchical regression predicting social anxiety, gender was entered in the first step and explained .6% of the variance and did not account for a significant portion; $F(1,288) = 1.75$, $P > 0.05$. In the second step, two factors of attachment explained an additional 28.1% of the variance; $F(2,286) = 56.45$, $P < 0.001$. In the second step, attachment-related anxiety emerged as a significant predictor of social anxiety ($t(286) = 10.01$, $P < 0.001$). Attachment-related avoidance was a marginally significant predictor ($t(286) = 1.90$, $P < 0.06$). In the hierarchical regression predicting factor 1 of social anxiety, social interaction anxiety, gender explained less than .1% of the variance; $F(1,288) < 1$. In the second step, two factors of attachment explained an additional 15.0% of the variance; $F(2,286) = 25.29$, $P < 0.001$. Both of attachment-related anxiety and attachment-related avoidance emerged as significant predictors of factor 1 (anxiety: $t(286) = 5.44$,

Table 3: Specificity of factors of attachment in predicting social anxiety and its four factors.

Measures	R^2	B	SE B	β	t
Predicting social anxiety	.281***				
Attachment-related anxiety		.414	.041	.506	10.011***
Attachment-related avoidance		.088	.046	.097	1.903‡
Predicting social interaction anxiety (F1)	.150***				
Attachment-related anxiety		.279	.051	.301	5.444***
Attachment-related avoidance		.209	.057	.202	3.640***
Predicting other concerned anxiety (F2)	.288***				
Attachment-related anxiety		.565	.052	.542	10.836***
Attachment-related avoidance		−.052	.059	−.045	−.888
Predicting specific anxiety (F3)	.240***.				
Attachment-related anxiety		.426	.047	.468	8.991***
Attachment-related avoidance		.092	.053	.090	1.725
Predicting being observed by others (F4)	.225***				
Attachment-related anxiety		.454	.051	.465	8.920***
Attachment-related avoidance		.050	.057	.046	.871

Note: ‡$P < 0.06$, ***$P < 0.001$.

$P < 0.001$; avoidance: $t(286) = 3.64$, $P < 0.001$). In the hierarchical regression predicting factor 2 of social anxiety, other concerned anxiety, gender explained 1.6% of the variance and significantly predicted factor 2; $F(1,288) = 4.68$, $P < 0.05$. In the second step, two predictors of attachment explained an additional 28.8% of the variance; $F(2,286) = 59.08$, $P < 0.001$. In the second step, only attachment-related anxiety emerged as a significant predictor of factor 2 ($t(286) = 10.84$, $P < 0.001$). In the hierarchical regression predicting factor 3 of social anxiety, specific anxiety, gender explained .6% of the variance and did not account for a significant portion; $F(1,288) = 1.60$, $P > 0.05$. In the second step, two predictors of attachment explained an additional 24.0% of the variance; $F(2,286) = 45.59$, $P < 0.001$. Only attachment-related anxiety emerged as a significant predictor of factor 3 ($t(286) = 8.99$, $P < 0.001$). In the hierarchical regression predicting factor 4 of social anxiety, being observed by others, gender explained 1.7% of the variance and significantly predicted factor 4; $F(1,288) = 5.11$, $P < 0.05$. In the second step, two predictors of attachment explained an additional 22.5% of the variance; $F(2,286) = 42.51$, $P < 0.001$. In the second step, only attachment-related anxiety emerged as a significant predictor of factor 4 ($t(286) = 8.92$, $P < 0.001$).

3.2.3. Relationships between Parenting and Social Anxiety. A series of hierarchical regression analyses were conducted to examine the specific contribution of two factors of parenting to social anxiety and its four factors. Predictor variables were entered in two steps. In the first step, gender was entered as a predictor. In the second step, parenting strictness and warmth were simultaneously entered as predictors.

The results of these analyses were presented in Table 4. In the hierarchical regression predicting social anxiety, gender was entered in the first step and explained .6% of the variance and did not account for a significant portion; $F(1,288) < 1$. In the second step, parenting strictness and warmth explained an additional 4.2% of the variance; $F(2,286) = 6.35$, $P < 0.01$. In the second step, only parenting strictness emerged as a significant predictor of social anxiety ($t(286) = 3.55$, $P < 0.001$). In the second hierarchical regression predicting factor 1 of social anxiety, social interaction anxiety, gender explained less than .1% of the variance; $F(1,288) < 1$. In the second step, parenting strictness and warmth explained an additional 3.8% of the variance; $F(2,286) = 5.66$, $P < 0.01$. In this step, only parenting strictness emerged as a significant predictor of Factor 1 ($t(286) = 3.27$, $P < 0.01$). In the hierarchical regression predicting factor 2 of social anxiety, other concerned anxiety, gender explained 1.6% of the variance and significantly predicted factor 2; $F(1,288) = 4.68$, $P < 0.05$. In the second step, parenting strictness and warmth explained an additional 1.8% of the variance, $F(2,286) = 2.64$, $P > 0.05$, but did not account for a significant portion. In the second step, parenting strictness emerged as a significant predictor of factor 2 ($t(286) = 2.10$, $P < 0.05$). In the hierarchical regression predicting factor 3 of social anxiety, specific anxiety, gender explained .6% of the variance and did not account for a significant portion; $F(1,288) = 1.60$, $P > 0.05$. In the second step, parenting strictness and warmth explained an additional 5.4% of the variance; $F(2,286) = 8.28$, $P < 0.001$. Only parenting strictness emerged as a significant predictor of factor 3 ($t(286) = 3.98$, $P < 0.001$). In the hierarchical regression predicting factor 4 of social anxiety, being observed by others, gender explained 1.7% of the variance and significantly predicted factor 4; $F(1,288) = 5.11$, $P < 0.05$. In the second step, parenting strictness and warmth explained an additional 3.0% of the variance; $F(2,286) = 4.46$, $P < 0.05$. In the second step, parenting strictness emerged as a significant predictor of factor 4 ($t(286) = 2.91$, $P < 0.01$).

3.2.4. Relationships between BIS/BAS and Social Anxiety. A series of hierarchical regression analyses were conducted to

Table 4: Specificity of factors of parenting in predicting social anxiety and its four factors.

Measures	R^2	B	SE B	β	t
Predicting social anxiety	.042**				
Parenting strictness		.223	.063	.207	3.547***
Parenting warmth		−.010	.060	−.010	−.174
Predicting social interaction anxiety (F1)	.038**				
Parenting strictness		.234	.072	.192	3.267**
Parenting warmth		−.086	.068	−.074	−1.261
Predicting other concerned anxiety (F2)	.018				
Parenting strictness		.170	.081	.123	2.097*
Parenting warmth		.049	.077	.037	.630
Predicting specific anxiety (F3)	.054***				
Parenting strictness		.277	.070	.231	3.979***
Parenting warmth		.019	.066	.016	.281
Predicting being observed by others (F4)	.030*				
Parenting strictness		.219	.075	.170	2.915**
Parenting warmth		.016	.072	.013	.223

Note: *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

Table 5: Specificity of factors of BIS/BAS in predicting social anxiety and its four factors.

Measures	R^2	B	SE B	β	t
Predicting social anxiety	.173***				
BIS		.510	.074	.438	6.854***
BAS		−.119	.065	−.116	−1.837
Predicting social interaction anxiety (F1)	.132***				
BIS		.485	.086	.369	5.612***
BAS		−.218	.075	−.189	−2.912**
Predicting other concerned anxiety (F2)	.153***				
BIS		.612	.096	.411	6.405***
BAS		−.121	.083	−.093	−1.465
Predicting specific anxiety (F3)	.055**				
BIS		.315	.089	.241	3.526***
BAS		−.011	.077	−.009	−.138
Predicting being observed by others (F4)	.149***				
BIS		.558	.089	.403	6.254***
BAS		−.071	.077	−.058	−.914

Note: **$P < 0.01$, and ***$P < 0.001$.

examine the specific contribution of BIS/BAS to social anxiety and its four factors. Predictor variables were entered in two steps. In the first step, gender was entered as a predictor. In the second step, BIS and BAS were simultaneously entered as predictors.

The results of these analyses were presented in Table 5. In the hierarchical regression predicting social anxiety, gender was entered in the first step and explained .5% of the variance and did not account for a significant portion; $F(1,225) = 1.21$, $P > 0.05$. In the second step, BIS and BAS explained an additional 17.3% of the variance; $F(2,223) = 23.53$, $P < 0.001$. In the second step, only BIS emerged as a significant predictor of social anxiety ($t(223) = 6.85$, $P < 0.001$). In the second hierarchical regression predicting factor 1 of social anxiety, social interaction anxiety, gender explained less than .1% of the variance; $F(1,225) < 1$. In the second step, BIS and BAS explained an additional 13.2% of the variance; $F(2,223) = 16.91$, $P < 0.001$. In this step, both BIS and BAS emerged as a significant predictor of factor 1 (BIS: $t(223) = 5.61$, $P < 0.001$; BAS: $t(223) = -2.91$, $P < 0.01$). In the hierarchical regression predicting factor 2 of social anxiety, other concerned anxiety, gender explained 1.9% of the variance and significantly predicted factor 2; $F(1,225) = 4.25$, $P < 0.05$. In the second step, BIS and BAS explained an additional 15.3% of the variance; $F(2,223) = 20.55$, $P < 0.001$. In the second step, only BIS emerged as a significant predictor of factor 2 ($t(223) = 6.40$, $P < 0.001$). In the hierarchical regression predicting factor 3 of social anxiety, specific anxiety, gender explained .8% of the variance and did not account for a significant portion; $F(1,225) = 1.91$,

Table 6: Specificity of factors of attitude toward group in predicting social anxiety and its four factors.

Measures	R^2	B	SE B	β	t
Predicting social anxiety	.037*				
Institutional interdependence		.067	.080	.071	.837
Affective interdependence		−.192	.073	−.211	−2.621**
Collective-self identification		.160	.066	.194	2.418*
Predicting social interaction anxiety (F1)	.036*				
Institutional interdependence		.036	.091	.034	.400
Affective interdependence		−.258	.083	−.250	−3.099**
Collective-self identification		.135	.075	.143	1.785
Predicting other concerned anxiety (F2)	.027*				
Institutional interdependence		.067	.102	.055	.654
Affective interdependence		−.112	.094	−.096	−1.197
Collective-self identification		.180	.085	.171	2.130*
Predicting specific anxiety (F3)	.072***				
Institutional interdependence		.209	.088	.198	2.387*
Affective interdependence		−.332	.080	−.327	−4.144***
Collective-self identification		.175	.072	.190	2.416*
Predicting being observed by others (F4)	.022				
Institutional interdependence		.039	.096	.035	.410
Affective interdependence		−.119	.088	−.109	−1.360
Collective-self identification		.168	.079	.170	2.115*

Note: *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

$P > 0.05$. In the second step, BIS and BAS explained an additional 5.5% of the variance; $F(2,223) = 6.58$, $P < 0.01$. BIS emerged as a significant predictor of factor 3 ($t(223) = 3.53$, $P < 0.001$). In the hierarchical regression predicting factor 4 of social anxiety, being observed by others, gender explained 1.6% of the variance and did not significantly predict factor 4; $F(1,225) = 3.55$, $P > 0.05$. In the second step, BIS and BAS explained an additional 14.9% of the variance; $F(2,223) = 19.89$, $P < 0.001$. In the second step, only BIS emerged as a significant predictor of factor 4 ($t(223) = 6.25$, $P < 0.001$).

3.2.5. Relationships between Attitude toward Group and Social Anxiety. A series of hierarchical regression analyses were conducted to examine the specific contribution of attitude toward group to social anxiety and its four factors. Predictor variables were entered in two steps. In the first step, gender was entered as a predictor. In the second step, three factors of attitude toward group were simultaneously entered as predictors.

The results of these analyses were presented in Table 6. In the hierarchical regression predicting social anxiety, gender was entered in the first step and explained .6% of the variance and did not account for a significant portion; $F(1,288) = 1.75$, $P > 0.05$. In the second step, three factors of attitude toward group explained an additional 3.7% of the variance; $F(3,285) = 3.62$, $P < 0.05$. In the second step, affective interdependence and collective-self identification emerged as significant predictors of social anxiety (affective interdependence: $t(285) = -2.62$, $P < 0.01$; collective-self identification: $t(285) = 2.42$, $P < 0.05$). In the second hierarchical regression predicting factor 1 of social anxiety, social interaction anxiety, gender explained less than .1% of the variance; $F(1,288) < 1$. In the second step, three factors of attitude toward group explained an additional 3.6% of the variance; $F(3,285) = 3.59$, $P < 0.05$. In this step, only affective interdependence emerged as a significant predictor of factor 1 ($t(285) = -3.10$, $P < 0.01$). In the hierarchical regression predicting factor 2 of social anxiety, other concerned anxiety, gender explained 1.6% of the variance and significantly predicted factor 2; $F(1,288) = 4.68$, $P < 0.05$. In the second step, three factors of attitude toward group explained an additional 2.7% of the variance; $F(3,285) = 2.69$, $P < 0.05$. In the second step, collective-self identification emerged as a significant predictor of factor 2 ($t(285) = 2.13$, $P < 0.05$). In the hierarchical regression predicting factor 3 of social anxiety, specific anxiety, gender explained .6% of the variance and did not account for a significant portion; $F(1,288) = 1.60$, $P > 0.05$. In the second step, three factors of attitude toward group explained an additional 7.2% of the variance; $F(3,285) = 7.46$, $P < 0.001$. All of the three factors of attitude toward group emerged as significant predictors of factor 3 (institutional interdependent: $t(285) = 2.39$, $P < 0.05$; affective interdependence: $t(285) = -4.14$, $P < 0.001$; collective-self identification: $t(285) = 2.42$, $P < 0.05$). In the hierarchical regression predicting factor 4 of social anxiety, being observed by others, gender explained 1.7% of the variance and significantly predicted factor 4; $F(1,288) = 5.11$, $P < 0.05$. In the second step, three factors of attitude toward group explained an additional 2.2% of the variance; $F(3,285) = 2.22$, $P > 0.05$. In the second step, only collective-self identification emerged as a significant predictor of factor 4 ($t(285) = 2.11$, $P < 0.05$).

4. Discussion

The SIAS and the SPS were developed in the Western context. The ten new items developed from qualitative interviews from Chinese participants were not present in the original Western constructed scales, and they represent culture-specific social anxious symptoms of the Chinese people. The revised social anxiety scales consisted of 50 items, including 40 items from the SIAS and the SPS and ten new items generated from the interview and focus group discussions among the Chinese people in a predominantly Chinese society, Singapore.

Among the 10 new items in the present study, two items are physical symptoms people experience with others around. One is "I feel that I need to take a deep breath when I am with others"; the other is "I stutter when I make a public speech." Two items are symptoms of being afraid of making others uncomfortable: one is "I am afraid of making others uncomfortable if I do not know them well"; the other is "I am afraid my inappropriate behaviors may cause stress in my friends." The remaining six items are symptoms if people could maintain their (or their family's) good image consistently in front of others: (1) I am afraid of being singled out to deal with difficulties; (2) I am worried people will laugh at my anxious behaviors; (3) I am afraid of being seen as a person with no proper upbringing; (4) I am worried that I could not always maintain a good image; (5) I am afraid of losing my friends if I behave in a wrong way; (6) I am afraid of being misunderstood as a loner.

According to the results of EFA and CFA, a four-factor structure best represents the constructs of the 50-item combined social anxiety scale. Factor 1 is social interaction anxiety measuring anxious symptoms while interacting with others. Factor 2 is other concerned anxiety, and most of the items in this factor were generated in the present study. Factor 2 assesses whether people's performance would make others uncomfortable or influence others in an unbeneficial way. Factor 3 is specific anxiety measuring specific anxiety in certain situations, like using public toilets, drinking with a group of people, and sitting facing people on a bus or a train. Factor 4 was labeled being observed by others assessing whether an individual or his anxious behaviors could be noticed by others. Previous factor analysis of social anxiety has found factors 1, 3, and 4, but factor 2, other concerned anxiety, was only extracted in the current study [43, 44]. The Chinese culture promotes the interdependent self, so individuals are reminded to be sensitive to the needs and expectations of the group, the others, rather than the individual self [45]. Traditionally, the Chinese culture emphasizes obligations to family (filial piety), making people worried whether their inappropriate behaviors may exert bad influences to or reflect badly on their family or their friends [46–48].

Study 2 examined the relationship between social anxiety and its risk factors, attachment, parenting, BIS, and patterns of interdependence. The results of Study 2 have supported the validity of the revised social anxiety scale and provided further evidence to understand the mechanisms of social anxiety from a cultural perspective. It was suggested that the Chinese culture-specific factor, other concerned anxiety, plays an important role as the other factors in the original social anxiety scale in being predicted by theoretically risk factors.

The results of predicting the role of attachment in social anxiety suggested that the association between social anxiety and attachment was independent of gender difference in social anxiety. Hierarchical regression analyses showed that attachment-related anxiety remained a more significant predictor of social anxiety and its four factors relative to attachment-related avoidance. The results implicated that social anxiety might be more likely experienced when people have an excessive need for approval from others and fear of interpersonal rejection or abandonment. However, the excessive need for self-reliance and fear of interpersonal intimacy or dependence may not operate as a relative vulnerability factor for the development of social anxiety. Therefore, attachment-related anxiety appears to better predict social anxiety symptoms.

In addition, hierarchical regression analyses showed that parenting strictness predicted social anxiety and its four factors. The finding was consistent with prior research that anxious symptoms were positively associated with rejecting and controlling parenting [49]. Furthermore, Chinese parenting has its own cultural specific characteristics as well as the general features found in Western cultures. In the Chinese parenting meaning system, parents are expected to be strict to their children in regulating the child's behavior and place a high emphasis and value on child's obedience to parental wishes [47]. Parents control their children's behaviors through the strict use of rules and regulations initiated by the parents. The strictness, however, is usually meant for the "good" of the child, to assist children's self-development and success [36]. Nevertheless, the present study found that strictness, though including some cultural specific manifestations, could also lead to more experiences of social anxiety, which may further cause more mental health problems in the long run. In addition, warmth, showing parents' love and support to children, was not significantly correlated with social anxiety. This finding was not consistent with prior research. Some previous research suggested that social anxiety in the child was associated with a parenting style characterized by high levels of low warmth [50]. Therefore, low warmth is supposed to increase social anxiety, whereas high warmth may function as a protective factor to reduce social anxious symptoms. The inconsistency may be due to the two intertwined concepts strictness and warmth in Chinese parenting meaning system. Both strictness and warmth are manifested in activities initiated by parents with the parent as the locus of decision. Parents are expected to take care of children of all ages to the extent of sacrificing their own needs. However, such care-taking is based on decisions made by the parents to ensure that only the best is provided for the children [51]. Furthermore, there is no clear distinction between appropriate warmth and overprotection or overinvolvement, which may also contribute to social anxiety [50].

Then, the relationship between BIS/BAS and social anxiety was also examined in the present study. Hierarchical regression analyses showed that only BIS emerged as

a stronger predictor of social anxiety and its four factors than BAS. This finding was consistent with prior research on relationships between BIS and anxiety that behavioral inhibition is associated specifically with the development of social anxiety [52]. The present results suggested that individuals are more likely to experience social anxiety if they are more sensitive to signals of punishment, nonreward, and novelty in interacting with social others.

With the relationships between risk factors above and social anxiety being examined, we would like to explore further whether social anxiety could be predicted by a cultural factor, patterns of interdependence. Patterns of interdependence were measured by attitude toward group scale. Hierarchical regression analyses showed that three factors of attitude toward group, institutional interdependence, affective interdependence, and collective-interdependence, significantly predicted social anxiety and its four factors. Among the three factors of attitude toward group, collective-self contributed more than affective interdependence, which contributed more than institutional interdependence. The positive relationship between institutional interdependence and social anxiety suggested that the more an individual perceived his functional relationship with the group, the more he would experience anxiety. The negative relationship between affective interdependence and social anxiety suggested that the more the people see their group as a source of a referent for their emotions, the more they are less likely to feel anxious. The third factor, collective-self, could predict social anxiety in a positive manner, indicating that the more one assumes the identity of the group, the more one's self-identity might be temporarily suspended but lead to more anxious symptoms. Therefore, in Chinese culture, when an individual's interests are in conflict with those of the group, the individual, as a moral principle, is expected to sacrifice his personal interests. However, restraining personal interests and feelings would lead to more negative affect, for example, anxiety.

5. Implications and Limitations

The present study suggested that social anxiety has unique meanings and manifestations in the Chinese culture, which is indicated by the new factor identified in the revised social anxiety scales. Similar to the other three factors, the new factor is a necessary component of social anxiety among Chinese people. Therefore, social anxiety could be more comprehensively measured with cultural specific manifestations, in addition to universal manifestations. The current findings also suggested that attachment, parenting styles, BIS/BAS, and patterns of interdependence all served as risk factors of social anxiety. People with an excessive need for approval from others and fear of interpersonal rejection or abandonment would be more likely to have social anxiety. Parenting strictness predicted social anxiety positively; however, low level of parenting warmth did not prevent the development of social anxiety in the Chinese culture. As in the Western culture, behavioral inhibition also predicted social anxiety positively. Furthermore, from the perspective of interdependence, the present study suggested that Chinese people may tend to sacrifice their own interests for the interests of collective. However, suppression of individual's own needs might result in high social anxiety.

Although the current study highlights the importance of the cultural specific factor of social anxiety among Chinese people, limitations of the study should be considered when interpreting the findings. First, the participants consisted of a small sample of undergraduate students without significant social anxiety. This convenient sample made it difficult to generalize the findings to a general population or those with significant difficulties in interacting with people. Second, the culture of Singapore is a mix of Chinese, Malay, Indian, and British cultures. Singaporean culture is different from Western cultures but also different from traditional Chinese culture. Cautions should be exercised when applying the current findings to other Chinese populations in different societies. In addition, the sample size to item ratio (5 : 1) was small to conduct an Exploratory Factor Analysis. The current 4-factor solution might not capture factor structure of the revised social anxiety scale correctly. Therefore, future research employing a larger sample size may further current understanding of social anxiety manifestations among Chinese people. Moreover, the present study is a cross-sectional study of social anxiety. To capture the development of social anxiety and its risk factors, such as attachment and parenting, a longitudinal study would be more reliable to detect the development of each construct and the relationships between these constructs.

Conflict of Interests

The authors have no potential conflict of interests.

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Research Article

Evaluation of the Effectiveness of a Psychoeducational Intervention in Treatment-Naïve Patients with Antidepressant Medication in Primary Care: A Randomized Controlled Trial

R. Casañas,[1,2,3] R. Catalán,[4,5,6,7] R. Penadés,[4,5,6,7] J. Real,[3] S. Valero,[7,8] MA. Muñoz,[3] LL. Lalucat-Jo,[1] and M. Casas[7,8]

[1] *Research Department, Centre Higiene Mental (CHM) Les Corts, C/Numancia, 103-105 Bajos, 08029 Barcelona, Spain*
[2] *Psychiatry and Legal Medicine Department, Universidad Autónoma de Barcelona, Barcelona, Spain*
[3] *Primary Healthcare University Research Institute IDIAP-Jordi Gol, Institut Català de la Salut (ICS), C/Sardenya 375, 08036 Barcelona, Spain*
[4] *Clinical Institute of Neurosciences (ICN), Hospital Clinic, Barcelona, Spain*
[5] *Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Barcelona, Spain*
[6] *Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[7] *Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain*
[8] *Department of Psychiatry, Hospital Universitari Vall d'Hebron, Universidad Autónoma de Barcelona (UAB), Barcelona, Spain*

Correspondence should be addressed to R. Casañas; rocio.casanas@chmcorts.com

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Background. There is evidence supporting the effectiveness of psychoeducation (PE) in patients with symptoms of depression in primary care (PC), but very few studies have assessed this intervention in antidepressant-naïve patients. The aim of this study is to assess the effectiveness of a PE program in these patients, since the use of antidepressant (AD) medication may interfere with the effects of the intervention. *Methods*. 106 participants were included, 50 from the PE program (12 weekly 1.5-hour sessions) and 56 from the control group (CG) that received the usual care. Patients were assessed at baseline and at 3, 6, and 9 months. The main outcome measures were the Beck Depression Inventory (BDI) and remission based on the BDI. The analysis was carried out on an intention-to-treat basis. *Results*. The PE program group showed remission of symptoms of 40% ($P = 0.001$) posttreatment and 42% ($P = 0.012$) at 6 months. The analysis only showed significant differences in the BDI score posttreatment ($P = 0.008$; effect size Cohen's $d' = 0.55$). *Conclusions*. The PE intervention is an effective treatment in the depressive population not treated with AD medication. Before taking an AD, psychoeducational intervention should be considered.

1. Introduction

Depression is one of the most prevalent mental disorders in the adult population worldwide, with a lifetime prevalence of 9–20% [1] and specifically 10.5% in Spain [2].

In primary health care there has been an increase in the detection of major depressive disorders in recent years, with a 12-month prevalence of 11% in Europe and 14% in Spain [3]. In fact, minor depressive disorders are the third leading cause of consultation in primary health care, with a prevalence rate of 5–16% [4–6], and it is an important risk factor for major depression, which develops in 10–25% of patients with subthreshold depression within 1–3 years [7].

A significant increase in the prescription of antidepressants in primary care in recent decades in Spain has been confirmed [8], possibly due to the use of so-called

"third-generation" antidepressants, as selective serotonin reuptake inhibitors (SSRIs) are the chosen treatment among patients with depression.

When we reviewed the interventions that have proven effective in treating minor depression, we found that most international clinical practice guidelines (CPG) for the management of depression recommend psychoeducational interventions and brief psychotherapy as an initial step in the treatment protocol [9–11]. These guidelines do not recommend antidepressant medication in patients with mild symptoms.

With regard to psychoeducation, it has been demonstrated that it is an effective therapy in the treatment of depression in adults [9, 12], as it reduces depressive symptoms and can prevent depression in primary care patients [13–15]. It has also been proven to reduce depressive symptoms in mild and moderate depression in both the short term and long term [16–19].

This intervention could be carried out by community nurses with previous training in primary care [18–22].

In most of these studies, we detected that the antidepressant medication variable had not been taken into account when evaluating whether it might have affected the results of the intervention. Some studies explain that some patients were taking antidepressants [19, 20], while in other studies this variable is omitted [23], even though the few studies that analyzed whether taking antidepressants might have an effect on the effectiveness of the intervention [17] have proven that the results obtained were maintained despite excluding participants taking AD medication.

We carry out a randomized, controlled, open-label, parallel-group trial [18] to assess the effectiveness of a psychoeducational program versus the usual care in a sample of 231 patients diagnosed with major depression (mild/moderate symptoms) recruited at 12 urban primary care centers (PCCs) in Barcelona. The intervention group ($n = 119$) participated in a psychoeducational program (12 weekly 1.5-hour sessions led by two nurses) and the control group ($n = 112$) received the usual care. This group program included aspects of personal care and a healthy lifestyle (diet, physical exercise, sleep, and pharmacological treatment), as well as the identification and management of depressive symptoms within the psychoeducational intervention and cognitive-behavioral techniques used in psychoeducation.

The results of the study showed that this psychoeducational intervention was more effective in patients with mild symptoms, since they had a higher symptom remission rate over the short terms and long term. Moreover, this improvement was associated with better quality of life. The data do not demonstrate that the intervention is effective over the long term in patients with moderate symptoms [18].

In this paper, the main objective is to assess the effectiveness of this intervention through the rate of remission in the sample of antidepressant-naïve patients. Among the secondary objectives, we were interested in analyzing how many patients had taken ADs during the intervention and at 6 and 9 months of follow-up, whether taking medication was associated with worsening of symptoms and whether the number of group sessions attended influenced improvement in symptoms.

2. Methods

A detailed description of the methodology has been reported previously [18]. In this study we will only specify the most important methodological aspects. The randomized, controlledtrial was conducted between December 2008 and April 2010 in Barcelona, Spain. Participants were recruited by general practitioners and nurses between December 2008 and March 2009 at 12 PCCs.

2.1. Participants. 231 participants were included in the study [18] and randomly assigned to the intervention group (IG) ($n = 119$) or the control group (CG) ($n = 112$). The subgroup of patients who had never taken pharmacological antidepressant treatment prior to participating in the study ($n = 106$) was extracted from this patient sample.

Inclusion criteria were (a) patients included in the study [18] who had never been treated with antidepressant medication; (b) male and female patients over 20 years of age; (c) patients diagnosed with a major depressive disorder according to the International Classification of Diseases 10th revision (ICD-10) [24]; (d) patients with mild to moderate symptoms according to the Beck Depression Inventory (BDI ≥ 10 and < 30); and (e) provision of signed informed consent.

Exclusion criteria were as follows: (a) patients who had been treated with ADs some time prior to participating in the study.

The information about antidepressant prescription was obtained from the primary care information system.

2.2. Procedure. Of the 231 patients included in the main study, 106 were included in this study.

All outcome variables were assessed four times: prior to start of the study (pretest), after 3 months (posttest), and at 6 and 9 months after inclusion (first follow-up and second follow-up, resp.) in individual data collection sessions.

2.3. Measures. Participant diagnosis was based on the International Classification of Diseases 10th revision (ICD-10) [24]. The diagnosis was made by the general practitioner (GP).

2.3.1. Beck Depression Inventory. The Beck Depression Inventory is a brief scale of 21 items which assesses the severity of depressive symptoms during the previous week. The score ranges from 0 to 63 points. The usually accepted cut-off points for classifying the intensity/severity are as follows: no depression: 0–9 points, mild depression: 10–18 points, moderate depression: 19–29 points, and severe depression: ≥30 points [25].

2.3.2. Remission. Clinical remission is based on the BDI, which is a self-reporting screening instrument. Remission is

defined as a mean BDI score of ≤11 [26]. On the BDI self-rating scale, a cut-off of BDI ≤ 11 emerged for remission with a sensitivity of 90% and specificity of 64%.

2.4. Group Treatments

2.4.1. Description of the Psychoeducational Group Intervention. The intervention consisted of 12 weekly 90-minute sessions led by two nurses. Each group consisted of 8–12 participants.

The program provided (1) health education about the illness: symptoms, diet, physical exercise, sleep, pharmacological treatment, and adherence to treatment; (2) breathing techniques; (3) problem solving, behavioral activation, and a cognitive-behavioral approach to depression; (4) self-esteem and self-image; and (5) pleasant activities, social skills, and assertiveness [27].

To enhance the active role of the patient, each session was accompanied with homework for the patient.

2.4.2. Description of the Control Group. Patients from the control group were no longer taking AD medication. Members of the control group received the usual treatment (visits with GPs and nurses). There was no pattern of visits established; the patients could go to the PCC when they needed to. The GPs and nurses used their own criteria to care for depressed patients.

2.5. Analysis. The analysis was carried out on an intention-to-treat basis. The analyses were based on the data of the 106 participants who completed some of the evaluations. The intention-to-treat analysis was carried out as follows: missing values were replaced by the scores from the previous assessment (the last observation carried forward (LOCF)) to ensure no increase. To examine baseline differences in the sociodemographic and clinical characteristics between groups, Student's t-test was applied for continuous variables and the Chi-square test for categorical variables.

The effect of the intervention on the outcome variables was measured by means of the difference in scores between groups and the effect size. Standardized effect size (SES) [28] is calculated as the mean difference between the intervention and the control groups, divided by the standard deviation (SD) of the control group. The SES is a standardized measure of the change that enables comparison between groups, between measures in the same study, and between different studies [29].

The standardized response mean (SRM) was used to measure the effect size within group comparisons. The SRM was calculated as the mean change divided by the SD of the change. Cohen's d allows the effect size to be classified into small (0.2 to 0.5), medium (0.5 to 0.8), and large (0.8 or over); these criteria can also be applied to the SRM [29, 30]. The IBM SPSS Statistics v.18 statistics package was used [31].

To evaluate the evolution of BDI scores between groups, we performed repeated measures of analysis of variance (ANOVA). We evaluated the goodness of fit using the Kolmogorov-Smirnov test of the residuals.

To evaluate the possible relationship between the number of sessions and the decrease in the BDI score in the intervention group, the Spearman correlation coefficient (r) was calculated for each time.

3. Results

The flow of participants is shown in Figure 1. Of the 246 allocated to the study, 140 were excluded: 125 were or had been on AD treatment, 12 did not meet the inclusion criteria, and 3 people chose not to participate.

3.1. Patient Characteristics. 106 patients were included in the study, 50 corresponding to the PE Group and 56 to the control group. These two groups were similar at baseline in terms of demographic and clinical characteristics, except with respect to gender ($P = 0.018$) and hypnotic medication ($P = 0.028$). Table 1 shows the baseline characteristics of the total study population and the intervention and control group. The typical patient was a native Spanish woman, approximately 53 years old, married/cohabiting, with primary studies, and self-employed. She had zero or two children and referred to a stressful event in the previous month.

Those allocated to the psychoeducational group received a mean of 8.74 (SD 4.26; range 1–12) sessions. Adherence to psychoeducational intervention was reasonably good, 38 (76%) receiving at least eight sessions or more. The sessions received by the intervention group were 12 sessions ($n = 21$); 11 sessions ($n = 4$); 10 sessions ($n = 8$); 9 sessions ($n = 3$); 8 sessions ($n = 2$); 3 sessions ($n = 1$); 2 sessions ($n = 4$); and 1 session ($n = 7$).

3.2. Attrition and Dropout. Of the sample of 106 patients included in the study, 26 were dropouts (dropouts = patients who were not evaluated at posttreatment and follow-up assessments at 6 and 9 months). Therefore, the overall dropout rate was 24.52%. The dropout rate was 20% ($n = 10$) in the intervention group and 28.57% ($n = 16$) in the control group. Dropouts from the experimental group did not differ statistically from those in the control group at follow-up assessments. The overall dropout rate was 23% of the initial study [18].

3.3. Intervention Effectiveness: Remission. The proportion of patients achieving remission (BDI score of ≤11) was examined using the Riedel remission criteria for major depression [26].

Posttest results showed that more participants in the intervention group ($n = 20$) had scored in the nonsymptomatic BDI range (BDI score of ≤11) than participants in the control group ($n = 7$). This means that 40% of the participants in the intervention group and 12.5% in the control group did not have depressive symptoms; the 27.5% difference between groups was statistically significant ($P = 0.001$, 95% CI 11.4 to 43.6). After 6 months of follow-up the results were similar: the proportion was 42% in the intervention group and 19.6% in the control group; the 22.4% difference between groups remained statistically significant ($P = 0.012$, 95% CI 5.2 to 39.6). After 9 months of follow-up, the proportion was

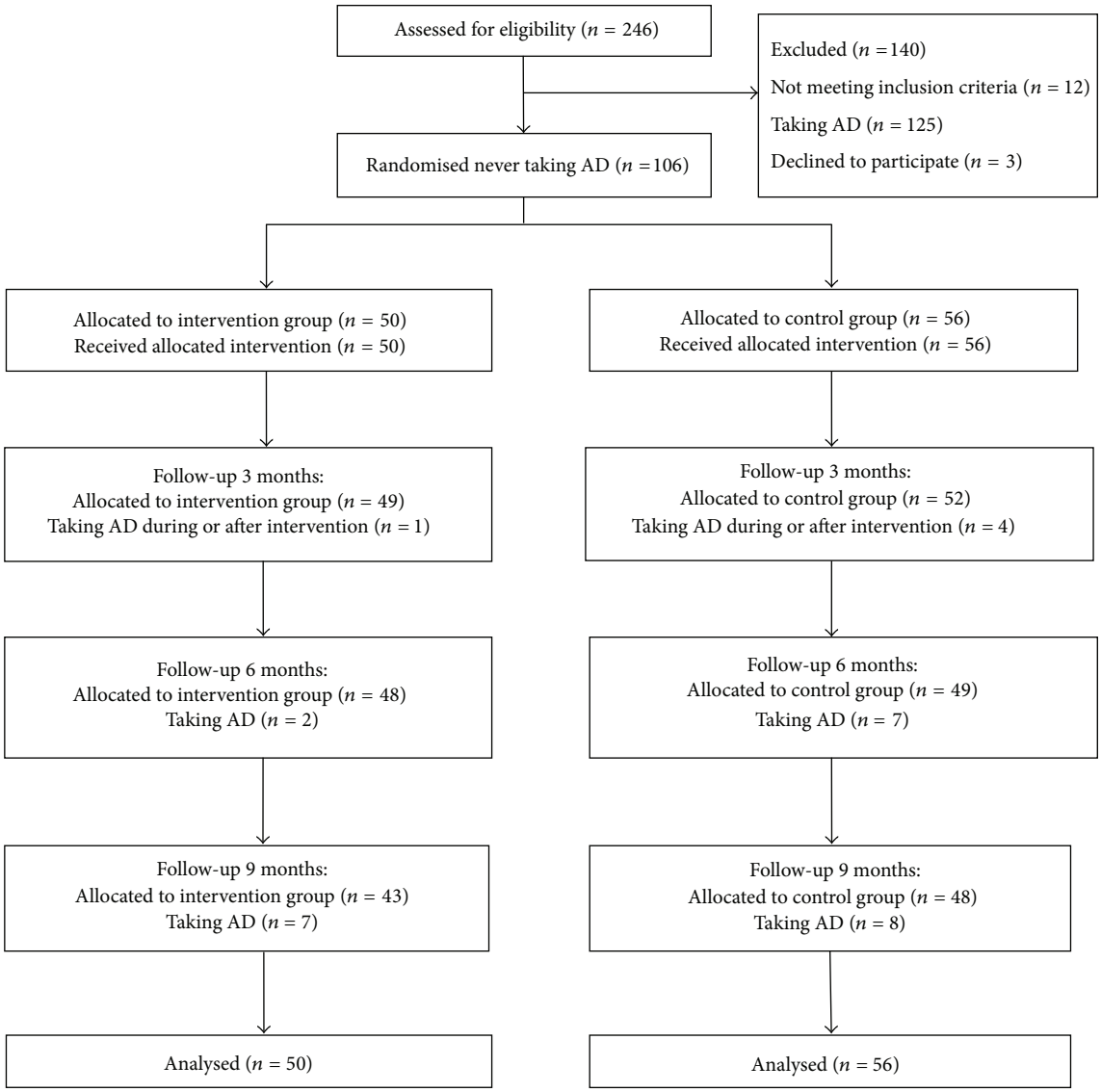

Figure 1: Flow chart of participants.

44% in the intervention group and 26.8% in the control group; however, the 17.2% difference between groups was not statistically significant ($P = 0.064$, 95% CI −35.5 to 0.79).

Table 2 shows the proportion of patients in the overall sample remitting through treatment.

The number needed to treat (NNT) to achieve remission is about 4 at 3 months (CI 95% 2.3 to 8.8), 5 at 6 months (CI 95% 2.5 to 19.3), and 6 for the long-term (after 9 months), that is, reducing the BDI score below 11.

3.4. Depressive Symptoms. Depressive symptoms were assessed using the Beck Depression Inventory (BDI). The difference between treatments at 3 months (psychoeducational intervention minus control) was estimated to be −3.61 (95% CI −6.25 to −0.95), which was significant ($P = 0.008$). The negative sign indicates that participants in the psychoeducational intervention group showed a greater decrease in depressive symptoms than those in the control group. The results at 6 and 9 months were not significant. Table 3 shows the changes in BDI score within and between the intervention and usual care groups, with missing data replaced using the last value carried forward.

The results showed that the evolution of the BDI scores over time between groups was significant in a nonlinear trend (P value nonlinear trend = 0.001). The effect size of this contrast was moderate ($d' = 0.55$) in the short term (posttest) and smaller ($d' = 0.18$) in the long term (at 9 months of follow-up). Figure 2 shows the evolution of the BDI score over time by groups.

As a secondary analysis, we were also interested in analyzing the evolution of the BDI score over time in the intervention group and control group separately.

Within the intervention group, a reduction was observed in the BDI score of 5.50 and 5.80 points posttreatment and

Table 1: Baseline characteristics of the total study population and the intervention group. Values are expressed as numbers (percentages).

Variable	Category	(n = 106) general n (%)	(n = 50) intervention n (%)	(n = 56) control n (%)
Gender*	Women	96 (90.6)	49 (98)	47 (83.9)
Age	Mean (SD)	52.79 (13.98)	52.14 (13.22)	53.38 (14.71)
Nationality	Spanish	97 (91.5)	45 (90)	52 (92.9)
Marital status	Single	18 (17.1)	9 (18)	9 (16.4)
	Married/cohabitant	51 (48.6)	25 (50)	26 (47.3)
	Divorced/separated	15 (14.3)	8 (16)	7 (12.7)
	Widow/widowed	21 (20)	8 (16)	13 (23.6)
Educational level	Did not complete primary education	13 (12.5)	6 (12)	7 (13)
	Completed primary education	38 (36.5)	18 (36)	20 (37)
	Secondary education	33 (31.7)	18 (36)	15 (27.8)
	University	20 (19.2)	8 (16)	12 (22.2)
Number of children	0 children	31 (29.2)	12 (24)	19 (33.9)
	1-2 children	51 (48.1)	25 (50)	26 (46.4)
	≥3 children	24 (22.6)	13 (26)	11 (19.6)
Employment status	Self-employed	97 (42.4)	56 (47.1)	41 (37.3)
	Disability or permanent disability	20 (8.7)	9 (7.6)	11 (10)
	Unemployed	32 (14)	18 (15.1)	14 (12.7)
	Works at home	36 (15.7)	19 (16)	17 (15.5)
	Retired	44 (19.2)	17 (14.3)	27 (24.5)
Core coexistence	Alone	22 (21.2)	8 (16)	14 (25.9)
	With children	15 (14.4)	9 (18)	6 (11.1)
	With his/her partner	24 (23.1)	13 (26)	11 (20.4)
	With his/her partner and children	25 (24)	13 (26)	12 (22.2)
	With parents	3 (2.9)	2 (4)	1 (1.9)
	With another family	5 (4.8)	2 (4)	3 (5.6)
	With other people	7 (6.7)	2 (4)	5 (9.3)
	Others	3 (2.9)	1 (2)	2 (3.7)
Employment economic status	Permanent contract	35 (35.7)	18 (37.5)	17 (34)
	Temporary contract	4 (4.1)	2 (4.2)	2 (4)
	Self-employment	6 (6.1)	3 (6.3)	3 (6)
	Working without contract	8 (8.2)	6 (12.5)	2 (4)
	No work, but has a salary	32 (32.7)	13 (27.1)	19 (38)
	No work, no salary	13 (13.3)	6 (12.5)	7 (14)
Stressful event	Yes	57 (57.6)	28 (60.9)	29 (54.7)
Medication: anxiolytics	Yes	40 (37.7)	20 (40)	20 (35.7)
Hypnotics*	Yes	6 (5.7)	0 (0)	6 (10.7)
Alternative treatment	Yes	28 (26.4)	13 (26)	15 (26.8)
Medication: blood pressure	Yes	30 (28.3)	11 (22)	19 (33.9)
BDI	Preintervention	19.58 (5.99)	20.14 (6.32)	19.07 (5.69)

Abbreviations: SD: standard deviation.
* P value significant (P = 0.018 and P = 0.028, resp.).

at 9 months of follow-up, respectively. In contrast, in the control group this reduction was only 0.80 and 3.40 points posttreatment and at 9 months of follow-up, respectively (Table 3).

By analyzing the intervention and control groups separately, the effect size within the intervention group (SRM) was high over time (d' = 0.80 postintervention and d' = 0.75 at 9 months of follow-up) and the effect size within the control

Table 2: Remission of depression in the overall sample.

Sample	Month	Control (n) ($n = 56$)	(%)	Intervention (n) ($n = 50$)	(%)	Difference at each follow-up (%)	(CI 95%)	P value*
Overall	**3**	7	(12.5)	20	(40)	27.5	(11.4 to 43.6)	0.001
	6	11	(19.6)	21	(42)	22.4	(5.2 to 39.6)	0.012
	9	15	(26.8)	22	(44)	17.2	(−35.5 to 0.79)	0.064

Abbreviations: CI: coefficient interval.
*The difference was calculated between the intervention and control groups.

group was small over time (d' = 0.16 postintervention and d' = 0.44 at 9 months of follow-up) (Table 3).

3.5. Antidepressant Treatment. Out of the 106 patients included in the study, 16 patients started AD treatment during the study, 7 from the IG and 8 from the CG. If we specify the time when AD treatment was prescribed, we find that 5 people were taking ADs after intervention, IG (n = 1) and CG (n = 4); at 6 months of follow-up (n = 9), IG (n = 2), and CG (n = 7); and at 9 months of follow-up (n = 15), IG (n = 7), and CG (n = 8). It should be mentioned that out of all the patients who initiated AD treatment during the study, only one patient from the CG initiated AD treatment after intervention and stopped after a month. The remaining patients continued with the prescribed treatment throughout the follow-up.

3.6. Number of Sessions and BDI. Regarding the number of sessions attended, an inverse relationship has been observed between the fall in BDI score compared to baseline and the number of sessions attended. Thus, participants who attended more sessions had a greater decrease in their BDI score both at 3 months (r = −0.354, P value = 0.012) and at 9 months of follow-up (r = −0.333, P value = 0.018).

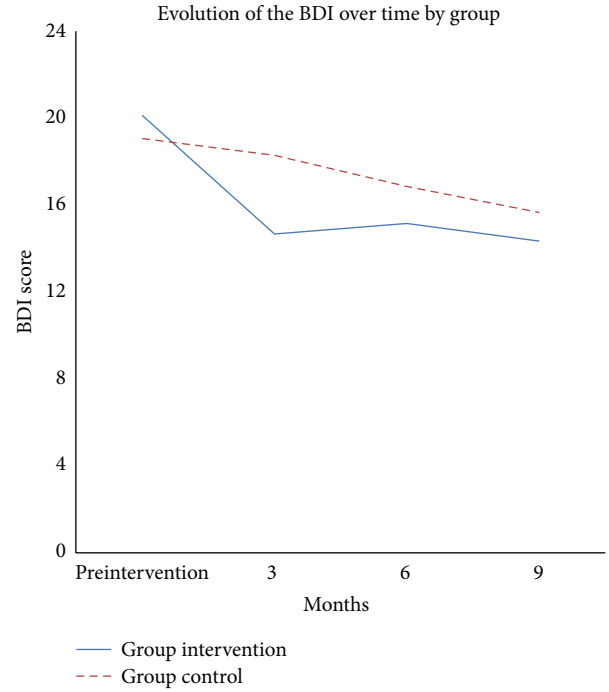

Figure 2: Evolution of the BDI score over time by group.

4. Discussion

We found a relationship between the psychoeducational group intervention and the remission of depressive symptoms in this sample of patients not taking antidepressants.

More patients from the IG had remission of their depressive symptoms (BDI score ≤ 11) [26] in the short term (posttreatment) and long term (at 6 and 9 months of follow-up) compared with the control group. The psychoeducational group intervention proved to be effective in the short term, showing a reduction of 5 points in the BDI score and this symptomatic improvement in BDI continued to follow-up at 9 months. In contrast, the control group needed 9 months to achieve a 3-point improvement in BDI. We could say that it is an effective intervention over the short term, although the effect size is moderate (effect size Cohen's d' = 0.55).

In this study, we do not analyze what type of population may benefit most from receiving the group intervention, whether participants are with mild (BDI score ≤ 11) or moderate (BDI score ≤ 18) depression. Of the 106 participants included, 47 had mild and 59 had moderate depression symptoms; therefore, the samples were too small for significant conclusions to be drawn.

Our results show that after 3 months (after intervention or short term), a considerable improvement is achieved in terms of both symptoms and symptom remission. It could be said that the psychoeducational group intervention reduces the duration of depressive episodes after a 3-month period, since the results show that 40% of the patients in the intervention group did not have postintervention depressive symptoms, compared to 12.5% in the control group, and this difference of 27.5% between groups was significant (P = 0.001). At 6 months of follow-up, the results remained constant (P = 0.012); however, after 9 months, the difference of 17.2% between groups was not significant (P = 0.064).

The data were consistent with those found in the study by Allart-van Dam et al. [16], which showed that 52.5% of the intervention group did not present postintervention depressive symptoms (BDI < 10) [25] versus 31.7% in the control

Table 3: Overall sample. Changes in BDI score within and between the intervention and usual care groups, with missing data replaced using the last value carried forward.

Sample	Months	Usual care group ($n = 56$)			Intervention group ($n = 50$)			Difference (95% CI) between groups (intervention group-usual care group)**	P value	SES$^{\$}$
		Mean (SD)	Difference* (95% CI)	SRM#	Mean (SD)	Difference* (95% CI)	SRM#	Difference		
Overall	**Preintervention**	19.07 (5.69)			20.14 (6.32)					
	3 (postintervention)	18.29 (6.53)	0.78 (−0.53 to 2.10)	0.16	14.68 (7.21)	5.46 (3.52 to 7.40)	0.80	−3.61 (−6.25 to −0.95)	0.008	0.55
	6	16.86 (6.91)	2.21 (0.19 to 4.24)	0.29	15.16 (8.92)	4.98 (2.53 to 7.43)	0.57	−1.70 (−4.75 to 1.36)	0.273	0.25
	9	15.66 (7.22)	3.41 (1.37 to 5.45)	0.44	14.34 (8.59)	5.80 (3.60 to 8.00)	0.75	−1.32 (−4.36 to 1.72)	0.392	0.18

Abbreviations: SD: standard deviation and CI: confidence interval.

*Differences were calculated between the baseline measurement and the follow-up measurement.

Positive differences indicate improvement; negative ones denote some worsening in clinical measures.

#SRM: standardized response mean, calculated as the mean change in score divided by the standard deviation of the change in score.

$SES: standardized effect size was computed as the mean difference between the intervention and control groups divided by the standard deviation of the control measurement.

A positive SRM or SES denotes improvement; a negative one denotes some worsening in clinical measures.

**The difference was calculated between the intervention group and the control group.

Negative differences indicate improvement in the intervention group; positive differences denote worsening in the intervention group.

Interpretation effect sizes: values of 0.2–0.5 represent small changes, 0.5–0.8 moderate changes, and >0.8 large changes.

group, with a significant difference of 20.8% ($P = 0.04$) between groups.

When we talk about the remission of symptoms in terms of number needed to treat (NNT), we observed that our NNT of 4 postintervention, 5 at 6 months, and 6 at 9 months of follow-up are supported by those obtained in the study by Dalgard [19] with a smaller sample of patients ($n = 155$), which was 6 at 6 months of follow-up, and the ODIN study [20] ($n = 452$), which was 7 at 6 months, supporting the effectiveness of the intervention. It must be mentioned that in these two studies the patients were taking ADs, but they did not analyze whether the pharmacological treatment could interfere in the results of the intervention.

Our results show a significant improvement in symptoms after intervention ($P = 0.008$; $d' = 0.55$), although the effect size is moderate, but this improvement is not maintained at 9 months of follow-up ($P = 0.39$; $d' = 0.18$). Our results coincide with those found in a review [32] which showed that psychological treatment for minor depression, including psychoeducation, is effective over the short term ($d' = 0.42$) and studies that had already demonstrated the effectiveness of psychoeducation over the short term [16, 22, 23]. With respect to the duration of the therapeutic effect of psychoeducation at 6 and 12 months of follow-up, the results are controversial.

These data also match those found in the study by Allart-van Dam et al. [17] ($n = 104$), which showed that the effect of the psychoeducational intervention was maintained after 6 and 12 months, even excluding participants who had taken ADs during the intervention ($n = 18$).

Based on the observation of results, it could also be stated that psychoeducational group intervention delays the prescription of ADs. ADs were prescribed to more patients from the CG during the intervention and at 6 months and 9 months of follow-up as compared to the IG.

If the patients from the IG that received ADs during the study ($n = 7$) are analyzed in more detail, we find that the only patient that received AD treatment after intervention and carried on taking it during the follow-up had only attended 2 group sessions and was only evaluated at baseline, with a BDI score of 27. The rest of the patients to whom an AD had been prescribed during the 9-month follow-up had attended an average of 11 sessions and their BDI score had decreased or was stable during follow-up, being 18.50 (SD = 6.60) at 9 months. None of their BDI scores was higher than 30. In the control group, more patients received postintervention AD treatment ($n = 4$) during the 6- and 9-month follow-up ($n = 7$ and $n = 8$, resp.), and two of them had a BDI score of 32 and 37 at postintervention time.

Good adherence to the psychoeducational therapy was observed, with 42% ($n = 21$) of the participants attending all 12 sessions and 76% ($n = 38$) attending at least 8 sessions. 24% ($n = 12$) of the patients showed poor adherence to treatment, as they only attended between 1 and 3 sessions. Although there are few studies that have evaluated adherence to psychological therapies in patients with depression [33, 34], a meta-analysis aimed at identifying effectiveness predictors in depression preventive programs [35] reached the conclusion that programs of more than 8 sessions with a 60–90 minute duration offered a large effect size and that the number of sessions is important for the patient to internalize the knowledge, the processes, and the skills learned during the intervention, meaning that fewer than 8 sessions are likely to be insufficient.

However, there are quite a lot of studies that have analyzed adherence to pharmacological treatment. Their conclusion is that there is low adherence to antidepressant treatment in primary care [36–38], most patients do not follow treatment recommendations [37, 38], low concordance is observed between the real practice of primary care physicians and CPG recommendations regarding depression [39], and a systematic review does not recommend antidepressants for the initial treatment of subjects with minor depression [6].

Psychoeducation has proven effective as psychotherapy for depressive symptom management in the primary care setting [16, 17, 19, 20, 22, 23], and it can be carried out by community nurses [19–22]. A systematic review about the effectiveness of psychoeducation for depression [40] suggests that psychoeducation is effective in improving the clinical course, treatment adherence, and psychosocial functioning of depressive patients.

Even though no consensus has been achieved on the definition of psychoeducation, all psychoeducational interventions share a group structure, some homework, and an educational approach [18, 35], even if they use different methods (cognitive-behavioral therapy [41], coping with depression course (CWD) based on cognitive-behavioral techniques [17, 19, 20], or multicomponent interventions [22]).

In general, psychotherapeutic and psychosocial interventions for depression in primary care are aimed at improving compliance with therapy and offering a therapeutic alternative to drugs. Some studies suggest the importance of having effective treatments for depression in primary care [42, 43] or increasing access for patients with depressive symptoms in primary care to psychological therapies that have proven effective in the short run, as they can have more prolonged benefits [44]. Studies show that the community could be a suitable setting in which to send patients for preventive interventions in cases where the person has a high symptom score but does not meet the criteria for major depression [42].

According to the results, this PE intervention is effective in the short term, with high rates of remission in patients with mild and moderate depressive symptoms not treated with AD medication. These results coincide with those found in an earlier study [18] which showed that this psychoeducational intervention was more effective in patients with mild symptoms, since they had a higher symptom remission rate over the short term and long term, but the intervention was not shown to be effective over the long term in patients with moderate symptoms.

Due to the high prevalence of depression in primary care and the increase in spending on antidepressants, it is necessary to implement interventions that have proven to be effective and that could contribute to an improvement in depression management and reduce its high costs.

Strengths and Limitations of This Study. Our trial has several strengths: firstly, it is the first study to assess the effectiveness of this psychoeducational group intervention in patients not treated with AD medication. The intervention includes health education about the disorder, healthy behaviors, social skills, and cognitive-behavioral techniques. Secondly, this study is the first multicenter, randomized study that assesses the effectiveness of a psychoeducational intervention in Spain. Thirdly, the sample population was representative of the whole of Barcelona. The participating PCCs were located in various areas throughout Barcelona, with different sociodemographic and economic resources.

Despite the positive findings, potential biases need to be considered when evaluating the study. Some of the limitations of the study could be as follows: firstly, we performed a randomization of patients, but with no double-blind the patients know who belongs to the intervention group and who belongs to the control group, as do the nurses and doctors at the PCC. It was difficult for researchers to remain blinded to group allocation. However, participants completed mood self-rating assessments. Therefore, that lack of blindness should not have affected our primary outcome to a great extent.

Secondly, the sample size is small, containing only 106 patients. Thirdly, the study employed only one outcome measure, BDI, as we wanted the study to be as close as possible to the usual practice at primary care centers. It is a naturalistic study. Thirdly, the remission of depression was assessed by a screening questionnaire (BDI) rather than a diagnostic interview. Fourth, the overall dropout rate was 24.52%. Dropouts from the experimental group did not differ statistically from those in the control group at follow-up assessment. The overall dropout rate was 23% of the initial study [18]. Further studies are required to confirm these results.

5. Conclusions

Our results show that this psychoeducational group intervention could be an effective treatment in the population with mild/moderate depressive symptoms not treated with antidepressant medication in primary care over the short term. Before taking an AD, psychoeducational intervention should be considered.

Abbreviations

AD: Antidepressant
CI: Confidence interval
d': Cohen's effect size
IG: Intervention group
CG: Control group
ITT: Intention-to-treat
NNT: Numbers needed to be treated
PC: Primary care
PCCs: Primary care centers
PE: Psychoeducation
SES: Standardized effect size
SRM: Standardized response mean.

Ethical Approval

Ethical approval was granted by the Jordi Gol i Gurina Foundation. Informed consent was obtained from all participants prior to their involvement in the study.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

R. Casañas designed the study, participated in the analysis and interpretation of the data, wrote the paper, and gave final approval of the version to be published. R. Catalán was involved in drafting and revising the paper and participated in interpreting the data. R. Penadés participated in the analysis and interpretation of the data. J. Real performed the statistical analysis and participated in the revision of the paper. MA. Muñoz critically reviewed the paper. S. Valero critically reviewed the paper. LL. Lalucat-Jo was involved in drafting and revising the paper. M. Casas participated in the study design and revision of the paper. All the authors contributed to the paper and approved the final paper.

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Review Article

Risk Factors for Depression in Children and Adolescents with High Functioning Autism Spectrum Disorders

Myriam De-la-Iglesia[1,2] and José-Sixto Olivar[2,3]

[1]*Departamento de Psicología, Facultad de Educación, Universidad de Valladolid, Campus María Zambrano, Plaza Alto de los Leones 1, 40005 Segovia, Spain*
[2]*Laboratoire LPPS, EA 4057, 92100 Paris, France*
[3]*Departamento de Psicología, Facultad de Educación y Trabajo Social, Universidad de Valladolid, Campus Miguel Delibes, Paseo de Belén 1, 47011 Valladolid, Spain*

Correspondence should be addressed to Myriam De-la-Iglesia; mdelaig@psi.uva.es

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The objective of our study was to examine, discuss, and provide proposals on diagnostic comorbidity of depression in children and adolescents with high functioning autism spectrum disorder (HFASD) in the following aspects. (1) *Prevalence*. It was concluded that there are an elevated depression rate and the need for longitudinal studies to determine prevalence and incidence based on functioning level, autistic symptoms, gender, age, type of depression, prognosis, duration, and treatment. (2) *Explicative Hypotheses and Vulnerability*. The factors that present the greatest specific risk are higher cognitive functioning, self-awareness of deficit, capacity for introspection, stressful life events, adolescence, quality of social relationships, and alexithymia. (3) *Risk of Suicide*. The need for control and detection of suicidal tendencies and bullying is emphasised. (4) *Depressive Symptoms*. Indicators for early detection are proposed and their overlap with HFASD is analysed, examining the *assessment techniques* used and arguing that specific adapted tests are needed.

1. Introduction

The new Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5 [1]), proposes Autism Spectrum Disorder (ASD) as the only diagnosis possible for the previous category of Pervasive Developmental Disorder (DSM-IV-TR [2]), as well as the elimination of Asperger Syndrome (AS). This change in name emphasises the dimensional consideration of the clinical picture in the various areas affected (social communication and mental inflexibility) and the difficulty of establishing precise limits between the subgroups within the same category. This new classification is based on empirical evidence that the majority of individuals with a diagnosis of AS meet the DSM-IV criteria for Autistic Disorder [3, 4]. However, several research teams hold different perspectives about the new DSM-5 classification [5].

In addition, there is a consensus as to the need to go deeper in reconsidering not only diagnostic issues, but also comorbidity, assessment, and intervention in ASD [6]. Individuals with ASD show significant variability in symptom expression and in the level of cognitive functioning (DSM-5 [1]). In addition, their condition can coexist with other disorders [7]. The studies that confirm the high risk of comorbidity with depression are notable. Fundamentally, in adolescence, individuals with high functioning autism spectrum disorders (HFASD) usually present a high degree of anxiety, stress, and depression, with mood disorders being the most common comorbidity (e.g., [8]). However, because the main symptoms of ASD cause significant impairment, other psychopathological symptoms are usually not the primary focus of screening, diagnosis, or treatment. Research suggests that such conditions can exacerbate the core ASD symptoms, compromising quality of life and long-term functioning level even more [9].

That is why there is a need for specialised attention to prevent the possible appearance of depressive symptomatology,

for early detection and for specific intervention if depression has appeared. However, studies that investigate the variables related to depression in autism are rare and their findings are inconsistent. This makes the work of experts in early detection and intervention more difficult. Furthermore, knowledge about the pattern of psychiatric comorbidity is scant. In spite of demonstrated idiosyncrasy in alarm signals, conclusive comprehensive studies that help to detect or lessen this risk are rare.

Study Objectives. In this study we carried out a critical review of scientific research on diagnostic comorbidity of HFASD and depression to ascertain the current state of the matter. We synthesised the main studies performed to date, critically analysing the findings that make it possible to improve early detection. Attempting to enhance professional praxis in prevention, early detection, and early intervention, we consequently proposed the following: (1) presenting the *rates of depression* in children and adolescents with HFASD; (2) analysing the possible *risk factors and explicative hypotheses* for diagnostic and/or symptomatological comorbidity of HFASD and depression, establishing a possible working hypothesis that supports studying the profiles of potential vulnerability and contributing factors; (3) assessing the implications of depression in HFASD (the *risk of suicide*); and (4) analysing the difficulties involved in *assessing* depression in children and adolescents with HFASD and proposing alternatives. All of these would make it possible to elaborate a proposal, in agreement with the results obtained from these analyses, that promotes and establishes possible future research paths, which would complement, refute, or confirm the studies carried out to date.

Study Hypothesis. This study established the hypothesis that the individuals with HFASD with higher cognitive levels and capacity for introspection would present greater risk of depression in adolescence, because they are more conscious of their difficulties with social relationships (e.g., [3, 4]). This risk would increase when the social interactions were more conflictive and these individuals could respond with suicide attempts. This hypothesis was chosen with the aims of improving prevention, as well as early detection and intervention, in depression and of attempting to clarify the most vulnerable target population.

2. Materials and Methods

2.1. Literature Search. A systematic search of computerized databases (PsyInfo, Pubmed, Web of Science, and ERIC) was undertaken using the words "Autism," "Asperger," "Pervasive Development Disorder," and "PDD" in various combinations with the words "depression," "depressive disorder," "suicide," "risk," "comorbid disorder," "vulnerability," "comorbidity," "prevalence," "psychiatric disorder," and "psychological disorder." The abstracts were reviewed by the first author for relevance. Abstracts were considered relevant if they described their sample as having ASD and if they reported a depression measure. Next, the reference sections for data-based papers not found by the computer search were checked.

2.2. Selection of Studies. The studies had to meet the inclusion criteria: 2010-March 2015 studies had to report on children and adolescents (participants' age: 3–20) with diagnosed ASD, autism, or HFASD. Our paper reviews and analyses the research on the topic of interest over the last five years, including as yet unpublished studies concerning risk factors for depression in children and adolescents in the framework of the new diagnostic classification for ASD consistent with DSM-5 criteria [1].

3. Results

Next, we present a summary for each section of the results analysed in this study, such as summaries about rates of depression in children and adolescents with HFASD, and the factors of risk studied: (a) histories of first-degree relatives and environmental context; (b) gender; (c) age; (d) cognitive level, capacity for introspection, awareness of deficits (insight), and alexithymia; (e) social support: quality of social relationships; (f) life events and the domain of repetitive and restricted behaviours and thoughts; and (g) biological factors and comorbidity.

3.1. Rates of Depression in High Functioning Autism Spectrum Disorders. Depression is common in prevalence in ASD, which has increased the growing interest in understanding the nature of depression in this group (e.g., [10, 36]). In addition, these problems could influence the family negatively, producing an increase in stress and conflicts, which are high in autistic people's caregivers [37]. However, there are no large population studies that assess the incidence and prevalence of depression in ASD. Estimates on prevalence of comorbid depression vary widely among studies. In the next few years we will be able to assess the empirical effects of the new conceptual framework for ASD resulting from the DSM-5 criteria [38] in the general context of the epidemiology of depression in ASD.

Links between affective disorders and autism have been suggested for decades [39] (see Table 1). The rates are very high, both in the early research, consisting basically of case studies [11, 12], when the study objective was analysing the patterns of prevalence of disorders coexisting with HFASD [7, 13, 14, 40], independently of the age groups studied [15–18], and when the levels of depressive symptomatology of individuals with HFASD are compared with peer control groups, neurotypical (NT) individuals, [10, 19–22] or with other clinical groups (e.g., with intellectual disability [23]).

3.2. Risk Factors and Explicative Hypotheses for Diagnostic and/or Symptomatological Comorbidity of HFASD and Depression. In the case of individuals with HFASD, the factors that lead to them having a greater risk of coexisting psychiatric symptoms (such as depression) are still not completely understood. However, based on preliminary reports, some generalisations can be made. We present studies on risk factors and related protective factors, which will make it possible to verify or refute our working hypothesis. Specifically, based on the biopsychosocial model, factors related to

Table 1: Results on prevalence rates, risk factors, and explicative hypotheses for depression in ASD.

Study	Sample: n (mean), years, age range	Diagnosis	Assessment of depression	Results on prevalence rates of depression	Risk factors and explicative hypotheses
Gillberg and Billstedt (2000) [7]	$n = 35$ (age: DK) Range: children and adolescents with autism	ASD	Review of the literature	33% had an additional psychiatric disorder, with depression being the most common diagnosis	Biological factors: comorbid conditions may be markers for underlying pathophysiology
Whitehouse et al. (2009) [10]	$n = 35$ AS (age: 14.2) Range: 12–17.6 CG: $n = 35$ NT (age: 14.4) Range: 13.2–16.10	HFASD	CES-DC (*Centre for Epidemiological Studies Depression Scale*)	33% self-reported significantly higher levels of depressive symptoms than the NT population	Social support: quality of social relationships
Kanner (1943) [11]	$n = 11$ (age: 5.4) Range: 2.4–11	ASD	DK	One showed tendency towards depression.	Social support: quality of social relationships
Wing (1981) [12]	$n = 34$ (age: DK) Range: 5–35	HFASD	DK	The most common psychiatric diagnosis was depression (10 subjects: approximately)	Age; cognitive level, capacity for introspection, awareness of deficits (insight), and alexithymia; life events and effects brought about by character came from the domain of repetitive and restricted behaviours
Ghaziuddin et al. (1998) [13]	$n = 35$ (age: 15) Range: 8–51	HFASD	K–SADS–E (*Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiological Version*)	65% had an additional psychiatric disorder, with depression being the most common (37%)	Histories of first-degree relatives and environmental context
Kanne et al. (2009) [14]	$n = 177$ (age: 7.3) Range: 3–18 CG: their siblings ($n = 148$)	Autism	CBCL (*Child Behaviour Checklist*) C-TRF (*Caregiver/Teacher Report Form*)	26% presented depression	Cognitive level; histories of first-degree relatives environmental context
Barnhill and Myles (2001) [15]	$n = 33$ AS (age: 15) Range: 12–17	HFASD	CDI (*Children's Depression Inventory*)	54% showed depressive symptoms	Cognitive level, capacity for introspection, awareness of deficits (insight), and alexithymia
Leyfer et al. (2006) [16]	$n = 109$ (age: 9.2) Range: 5–17	Autism	ACI-PL (*Autism Comorbidity Interview-Present and Lifetime Version*): this is a modification on the Kiddie Schedule for Affective Disorders and Schizophrenia	13% major depression	Biological factors: comorbidity
Mayes et al. (2011) [17]	$n = 627$ (age: 6.6) Range: 1–17	ASD (64.4% HFASD)	PBS (Pediatric Behaviour Scale)	The maternal descriptions indicated depression in 72% of the HFASD cases	Gender; age; cognitive level, capacity for introspection, awareness of deficits (insight), and alexithymia; social support: quality of social relationships
Mayes et al. (2011) [18]	$n = 233$ (age: 8.3) Range: 6–16	HFASD (IQ > 79)	PBS	54% of the mothers reported depression in their children	Age; cognitive level, capacity for introspection, awareness of deficits (insight), and alexithymia

Table 1: Continued.

Study	Sample: n (mean), years, age range	Diagnosis	Assessment of depression	Results on prevalence rates of depression	Risk factors and explicative hypotheses
Green et al. (2000) [19]	$n = 20$ AS (age: 13.75) Range: 11–19 CG: $n = 20$ (age: 14.47) Range: 11–19	HFASD	ICD-10 (*Tenth Revision of the International Classification of Disease*)	Higher levels of depression than in the CG. Although only 5% satisfied criteria for major depression, 40% showed chronic unhappiness and 55%, irritability	Biological factors: comorbidity
Hurtig et al. (2009) [20]	$n = 43$ AS or HFA (age: 13) Range: 11–17 GC: $n = 217$ (age: 13.5)	HFASD	YSR (*Youth Self-Report*) CBCL (*Child Behaviour Checklist*) TRF (*Teacher Report Form*)	33% self-reported significantly higher levels of depressive symptoms than the NT population	Gender
Kim et al. (2000) [21]	$n = 59$ (19 AS; 40 HFASD) (age: 12) Range: 9–14 CG: $n = 1751$ Range: 9–14	HFASD	OCHS-R (*Ontario Child Health Study-Revised*)	17% significant clinical symptomatology of depression	Biological factors: comorbidity
Meyer et al. (2006) [22]	$n = 31$ AS age: 10.1 Range: 8–14 CG: $n = 33$ NT	HFASD	BASC-SRP (*Behaviour Assessment System for Children-Self Report of Personality*) BASC-PRS (*Behaviour Assessment System for Children-Parent Report Scale*)	Self-reported symptoms of depression higher than in CG	Cognitive level, capacity for introspection, awareness of deficits (insight), and alexithymia
Brereton et al. (2006) [23]	$n = 381/367$ ASD (age: 7.4) Range: 3.8–24 GC: $n = 581$ intellectual disability without ASD	ASD	DBC-P (*Developmental Behaviour Checklist*)	Parents offered significantly higher scores for behaviour problems, anxiety, depression, and irritability compared with normality, as well as higher degrees of anxiety, behaviour problems, depression, and attention-deficit/hyperactivity disorder than in CG	Gender; age

ASD: Autism Spectrum Disorder; AS: Asperger Syndrome; CG: control group; HFASD: high functioning autism spectrum disorder (IQ > 70); NT: neurotypical.
DK: it indicates that the symptom/sign was not discussed in the paper, not that the authors were unable to assess it.

depression can be seen from all spheres, which are as much psychological as well as biological and social.

(a) Histories of First-Degree Relatives and Environmental Context. In the general population, familial-genetic factors play an important role in the aetiology of depression in both children and adults [41]. When we are dealing with children with ASD, studies also recognise that (just as in the NT population) children with autism that have depression are more likely to have a family history of depression. For example, when Ghaziuddin's team compared the family histories of 13 participants with ASD and depression to 10 children with ASD lacking a previous recurrent history of depression, they found that 77% of the first group had a family history of depression but the percentage dropped to 30% in the group of children without depression [13].

Studies suggest greater prevalence of affective disorders in first-degree relatives with ASD [42] than in control NT individuals or those with Down's syndrome [43] and individuals with nonautistic developmental disorders [44]. This does not seem to be a reaction to having a child with ASD, given that the onset of the mood in most of the cases was registered before the individual with ASD was born [44]. Furthermore, it has been shown that parents of children with ASD and altered serotonin levels score high in depression [45], which suggests a possible interaction of shared neurochemical factors between depression and autism, at least in some cases. A recent study on 33,332 cases and 27,888 controls of European descent is interesting in this regard, as it found specific variations that underlie the genetic effects shared among ASD, schizophrenia, bipolar disorder, and major depressive disorder [26].

Many other psychosocial factors, especially those family-related (i.e., the parent-child relationship and parenting style) and their influences, may be important. The work by Rezendes and Scarpa [46] examines the roles of parenting stress and parenting self-efficacy as mediators between child behaviour problems and parental anxiety/depression, using a sample of 134 mothers with an average age of 39 and children with ASD within the age range 3–16 years. The research suggests that parental factors may influence the relationship between child behaviour problems and parenting stress and depression, including the role of parenting self-efficacy within the parenting experience, thus bringing about a two-way relationship between the parents' stress factors and the behavioural problems of children with ASD.

(b) Gender. When studying this variable in individuals with ASD, most authors fail to find gender differences [20, 47] or significant relationships between depressive symptoms, gender, ethnic group, or father's occupation [17]. The lack of gender effects is even more notable when we consider that they are indeed present in the general population. For this reason, the authors postulate that the absence of gender effects in autism (in contrast with the general population) "could reflect shared neurobiological deterioration," independently of sex and "the predominant influence of the dysfunction of the organic brain in psychopathology" [23, p. 867-868]. This would imply a greater relative weight of organic factors in the appearance of depression in this collective.

(c) Age. A study on 34 cases with HFASD reported the presence of clinical depression in both adolescence and in adulthood, and that these characteristics seem to be related to the fact that the individuals are painfully consciousness of their handicap and of being different from other people [12, p. 118].

Current studies confirm that depression is more common in adolescents and adults than in children [23, 40]. In addition, the majority of the studies on children with autism show that the older the child and the greater the intelligence quotient (IQ), the greater the incidence of depression [23, 48]. Specifically, research on this topic [17] has found that depression is positively related to IQ, but also, especially, to age. Those authors state that this psychopathological pattern begins very early in children with autism and that, independently of the level of cognitive functioning, adolescents present greater depression than preadolescents, who in turn are more depressed than preschool age children. The authors explain these results based on the assumption that individuals of greater age and/or IQ might have greater capacity for introspection.

Studies such as the one conducted by Vickerstaff's team [48] also find that the older the youngsters with HFASD, the greater the self-reporting of symptoms of depression. However, this study adds the finding that there is a direct correlation with the fact that those who are older have greater subjective perception of difficulties in social competency. It is possible that society's expectations of these individuals begin to have a greater effect in adolescence and adulthood. The stress caused by the transition to adulthood can add even more difficulties in relating to peers. Adolescents and adults with ASD may be aware that they are behind their peers developmentally and desire to achieve milestones of development typical of adults, but they lack the adaptive skills or the executive planning abilities to take the steps needed to develop an independent life. Feelings of extreme depression may also affect the motivation required to make these life changes.

(d) Cognitive Level, Capacity for Introspection, Awareness of Deficits (Insight), and Alexithymia. Several studies have specifically investigated the relationship between different IQ levels, symptoms of autism, and symptoms of depression in individuals with ASD. Examples are [49] with 1,202 children with ASD aged between 4 and 17 years and with a wide range of intellectual levels [17, 30]. Based on these results it appears that a higher cognitive level and less serious symptoms within the spectrum predict a greater risk of depression.

The majority of higher functioning individuals with ASD are aware of their social difficulties and this awareness may in turn lead to greater pathology and the development of comorbid psychiatric problems [50]. Some authors [12, 39] initially suggested a possible relationship between greater self-consciousness of social problems and depression. This author indicated that young people with ASD that are sufficiently conscious of themselves and of their social difficulties

tend to experience greater emotional pain when faced with social failures.

Supporting the hypothesis that higher IQ also increases social comparison and consequently deficit insight, [51, 52] gave information on the relation between the processes of social comparison and depressive symptoms in 36 adolescents with HFASD aged between 10 and 16 years. When this greater consciousness of their failures in social life is added to assumption of responsibility and internalisation of the negative events, it contributes to lowering self-esteem and increasing discouragement, which can also increase the risk for depression in individuals with ASD [15]. Meyer's team [22] found a significant correlation between depressive symptoms and social comparison scale with children aged between 7 and 13 years with HFASD when they assessed whether certain patterns of social information processing and social attribution were related to depression in the youngsters with ASD. The participants demonstrated the capacity to interpret and make attributions about social situations and to report their lower satisfaction and competence in interpersonal relationships as well as their own emotional and social difficulties. These findings represent the confirmation that many children with HFASD are aware of their social difficulties and their differences with respect to peers and that they are capable of showing enough introspection to self-report their problems.

Nevertheless, adults with ASD have alexithymia (understood as the incapability to identify, describe, and interpret emotional states) to a greater extent than the general population [53]. Alexithymia is frequently present in depression [54]. For that reason, some research teams are focusing on the differential diagnosis between HFASD and alexithymia, due to some similarities in their clinical presentations [55].

(e) Social Support: Quality of Social Relationships. Children and adolescents without friends and with poor quality social relationships and friendships run the risk of loneliness, stress, depression, negative affect, and concomitant developmental psychopathologies [56, 57]. For this reason, it is possible that the feeling of loneliness, fuelled by the poor social relationships that individuals with ASD have, contributes to greater levels of depression. There is evidence that social disabilities correlate with a negative state of mind in children and adolescents with HFASD [52, 58], and specifically with anxiety and depression [59] Despite this, few studies have examined the relation between these problems and the social impairment that is at the core of the disorder.

In fact, individuals with ASD and autism are traditionally conceived to have no problems with or even prefer social isolation. For example, Kanner [11, p. 249] described individuals with ASD as having a "powerful desire" for aloneness (p. 249). However, research suggests that individuals with HFASD, especially those with Asperger's Disorder, have more interest in social interaction but lack the abilities needed for success in social relationships [60]. Individuals with HFASD are integrated into their groups of reference and, consequently, are going to experience greater exposure to their peers and to social stimulation than individuals with a lower level of cognitive functioning. This stress, which involves an increase in social demands, can lead to symptoms of depression [17]. Specifically, studies on the internalisation of problems are beginning to reveal that there is a two-way relationship between negative social self-perception and difficulties with peers and that the combination of these factors predicts an increase in depression [61, 62]. For example, there is evidence that NT children rejected by their peers experience higher levels of anxiety and depression [63] and that, in individuals with ASD as well, a history of nonsuccessful interactions and social isolation can contribute to low self-esteem, frustration, and depression [50].

In NT individuals, there seems to be a protective function in children that have at least one friend. These children show higher self-esteem, less anxiety, less loneliness, and fewer episodes of victimisation [64]. In contrast, Mazurek and Kanne [49] found that, when they investigated the relation between friendship, seriousness of autistic symptoms, and depression, the high rates of depression obtained were shown in children with poor quality friendships. They also found that the absence of friendships (children with few, very poor quality or no friendships) could protect against emotional problems.

It is relevant to emphasise that there are few studies on how children with ASD perceive friendships or their lack or whether such friendships can carry out a protective function similar to that found in the reference population. As we will see, current results indicate that adolescents with HFASD generally have poorer quality friendships than their NT peer group, less intrinsic motivation to engage in friendships, and elevated levels of loneliness and depressive symptoms. These associations between friendship, lonesomeness, and depression indicate that the development of meaningful relationships may have significant effects on mental health in this population. This leads to the importance of intervention in this area for improving prevention. However, the reverse interpretation may also be true (i.e., depression may negatively affect the ability to develop relationships with others). It is also possible that there is not a causal relationship (i.e., both may be independently related to autism, which would explain the correlation between the two). Of course, all three explanations may be operating simultaneously. The need for controlled prospective studies to empirically determine risk factors should be listed as a future research necessity.

The team of Bauminger [35, 65, 66] carried out a series of studies that sought to quantify the impact of poor quality social relationships on the emotional functioning of children with HFASD. In all the series, the children with autism perceived their friendships to be of poorer quality than the NT control group did, and they reported greater feelings of loneliness. In the first of the series, Bauminger and Kasari examined the perceptions of friendship and the experiences of loneliness in a sample of children aged from 8 to 14 years with HFASD, compared to a control group paired in age and IQ [35]. The authors found high loneliness levels and friendships of poor quality. The results indicated that children with autism also differed in their understanding of friendship, which they defined in terms of company, safety, confidence, and friendliness. These children also seemed to understand loneliness in a different way (defining it from

a cognitive rather than an emotional viewpoint), showing fewer associations between friendship and loneliness than the NT children. It consequently seems that children with autism may lack the capacity to link the possibility of reducing loneliness to friendship [35, 67]. A year later, the same team confirmed that the children and teens with HFASD self-reported more feelings of both social and emotional loneliness than the NT control group. This led them to suggest that young people with ASD (independently of whether or not they experience anxiety-provoking situations) may tend to feel emotionally disconnected or alone [65]. However, in a later study these authors concluded that friendship has a protective function for children with HFASD, given that greater fellowship, intimacy, and proximity with a friend are associated with higher levels of self-esteem [66].

The team of Whitehouse [10] linked the poorer quality of friendship in adolescents with HFASD to greater loneliness and greater depressive symptoms with respect to the comparison group. This finding complements work [35] showing that these feelings of loneliness indicate greater vulnerability to depression if low quality friendships are accompanied by feelings of social isolation.

(f) Life Events and the Domain of Repetitive and Restricted Behaviours and Thoughts. Negative life events play an important role in precipitating depression [56]. Negative events such as parents getting divorced, illnesses, death, frequent parental discord, or changing residences have been related to clinical depression, both in children and in adults [68]. Studies carried out with individuals with ASD find similar results, which suggest that children with ASD and depression experience more negative events compared to controls [69]. For example, in a study with 11 children with ASD and depression, the team for Ghaziuddin found that the depressed group had experienced an overload of adverse life events (e.g., losses significant for the child, divorce, or parental separation) in the 12 months before depression onset [70].

As for the type of negative events related to the risk of depression in this collective, we analysed the possible influence of the "age" factor in a previous section, concluding that adolescence constitutes one of the risk factors over which the greatest scientific agreement exists. We emphasise that, although this variable belongs to the biological sphere, it seems that the psychosocial area is where we can understand its possible risk effect, as a stressful life experience. This is true insofar as aging constitutes a developmental moment in which social demands increase, along with self-awareness of the difficulties involved in facing these demands.

Another stressful life event of risk for individuals with ASD is peer abuse, which studies have linked to symptoms of depression, anxiety, loneliness, and suicide [71]. Bullying frequently occurs among children with ASD. For example, 34 parents of children aged between 5 and 21 years with ASD indicated that approximately 65% had been victims of their peers [72]; in the study by the Mayes team [73] in their sample of 791 children with ASD, 57% of the mothers reported mocking and bullying. Research conducted by Wainscot and his team [74] found similar rates among 57 young people with HFASD. Other studies report rates that are even higher, reaching 75% of the adolescents with HFASD [75] or 94% when mothers of children with HFASD or with nonverbal learning disabilities were asked [76]. Studies generally indicate that between 44% and 77% of these young people have experienced bullying in the last month [32, 33, 72, 74]. This is very much higher than the rates found among NT individuals, in which they are about 10%–20% [77]. Within the spectrum of individuals with ASD, those with a higher level of functioning present greater risk than those affected with intellectual limitations. The reason appears to be that the greater severity of the symptoms accentuates the prosocial attitudes of the peers [78], but it is also because individuals affected more greatly usually function in special education centres [33].

Most authors attempt to explain these high rates by many factors related to the core symptomatology or symptoms associated with individuals with ASD and their differentiation with respect to their peer group. Examples are difficulties in social interactions and communication or the risk of being the object of jokes and attacks due to their rigidity (repetitive and restricted behaviours and thoughts), lack of assertiveness, possible intense emotional and/or behavioural reactions, their isolation, naiveté, eccentricity, difficulties with mental abilities, and so forth. For example, Cappadocia et al. [32] found direct associations between bullying and some behaviours that can be observed in autism (e.g., stereotypic behaviour, self-injury, communication difficulties, and hypersensitivity), as well as with symptoms of anxiety and hyperactivity, in a sample of 192 parents of children with ASD aged between 5 and 21 years (54% having HFASD).

This becomes worse when individuals with HFASD, perhaps from their possible lack of understanding of the negative intention of the abusive interaction (due to their mental difficulties: repetitive and restricted behaviours and thoughts), reinforce the abuse by responding submissively to the aggressor (e.g., obeying a humiliating order because they want to feel closer to the peer group). Another way they can reinforce the abuse is by not defending themselves against aggressions (e.g., agreeing with a hurtful ironic statement about themselves, due to their difficulties with the indirect uses of language, in turn connected with their repetitive and restricted behaviours and thoughts). In addition, as the study by the Storch team indicated, we can even find a two-way relationship between the signs of anxiety in the individual with ASD facing an episode that generates even more anxiety when it happens, which will reinforce the aggressor as to the possibility of a further attack and so on, successively [79]. These authors found positive relationships between peer abuse and depressive symptoms, loneliness, and anxiety in the 60 participants aged between 11 and 14 years (11 with HFASD) studied.

Another related question is the response that this collective has to such adverse life events. It is not clear, for example, if the individuals with the highest functioning respond more seriously to negative events than the general population does or than individuals with different degrees of intellectual disability do [40] or whether, at least, they do so in a different way [68]. This has traditionally been explained by the fact that this group seems to be more vulnerable than

control group individuals to developing affective disorders and depressive symptoms [80], and this vulnerability seems to be correlated with a genetic predisposition [68]. Ghaziuddin and colleagues [40] argue that autistic response to negative events with depressive symptoms is likely to stem from the fact that they are genetically predisposed to depression. However, no systematic studies have been performed to evaluate the degree to which response to life events and onset of depression in this group is mediated by genetic factors.

An issue that often arises involves the domain of repetitive and restricted behaviours. On the basis of answers given by 89 parents of children aged 5 to 17 and diagnosed with ASD, Stratis and Lecavalier [81] found that adolescents with high levels of ritualistic and sameness behaviour tend to show more severe symptoms of depression. They furthermore concluded that high levels of restricted interests are associated with less severe symptoms of depression and argued that restricted interests may be a protective factor against depression in individuals with ASD.

(g) Biological Factors and Comorbidity. As we already pointed out regarding the risk factor discussed in the first section *(Histories of First-Degree Relatives and Environmental Context)*, the question arises as to whether there are any biological factors, that is, neurotransmitters, or character structure that contribute to the pathophysiology of depression in ASD. Indeed, a correlation mechanism between ASD and depression has been identified [26, 45]. Such findings may be in accordance with evidence from a recent genetic study examining risk loci that demonstrates shared effects on ASD, attention deficit/hyperactivity disorder, schizophrenia, bipolar disorder, and major depressive disorder [26].

Equally well-known is the fact that serotonin (monoamine neurotransmitter) is involved in conditions like depression and ASD. Several findings show that changes in serotonin levels can influence the brain through various mechanisms and support the hypothesis that serotonin plays a major role in the development of mood disorders and ASD [82]. The question is whether it is a cause or rather an effect of these phenomena.

The involvement of genetic factors is evident from the results of a twin study, while many gene variants that seem to affect brain development and synaptic functions have been reported in association with ASD [38, 83].

From the reviewed literature we may conclude that even though there is a promising research line on underlying biological mechanisms that may possibly be shared by both ASD and mood disorders, the scientific evidence regarding this question is not yet strong enough.

With regard to comorbidity [7], several studies deal with the cooccurrence of ASD and a number of psychiatric disorders (e.g., clinical youth aged 7–17 that had been diagnosed with mood or anxiety disorders, etc.). Pine et al. [84] observed that 57% of youth patients with bipolar disorder, 38% with major depressive disorder, and 25% with anxiety disorder likewise presented ASD-related symptoms. These findings suggest that ASD is closely associated with mood alterations in pediatric patients, although the etiological relevance of this correlation is unclear [85].

3.3. Implications of Depression in Individuals with HFASD: Risk of Suicide. There is presently a renewed interest in the importance of studying and assessing suicide. The American Psychiatric Association has developed some guides for preventing and assessing suicide risk. It also recommends, in the 5th edition of the DSM, that the presence or absence of suicide risk should be assessed as a sixth separate axis ("V 02 Suicidal Behaviour Disorder" [1, 86, 87]).

In the general population, suicide ranks among the top causes of death in adolescents and is tending to grow [88]. However, studies usually focus on cases of completed suicide, which leads to an underestimation of the true prevalence. In individuals with ASD, systematic studies focusing on suicidal behaviours are rare and have been carried out with very small samples, sometimes even with just 1 or 2 cases (see [89–91]). We know that the risk of suicide in individuals with ASD is also underestimated. This may stem from the low index of completed suicide in children and preadolescents and from the fact that ASD represents one of the most commonly forgotten diagnoses in adult psychiatry [24, 89]. Furthermore, the pathognomonic features of ASD can mask the symptoms that indicate immediate risk of suicide. Deterioration in communication and social interaction, inappropriate or strange behaviours, cognitive deficits, and negative symptoms can make this difficult to detect when assessing individuals with ASD [92]. Nevertheless, it is essential to evaluate this risk in this collective. One reason for this is the high prevalence of suicidal ideation and attempts. Another (as some studies indicate) is that these individuals are more likely to complete the suicide successfully on their first attempt, especially when they are adults [93] and they perform the act using violent methods (e.g., hanging, shooting or poisoning themselves, or jumping [94]).

Among the few epidemiological studies on suicide and ASD, we can point out the one by Balfe and Tantam [95]. They studied 42 adolescents and adults with HFASD (mean age, 26.21 years) and found that 15% had attempted suicide. The team of Storch reported that approximately 11% of the 102 youngsters aged between 7 and 16 years with HFASD studied showed suicidal ideation and behaviours associated with depression and posttraumatic stress disorder [25]. The team of Raja also provided similar data when they studied 26 adult patients with ASD and psychotic comorbidity, reporting 7.7% of suicides (2 cases), 3.8% suicide attempts (1 case), 3.8% self-injury (1 case), and 30.8% (8 cases) with suicidal ideation [92]. In reference to this last behaviour (suicidal ideation), Shtayermman [96] found it in 50% (5 cases) of adolescents and young adults with autism; and Wing [12] indicated that 18.75% (3 cases) of a sample with AS showed suicidal ideation or attempts. Such thoughts are significantly present to a greater degree in children with autism than in the NT [97].

In other studies on suicide in this collective, the working procedure is the reverse; ASD is diagnosed starting with populations admitted to hospital for suicide attempt. For example, in the study by the team for Høg with 126 children, 97% (123 cases) were diagnosed with at least one psychiatric diagnosis and, among them, 7 children presented psychosis and ASD [98]. In their retrospective study, Mikami's team

found that, of 94 adolescents aged less than 20 years, 12.8% (12 cases) presented ASD [99]. In a similar study, Kato et al. [93] studied 587 patients aged over 18 and found that 7.3% (43 cases) presented ASD. In all these studies, the prevalence of individuals with ASD was much higher than that found in the general population.

In young NTs, poor interpersonal problem-solving skills, impulsiveness and aggressive behaviour have been linked to a greater risk of suicidal behaviour [99]. There is also evidence that depression constitutes a risk factor for suicide attempts among adolescent NTs [27, 100]. Higher-functioning individuals with ASD can attempt suicide or complete a suicide, especially when experiencing depressive symptoms. In fact, as the team for Mayes concluded [73], depression and, to a lesser degree, behavioural problems and school bullying are among the psychological problems most highly predictive of suicidal ideation or suicide attempts. Specifically, this team found that suicidal ideation and attempts were 28 times more frequent in children of up to 16 years old with autism (14%, $n = 791$; 537 with HFASD) than in NT children (0.5%, $n = 186$) but 3 times less frequent than in children that were depressed (43%, $n = 35$). Around 50% of mothers of children with autism reported depression and 77% of the children with suicidal ideation or attempts were considered depressed by their mothers. The researchers concluded that certain demographic variables (age of 10 years or older, male, black, or Hispanic ethnic group, low standing of father's professional activity, and history of school bullying) constituted factors of risk with suicidal ideation and attempts in autism. They also concluded that behavioural problems (disobedience, rebellion, and aggressivity), impulsiveness, depression, and mood dysregulation (explosive, irritable, and with tantrums; [73]) were likewise factors of risk in the same way.

This team found that suicidal ideation or suicide attempts were 3 times more frequent in children that suffered school bullying than in children that did not [73]. The team for Mikami [99] also identified conflicts in personal relationships, such as being a victim of bullying, as the main events precipitating suicide attempts in their sample of adolescents with ASD. Nine out of 12 psychiatric patients hospitalised after a suicide attempt had this problem. The researchers interpreted that these patients, due to their rigid thought patterns and lack of imagination, had difficulties in developing relationships with peers and that the feelings of isolation due to the lack of social support seemed to be the most common psychosocial factors predisposing to suicide attempts in adolescents with ASD [99]. In the NT population, studies such as that by the team for Cui [101] concluded that victimisation from bullying was a significant predictor of subjective perception of suicidal ideation and attempts in their sample of 8,778 Chinese adolescents.

Traditionally, suicide attempts in HFASD have been described as more frequent in adolescence or early adulthood [12, 94]. However, such attempts have also been registered in adults (at the age of 23 years: [102]) (at that of 44 years: [103]) and children of more than 10 years [73]. Cases of completed suicide are rare in younger children [104]. This greater frequency of suicidal acts in adolescence has been related to possible intimidation and feelings of inadequacy in facing all the social demands produced in puberty [94]. It could be assumed that these stressful situations have to last over time, given that some studies indicate that their sample was less prone to attempt suicide based on incidents that had happened in the previous 24 h [93]. This finding led them to suggest that occasional stressful factors had less explicative strength in the group with ASD compared to the control group (adult patients that had also attempted suicide).

Consequently, the most accepted factors of risk for suicide in individuals with ASD [24, 25] include different variables (see Table 2).

3.4. Detecting Depression in Individuals with HFASD: Assessment Difficulties and Proposals. Based on our review of the studies to identify and assess depression in individuals with ASD, we can conclude that the symptoms described in the literature include the behavioural indicators most used for the diagnosis of depression in the general population. However, the presentation of depression varies considerably in this collective. Apart from the most generalised symptoms of persistent sadness and loss of interest in activities, depressed autistic individuals may present certain unique features, manifesting depression in a nontypical manner.

For that reason, symptoms from the DSM-5 for major depressive disorder [1, Box 1] are included, with special emphasis on those most related to this collective.

In addition to these DSM-included symptoms, studies on depression in individuals with HFASD include the following as the most representative: (1) increase in behaviours that indicate poor adaptation, including irritability, self-aggression, and heteroaggression [21, 105–108]; (2) recurrent thoughts about death (not just fear of death), suicidal ideation, and suicide plans or attempts [107]; (3) low self-esteem and/or reduced abilities of self-care, hygiene, general appearance, or work performance [107]; (4) decrease or lack of interest in their special interests and rituals and so forth or change in the frequency of their obsessive-compulsive, repetitive, and stereotypic behaviours [107].

With respect to the last symptom, we know that anxiety and obsessive-compulsive spectrum disorders (OCSD) are highly comorbid in this population (see [109]). In fact, growing evidence supports a phenomenological overlap between OCSD and ASD [110]. However, there is no consensus as to whether the presence of depression increases or decreases these symptoms in individuals with ASD. The some authors argue that individuals with ASD and depression present a significant increase in symptoms related to anxiety and OCD, such as stereotypic behaviour, obsessions and/or compulsions and self-destructive behaviours [35, 107]. Authors such as Perry et al. [111] indicate that depression not only increases this nucleus of symptoms, but also can exacerbate the pathology in the rest of core autistic characteristics (decreased communication, language, and social interaction). On the opposite side of the debate, traditional studies such as Gillberg [112] or, more currently, the Mazzone team [68] postulate that the onset of depression in individuals with HFASD is generally (although not always) associated with a decrease in repetitive and obsessive behaviours. When this remission occurs, there is a risk that it might be considered

Table 2: Overview of factors of risk for suicide in Autism Spectrum Disorder (ASD). Most vulnerable population with ASD (modified from [24, 25]).

	Factors and variables	Studies
Biological	Genetic and biological factors (adolescence, gender, and ethnicity)	[26–28]
	History of relatives (psychiatric disorder or suicide)	[27, 28]
	Substance abuse	[28]
	Comorbidity	Anxiety [29] Depression [25, 27, 28, 30]
Psychological	Impulsiveness	[31]
	Higher cognitive, social development, and communication levels	[24]
	Life events and effects brought by characters came from domain of repetitive and restricted behaviours and thoughts: frequent abuse and school bullying	[27, 32–34]
Social	Poorer social support networks: social isolation	[35]

an improvement of the nuclear symptomatology instead of a concurrent depressive state, masking depression even more in this group.

The disorder of ASD often involves the presentation of symptoms that are hard to differentiate from depressive symptoms; these can overlap and go undetected among the core syndrome symptomatology (communicative and social isolation and mental rigidity) or associated symptoms (e.g., sleep and eating disorders [106, 107]). However, in cases with ASD in which these behaviours appear, they remain in a chronic form, not episodic as in depression. In contrast, the presence of fluctuations in behaviour and a stable negative variation in mood unrelated to environmental changes helps to discern that the change is more likely to be the onset of depression and not from a variation in the environment that affects the individual's "desire for sameness" [11], which would translate into greater agitation, uneasiness, or episodic stress.

This process becomes even more complicated, given that diagnosing depression depends primarily on verbal skills and communication of symptoms. In this collective, individuals find it hard to express feelings such as sadness, to carry out reciprocal conversations, speak about themselves, use abilities of the theory of mind, and feel empathy for their own feelings or those of others; for that reason, the individuals affected may not be able to interpret or communicate many of the key characteristics of depression [68, 113]. These difficulties in reporting on their moods could be considered similar to those found in individuals with intellectual restriction, but in autism, in which alexithymia is often found [53], these features are present independently of cognitive level [107]. In fact, there is evidence that young people with HFASD tend to report fewer depressive symptoms than those they really present [79] and they do so in terms related to deterioration of cognition, language, behaviour, or activity more than in terms related to their mood [114]. Along these lines, when parents' assessments, self-reports, and self-assessment of emotional symptoms in children were compared, the children with ASD reported significantly lower levels of depression than those indicated by the parents of 54 students with HFASD [115], with children aged from 7 to 13 years [116] or children from 7 to 13 years [48]. The results of the Mazefsky team with 38 children aged from 10 to 17 years with HFASD led them to conclude that it was necessary to be very cautious in interpreting the scores of individuals with HFASD when evaluating a possible diagnostic comorbidity using self-reports [117]. Specifically, when evaluating depression rates using the short form of the Children's Depression Inventory (Children's Depression Inventory-Short; CDI-S; [118]), they observed a high rate of false negatives, with lower sensitivity and specificity than in the typical population.

The difficulty existing in diagnosing this type of comorbidity is well documented, but it is necessary to consider this possible concurrence to establish appropriate treatment for children and adolescents with HFASD in a situation of risk. The approach to depression and the risk of suicide in youngsters with HFASD includes techniques of prevention and modification of risk factors, along with therapeutic intervention once the risk is detected. There are many interventions available to improve the quality of life of individuals with ASD [119, 120], including social skills training, behavioural therapy, and cognitive-behavioural therapy, which reduce the affective problems in children with HFASD [121, 122]. Treatment should also include interventions aimed at alleviating the coexisting problems that can add to depression and/or suicidal ideation and attempts, such as mockery, behavioural problems, impulsivity, mood dysregulation, and stress [73]. Some studies suggest that serotonin reuptake inhibitors improve mood in cases of ASD [123, 124]. However, there are no clear conclusions on the impact of these therapies in depressive symptoms or their efficacy in children with ASD having lower cognitive functioning [17].

4. Discussion and Conclusions

In this study we have reviewed the reports published on children and adolescents with ASD in general and on those with HFASD in particular. We now turn to presenting and discussing the possible implications of the study performed, bearing in mind the study objectives: (1) presenting the *depression rates* in children and adolescents with HFASD; (2) analysing the possible risk factors and explicative hypotheses for diagnostic and/or symptomatological comorbidity of HFASD and depression collected mainly from the literature, and establishing a possible working hypothesis supported

by the profiles of potential vulnerability and contributing factors; (3) evaluating the implications of depression in HFASD (the *risk of suicide*); and (4) analysing the difficulties for *assessment* of depression (and risk of suicide) in children and adolescents with HFASD and proposing alternatives.

(1) As for *prevalence* rates, all the studies ratify that depression seems to be common in cases of ASD. However, until now, it has been difficult to establish a generic prevalence rate (see Table 2). No study has shown conclusive results based on a representative sample of individuals with ASD in general or with HFASD in particular. That is why there is a need for large-scale longitudinal population studies, which not only would make it possible to establish incidence, but would also help to identify the type, prognosis, duration, and treatment of depression in ASD. Likewise, such studies would help to ascertain its incidence based on variables such as cognitive functioning or autistic symptomatology, gender, and age.

With respect to this, it is important to highlight some *methodological* problems and limitations found in the studies on depression in autism. Comparing results between the different studies turns out to be difficult, because the sample characteristics vary considerably. For example, they differ in age and gender of the participants, diagnostic criteria and methods of sampling, as well as in symptom assessment in both depression (diagnostic or symptomatological) and in ASD itself (cognitive and symptomatological levels of individuals with ASD). This makes it hard to be able to establish comparisons and generalisations from these data.

(2) As for *explicative hypotheses and risk factors*, we have been able to establish the variables that are related the most according to the literature. Although there is not sufficient empirical evidence for any of these factors, the results can be of help in prevention and early detection.

Our working hypothesis was confirmed, although the results of the studies carried out to date are scant. It seems that the individuals with ASD and a higher cognitive level are more vulnerable to depression and that depression can put the person with ASD at risk of suicide. This higher level of cognitive functioning is, in turn, related to the individual's greater awareness of his/her own limitations, their impact, and implications, and greater capacity for introspection and skills to self-report the symptoms [17].

(3) Concerning *depressive symptomatology*, in the results of the review performed, which gave rise to the proposal for indicators that facilitate detecting depression in this collective (see Table 1), we can see that individuals with ASD that are depressed can show a wide range of symptoms ranging from irritability and sadness to aggressive outbursts and suicide [40]. In the few published studies on suicide in cases of ASD, depression and social relationships with a history of abuse are reported to be psychosocial factors that are especially relevant for early suicide detection. Given that suffering peer bullying is very frequent in this population, watchfulness and intervention in the face of possible cases in children and adolescents with HFASD are important and they are essential when a repeat history of this type of abuse is detected. Insofar as biological factors, the research is less conclusive. For example, gender and ethnic differences in ASD cases are a bit inconsistent in the samples of adolescents, while suicidal ideation is found more often in children, with no effect by gender on suicide attempts. Both ideation and attempts are significantly more frequent among minors of black and Hispanic ethnicity [73].

The high index of depression in this collective emphasises the need to detect suicidal tendencies. We also know that a previous attempt should not minimise the concern about the risk of suicide, because many individuals commit suicide on their first or second attempt [125]. Assessment of the risk of suicide is difficult in this population and can lead to error, suicidal attempts are very frequent in this collective [92], and individuals with ASD do not always give information about themselves or confide in others when experiencing depressed moods [107]. Consequently, it is imperative to maintain a high level of suspicion during clinical evaluation or treatment. This is especially true when there is a history of a recent change in the level of functioning, particularly around the time of puberty.

(4) With respect to the *difficulties in evaluating the indicators for detection of depression in individuals with HFASD*, it is hard to define indicators and criteria for a differential diagnosis of mood disorders (see Box 1), due to the overlap between the symptoms of HFASD and depression [107]. Another difficulty is the characteristics themselves of individuals with ASD, such as alterations in verbal and nonverbal communication, which can affect how the person expresses her/his depressive symptoms, especially when using self-assessment. For that reason, it is essential to establish adequately both the criteria on which the *assessment techniques* employed are based [126–128] and the *informants* (in most studies, the individuals with HFASD themselves or their relatives).

As for the first aspect (assessment techniques), there are currently no scales designed specifically for evaluating this collective or psychiatric comorbidity in general and depression specifically (neither by third-party information or by self-reports). That is why instruments, questionnaires, lists of verification/control, and scales, designed for use in the general population or in the population with learning disabilities have been used in the majority of the studies, or the researchers have turned to the diagnostic criteria in the DSM-IV-TR [2]. Three of the most widely used scales for diagnosing and evaluating the severity of depression and which can constitute a reference for adapting them for this collective are Hamilton's depression scale (Depression Rating Scale [129]), the short form of the Children's Depression Inventory (Children's Depression Inventory-Short; CDI-S; [118]), and the Beck Depression Inventory [130].

All these instruments possess various limitations, as they have not been adapted specifically to take into consideration the neuropsychological characteristics of individuals with ASD with respect to their difficulties in identifying, processing, understanding, and communicating their own inner states, feelings, and emotions, as well as their problems with reciprocal communication and possible alexithymia. The instruments include questions in which the individuals are asked to subjectively evaluate their mood and how they feel. These abilities can be compromised in this collective,

(A) Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly attributable to another medical condition.
(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
(Note: In children, consider failure to make expected weight gain.)
(4) Insomnia or hypersomnia nearly every day.
(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
(6) Fatigue or loss of energy nearly every day.
(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
(B) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
(C) The episode is not attributable to the physiological effects of a substance or to another medical condition.
Note: Criteria A–C represent a major depressive episode.
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.
(D) The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
(E) There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition

Box 1: Diagnostic criteria for major depressive disorder in the DSM-5 [1, pages 160–165].

with subsequent decreases in the sensitivity of the clinical evaluation. In some sections in the assessment can also focus on alterations related to appetite, sleep, interest in activities, and psychomotor delay; these can be masked by some of the symptoms associated with autism and others that are important in individuals with ASD, such as maladaptive behaviours, can be neglected in evaluation [107].

Consequently, in the absence of specific psychometric instruments to evaluate comorbid psychopathological symptoms in ASD, an alternative strategy could be gathering information of different configurations, including both directed observation and multiple evaluations with rating scales [36] by the individuals themselves as well as by the rest of the informants. The team for Stewart [107] proposes using the diagnostic criteria for psychiatric disorders for adults having intellectual disability/mental retardation (DC-LD: Diagnostic Criteria-Learning Disabilities; [131]), although recognising that these criteria should also be modified for use in individuals with ASD. Furthermore, given that inventories and rating scales are generally inflexible, they do not permit exploring answers and run the risk of poor interpretation by informants with ASD. For these reasons, future evaluations should attempt to complement the results from these tools with structured clinical interviews that make it possible to explore replies and ask for in-depth clarification, bearing in mind the specific difficulties of this collective (e.g., literal interpretation of questions, intersubjective difficulties with the interviewer, etc.).

Concerning the second aspect (the informants), using multiple sources is recommended [14]. It would be important to contrast the relatives' information and that of the affected individuals themselves with that of the teachers and/or professionals working with the individuals with HFASD [132]. This could help to establish whether the parents' perceptions are consistent with the professionals', who have greater longitudinal experience with human development. It would also permit data triangulation, given that parents usually report significantly greater emotional symptoms than the children with HFASD themselves [48, 115, 116]. All of this should bear in mind that, in NT individuals, parents

and teachers are unable to estimate the symptoms of sadness and anxiety appropriately and cannot identify internalising disorders [133, 134].

As for *possible paths of future research*, which would complement, refute, or confirm the studies carried out to date, we have seen that depression is a disorder that affects the functioning and quality of life of the person with HFASD. It has important specific consequences, among which is the risk of suicide, and can make the pathognomonic symptomatology of ASD worse. Prevention is, therefore, crucial. It can be carried out on three levels: (1) promoting research that examines or reaches conclusions on risk factors in greater detail, which would make it possible to focus preventative efforts on the most vulnerable populations with ASD; (2) increasing the number of studies that improve the capability of early detection once the depressive episode starts or symptoms appear; and (3) investigating the effect of intervention focused on the advancement and improvement of social relationships from the first years, promoting self-esteem, and on the conditions for cognitive and emotional development of the children. Specifically, it would be reasonable and effective to evaluate how interventions on attributions, self-concept, and social information processing influence depression in individuals with ASD [135]. Future studies in this field would help us to confirm whether this type of interventions is the most appropriate for both preventing the appearance and improving the evolution of depression. It would also allow the empirical establishment of the relative weight of variables such as risk factors in the onset and evolution of depression and risk of suicide in ASD. This would be made possible by verifying if depressive symptoms and suicide decrease when these individuals improve their social and communication difficulties.

To perform these new studies it will be necessary to establish new instruments for the specific assessment of affective disorders in ASD, tools that facilitate improvements in prevention, identification, and treatment. These should not only prove their validity, but also show their specificity for differential diagnosis and assessment of depression in individuals with ASD, resolving the difficulty that standardised administration generates in this population [107] . To accomplish this and in agreement with the needs detected and analysed in our work, large-scale population studies that are descriptive, epidemiological, and etiological and by intervention should be carried out. Such studies would make more in-depth research possible on incidence and risk groups, symptomatological expression, differential diagnosis, duration, prognosis and treatment of depression, and prevention of suicide, in the individuals with ASD.

Abbreviations

AS: Asperger Syndrome
ASD: Autism Spectrum Disorder
HFASD: High functioning autism spectrum disorder
NT: Neurotypical
OCSD: Obsessive-compulsive spectrum disorders.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

The State of the Art of the DSM-5 "with Mixed Features" Specifier

Norma Verdolini,[1,2] Mark Agius,[3,4] Laura Ferranti,[5] Patrizia Moretti,[2,6] Massimiliano Piselli,[7,8] and Roberto Quartesan[2,6,7]

[1] *School of Specialization in Psychiatry, Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia, Piazzale Lucio Severi 1, Edificio A, 06132 Perugia, Italy*
[2] *Santa Maria della Misericordia Hospital, Perugia, Italy*
[3] *Department of Psychiatry, East London Partnership Foundation Trust, Bedfordshire Centre for Mental Health Research in Association with the University of Cambridge, University of Cambridge, Charter House, Alma Street, Luton LU1 2PJ, UK*
[4] *Clare College Cambridge, The University of Cambridge, Cambridge, UK*
[5] *Biotechnologies and Biomaterials in Vascular and Metabolic-Endocrine Diseases, University of Perugia, Piazzale Lucio Severi 1, Edificio A, 06132 Perugia, Italy*
[6] *Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia, Piazzale Lucio Severi 1, Edificio A, 06132 Perugia, Italy*
[7] *Functional Area of Psychiatry, University of Perugia, Piazzale Lucio Severi 1, Edificio A, 06132 Perugia, Italy*
[8] *AUSL Umbria 2, Servizio Psichiatrico Diagnosi e Cura, Ospedale S. Giovanni Battista, Via Massimo Arcamone, 06034 Foligno, Italy*

Correspondence should be addressed to Norma Verdolini; norma.verdolini@studenti.unipg.it

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The new DSM-5 "with mixed features" specifier (MFS) has renewed the interest of the scientific community in mixed states, leading not only to new clinical studies but also to new criticisms of the current nosology. Consequently, in our paper we have reviewed the latest literature, trying to understand the reactions of psychiatrists to the new nosology and its epidemiological, prognostic, and clinical consequences. It seems that the most widespread major criticism is the exclusion from the DSM-5 MFS of overlapping symptoms (such as psychomotor agitation, irritability, and distractibility), with a consequent reduction in diagnostic power. On the other hand, undoubtedly the new DSM-5 classification has helped to identify more patients suffering from a mixed state by broadening the narrow DSM-IV-TR criteria. As for the clinical presentation, the epidemiological data, and the therapeutic outcomes, the latest literature does not point out a univocal point of view and further research is needed to fully assess the implications of the new DSM-5 MFS. It is our view that a diagnostic category should be preferred to a specifier and mixed states should be better considered as a spectrum of states, according to what was stated many years ago by Kraepelin.

1. Introduction

The current notion of mood disorders is based on the contrast between two most important concepts: on the one hand, Kraepelin [1], together with his famous successor Weygandt, considered all recurrent mood states, whether depressive or manic, as one illness, manic-depressive insanity, and thought that mixed states were the most common version of manic-depressive illness [2]. On the other hand, Leonhard distinguished patients with unipolar disorder from those with bipolar disorder on the basis of genetic and course findings, leading to the bipolar/unipolar dichotomy [3].

The DSM nosology of mood is neo-Leonhardian and not Kraepelinian [4]. Consequently, mixed states, as an overlapping of manic and depressive symptoms, have been almost completely neglected for decades, mainly under the influence of Kurt Schneider who promoted the idea that what may give the impression of the combination of manic and

depressive features actually should not be considered a mood disorder [5].

A renewed interest in mixed states has developed after the new DSM-5 "with mixed features" specifier (MFS), even though the latest literature does not point out a univocal point of view [6] on the validity and utility of this new classification for mixed states. Some authors [7] suggest that it would capture subthreshold nonoverlapping symptoms of the opposite pole; others consider it to lead to more misdiagnosis and inadequate treatment [4]. Consequently, there is pressing need to validate the DSM-5 MFS in further research [8].

But what is the state of the art of the DSM-5 MFS? In order to give an answer to this question, we reviewed the latest literature on mixed states, in consideration of the new MFS in DSM-5, trying to understand the reactions of the psychiatric scientific community to the new nosology and its epidemiological, prognostic, and clinical consequences.

2. Materials and Methods

An electronic search using the MEDLINE database of published peer-reviewed papers was conducted in order to find the most up-to-date studies about mixed states according to the new DSM nosology, considering those published between January 2011 and February 2015. We used two groups of key words linked with the word AND: (1) bipolar mixed features, depressive mixed features, mixed features, mixed states; (2) DSM-5. We excluded studies published in other languages than English, "grey literature," letters to the editor, studies about a paediatric population, and those using DSM-IV-TR criteria for mixed states.

3. Results

In our electronic search we found 37 papers and included in our review 19 papers according to our exclusion criteria. We decided to divide the papers into two main categories: (1) reviews and opinions about mixed states in DSM-5 ($n = 9$); (2) research reports ($n = 11$), with three subcategories: (2.1) clinical research reports ($n = 5$); (2.2) research reports about pharmacological treatment in the presence of MFS ($n = 3$); (2.3) research reports about diagnostic tools for mixed states ($n = 2$). The papers considered in the review are listed as follows, divided according to the specific categories.

Summary of the Papers Considered in the Review, Divided according to Specific Categories

(1) Reviews and opinions about mixed states in DSM-5:
Koukopoulos et al., 2013 [4],
Koukopoulos and Sani, 2014 [9],
Uher et al., 2014 [10],
Perugi et al., 2014 [5],
Vieta and Valentí, 2013 [7],
de Dios et al., 2014 [11],
Liu and Jiang, 2014 [12],
Castle, 2014 [13],
First, 2011 [14].

(2) Research reports:

(2.1) clinical research reports:
McIntyre et al., 2015 [15],
Malhi et al., 2014 [16],
Vieta et al., 2014 [17],
Perlis et al., 2014 [18],
Takeshima and Oka, 2015 [19],

(2.2) research reports about pharmacological treatment in the presence of MFS:
McIntyre et al., 2013 [8],
Tohen et al., 2014 [20],
Tohen et al., 2014 [21],

(2.3) research reports about diagnostic tools for mixed states:
Hergueta and Weiller, 2013 [22],
Zimmerman et al., 2014 [23].

3.1. Reviews and Opinions about Mixed States in DSM-5. According to Koukopoulos and colleagues [4], the new DSM-5 MFS can lead to more problems in diagnosis, mainly in mixed depression. In fact, the DSM-5 task force decided to exclude from the MFS those manic and depressive symptoms that can overlap, leading to the exclusion of psychomotor agitation, irritability, and distractibility.

In an empirical study [9] the same authors found out that the frequency of mixed-mood states similar to the DSM-5 definition ranged from 0 to 12%. On the contrary, using a definition including those overlapping symptoms as central features of mixed depression, the frequency ranged from 33 to 47% [4].

It is for this reason that the authors [4] proposed the traditional name of "agitated depression" for depressive syndromes with psychomotor agitation and that the name "mixed depression" can be used in the absence of psychomotor agitation.

Furthermore, Uher and colleagues [10], when considering the implications for clinical practice and research of the changes between DSM-IV-TR and DSM-5, pointed out that the symptom of psychomotor agitation has been deleted from the MFS but added in the "with anxious distress" DSM-5 specifier in the fourth grade ("severe"), with the possibility of more misdiagnosis. In addition, they pointed out that irritability, which is seen in up to 40% of outpatients with major depressive disorder (MDD), contributes to episode severity and predicts recurrence but is not included among criteria for MDD in adults, not even in the MFS.

In addition, Perugi and colleagues [5] reported that even though the DSM-5 definition is based on the speculative wish to avoid "overlapping" manic and depressive symptoms, this combinatory model seems more appropriate for less severe forms, in which mood symptoms are clearly identifiable.

Another major criticism that Koukopoulos and colleagues [9] have made to the new DSM-5 MFS was that those

hypo/manic symptoms required in a depressive episode to consider the MFS (i.e., elevated/expansive mood or grandiosity) are the least common symptoms that actually arise in depressive mixed states.

In 2013 Vieta and Valentì [7] published an enthusiastic review about mixed states in DSM-5. They stated that the new classification would capture subthreshold nonoverlapping symptoms of the opposite pole and would have a substantial impact in several fields, mainly because it would overcome the extremely narrow definition in DSM-IV-TR. In fact, fewer symptoms (than in DSM-IV-TR) of the opposite polarity are included in the MFS and the definition can be applied in more groups of disorders, not only in bipolar disorder I-BDI but also in bipolar disorder II-BDII, bipolar disorder not otherwise specified (BD-NOS), and, in particular, MDD, which is a link to the mood spectrum concept of Akiskal [24]. However, in the conclusions, the authors stated that the specificity and sensitivity of this diagnostic construct would need to be assessed by new and additional empirical studies.

In fact, the same group [11] published in the following year a review about bipolar disorders in DSM-5 focused on the fact that the decision to exclude common symptoms such as irritability, distractibility, or psychomotor agitation in spite of recognising the need to change the previous DSM-IV-TR strict criteria has been criticised as not very scientific and as lacking validity. Furthermore, they pointed out that the mixed nature of affective episodes became a course specifier with the disappearance of the category of mixed episode in bipolar disorders. In addition, the authors reported that agreement in diagnosis based on separate interviews by physicians who received training in the use of DSM-5 is moderate for bipolar disorder type (kappa: 0.56) and somewhat less for type II (kappa: 0.40) [11] and is the lowest ever reported for the MDD diagnosis (kappa: 0.28) [10].

Liu and Jiang [12] believed that one of the reasons for this could be the blurring of the depressive/bipolar disorder boundary.

Castle [13] stated that a major problem with the mixed states literature is the lack of uniform ways of measuring these syndromes and reported two examples of scales, one by Cavanagh et al. [25] comprising 18 items divided into an A group of manic items and a B group of depressive items. The author considered this scale of clinical utility because it is brief but requires validation in a depressed sample. The Multidimensional Assessment of Thymic States (MAThyS) was instead proposed by Henry et al. [26] and rated two dimensions, namely, activation/inhibition and emotional reactivity. The former was seen to be associated only with depression and the latter with manic and mixed symptoms.

Finally, according to the cost-benefit analysis drawn up by First [14], the new DSM-5 MFS is at odds with the previous empirical data and its overall treatment implications are also unclear. It was suggested that, by raising clinicians' awareness of the presence of mixed features through the introduction of this specifier, pressure will be exerted to do something with this information but without empirical evidence as a guide, it was not clear whether the possible interventions would do more good than harm.

3.2. Research Reports

3.2.1. Clinical Research Reports. In 2015, McIntyre and colleagues [15] published the results of The International Mood Disorders Collaborative Project (IMDCP). A total of 982 individuals who met criteria for a current mood episode as part of MDD ($n = 506$) or BD ($n = 346$; BDI: $n = 216$, BDII: $n = 130$) were included in the analysis and the DSM-5 MFS was evaluated using proxies by means of the Young Mania Rating Scale (YMRS) or the Montgomery Asberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale-17 items (HAMD-17). The authors found that 26.0% ($n = 149$) of patients diagnosed with a MDD, 34.0% ($n = 65$) of BDI patients, and 33.8% ($n = 49$) of individuals with BDII met the criteria for MFS during a mood depressive episode (MDE). On the contrary, MFS during a hypo/manic episode was identified in 20.4% ($n = 52$) of BDI participants and in 5.1% ($n = 8$) of individuals suffering from BDII.

Malhi and colleagues [16] conducted a study in order to examine the relative distribution of psychomotor agitation and distractibility in 200 patients divided into four groups: BD, BDspectrum, and unipolar depression (UP) and mixed depression (UPmix). The study was based on a self-report structured diagnostic assessment and a clinical psychiatric evaluation. The authors found that increased distraction, racing thoughts, and increased irritability were the most commonly reported manic symptoms amongst the UP group ($n = 24$, 17.6%). Furthermore, UPmix and BDspectrum groups had significantly higher psychomotor agitation ($F(3, 122) = 8.04$, $P < 0.001$) than the other two groups and distractibility was more represented in the UPmix (71%) and BDspectrum (67%) than in the UP (54%) and BD (40%) groups.

As for hypo/manic episodes with mixed features, in 2013 Vieta and colleagues [17] published the results of a multicenter, international online survey (the IMPACT study) conducted in order to describe the phenomenology of mania and depression in bipolar patients experiencing a manic episode with mixed features. Seven hundred patients with a manic episode with or without DSM-5 criteria for mixed features from 7 countries completed a 54-item questionnaire on demographics, diagnosis, symptomatology, communication of the disease, impact on life, and treatment received. Data was collected between March 26 and July 31, 2012. The authors found that 39% ($n = 275$) of patients reported ≥3 DSM-5 depressive symptoms during a past manic episode. These patients were more likely to have had a delay in diagnosis, were more likely to have experienced shorter symptom-free periods, and were characterized by a marked lower prevalence of typical manic manifestations. Indeed, only physical aggression and abusive behaviour towards others were more frequently reported by individuals in the mania with depressive symptoms group ($P = 0.001$ and $P = 0.02$). Furthermore, the authors also recorded a high rate of misdiagnosis (39% in the case of mania with depressive symptoms group); in particular these patients were significantly more frequently misdiagnosed as having insomnia than those without depressive symptoms (46.7% versus 27.9%; $P < 0.0001$).

As for MDE with mixed features, Perlis and colleagues [18] examined outcomes between patients with MDD participating in the Sequenced Treatment Alternatives to Relieve Depression (STAR∗D), hypothesizing that mixed symptoms in MDD would be associated with poorer antidepressant treatment outcomes. 9.6% ($n = 231$) of patients reported three or more mixed symptoms. The presence of such symptoms, in particular expansive mood and cheerfulness, was associated with a greater likelihood of remission (adjusted hazard ratio 1.16, 95% confidence interval 1.03–1.28). The authors concluded that this challenges the view that mixed features may be associated with poorer outcomes in MDD and questioned the notion that these features are or are not to be considered to be in the "bipolar spectrum."

Takeshima and Oka [19] reported the data of 217 patients with MDE (BDII: $n = 57$, BD-NOS: $n = 35$, MDD: $n = 125$) firstly diagnosed according to DSM-IV-TR; at a later stage, the authors analyzed the prevalence of mixed depression according to both the DSM-5 MFS and Benazzi's definition (which includes all manic/hypomanic symptoms in MDE). The aim of the study was to assess if the lack of the three symptoms, irritability, psychomotor agitation, and distractibility, in the DSM-5 MFS could cause underdiagnosis of mixed depression. The authors identified more patients with Benazzi's mixed depression and DSM-5 defined mixed features in BD than in MDD (46.7% versus 12.8%, $P < 0.0001$, resp., according to Benazzi; 4.3% versus 0%, $P = 0.0208$, resp., according to DSM-5). Furthermore, they stated that the sensitivity/specificity for BD diagnosis according to Benazzi's mixed depression and DSM-5 defined mixed features were 55.1%/87.2% and 5.1%/100%, respectively.

3.2.2. Research Reports about Pharmacological Treatment in the Presence of MFS. McIntyre and colleagues [8] described the frequency of depressive mixed features in BDI patients with manic episode by using MADRS and PANSS items as proxies for the DSM-5 MFS. They found that 34.2% ($n = 328$), 17.5% ($n = 168$), and 4.3% ($n = 41$) of the patients had at least 3 MADRS items with mild, moderate, and severe symptoms, respectively. Furthermore, the authors randomized the patients to asenapine, placebo, or olanzapine, showing that the symptomatic improvement of the manic/hypomanic symptoms was significant and superior to placebo for both asenapine and olanzapine, but for the former this was true regardless of depressive symptom severity, while on the contrary, for the latter the statement was true only in individuals with lower baseline depressive symptom severity.

Tohen and colleagues [20] investigated the correlations between the efficacy of olanzapine monotherapy (evaluated by change in MADRS total score from baseline to 6 weeks) and the number of concurrent manic symptoms (as measured by a Young Mania Rating Scale item score ≥1) in patients treated for bipolar depression. The percentage of patients in mixed feature ≥3 categories was 30.5% by using the 11 YMRS items and 11.9% by using the 6 YMRS items. Due to the fact that the least-square mean differences in MADRS total score and the effect sizes were similar when the authors considered 0, 1, or 2 and ≥3 mixed symptoms, they concluded that olanzapine worked similarly on bipolar depression irrespective of the number of concurrent manic symptoms.

The same authors published in a following paper [21] data about the comparison of the efficacy of olanzapine (evaluated by changes in the baseline-to-3-week YMRS total score) in patients with bipolar mania with or without DSM-5 mixed features (as determined by HAMD-17-item score ≥1). Sixty-six patients in the placebo group and 59 in the olanzapine group showed ≥3 mixed symptoms, in total 28% of the sample. Contrary to what happened for bipolar depression [20], olanzapine was efficacious in the treatment of bipolar I mania, in both patients without and with mixed features, but greater efficacy was seen in patients with mixed features who had more severe depressive symptoms (with mixed features effect size = 0.34; without mixed features effect size = 0.20).

3.2.3. Research Reports about Diagnostic Tools for Mixed States. Hergueta and Weiller [22] reported the results of a validation study about a new module of the Mini International Neuropsychiatric Interview (M.I.N.I.) developed as a patient-completed questionnaire in order to evaluate the DSM-5 MFS for hypo/manic episodes. The study was conducted in two phases; the first one involved verification of bipolar patients' acceptance and comprehension of the questions in the module; the second consisted in the assessment of the degree of agreement between patients' responses using the M.I.N.I. module versus DSM-5 criteria as evaluated by psychiatrists. First of all, the authors reported that according to psychiatrists 46.5% (46/99) of patients met the DSM-5 MFS criteria but patients were more likely than psychiatrists to report the presence of at least three depressive symptoms (58.6%, 58/99). As for the agreement, it was substantial (Cohen's kappa coefficient = 0.60), the overall sensitivity of the M.I.N.I. was 0.91; and its specificity was 0.70. The module's positive and negative predictive values were 0.72 and 0.90. Interestingly enough, the highest levels of agreement were for the most common symptom (depressed mood, 79%) and the most severe symptom (suicidal thoughts, 85%), and the lowest level of agreement was for the least severe symptoms (i.e., fatigue, 64% to 65%). As a consequence, the authors considered this tool useful in clinical and epidemiological research and suggested that it should be incorporated into routine psychiatric evaluation of patients with manic episodes and that a corresponding module should be developed for evaluating "hypomanic features" during bipolar or unipolar major depressive episodes.

In fact, in 2014 Zimmerman and colleagues [23] modified their previously published depression scale (Clinically Useful Depression Outcome Scale (CUDOS)) to include a subscale assessing the DSM-5 MFS (CUDOS-M) in order to acknowledge the clinical significance of manic features in depressed patients. The CUDOS-M demonstrated excellent internal consistency (Cronbach's $\alpha = 0.84$), the test-retest reliability of the total scale was high ($r = 0.72$), and the test-retest reliability of each item was significant (mean $r = 0.56$) though 3 items had a test-retest reliability of less than 0.30; consequently, the authors stated that repeated administration of such a measure during the course of treatment could enable

clinicians to identify patients whose depressive episodes are evolving into a mixed state more readily and quickly.

4. Discussion

In our review, the percentage of hypo/manic episodes with mixed features ranges from 4.3% [8] to 58.6% [22]. The percentage of MDE with mixed features is lower and ranges from 0 [9, 19] to 34% [15]. These extremely broad ranges can be due to the quite low sensitivity of the DSM-5 MFS (5.1%) [19].

In fact, some authors suggested that DSM-5 has lowered the threshold for mixed states by limiting the symptoms that confer mixed features (psychomotor agitation, irritability, and distractibility), losing the essence of the clinical presentation [16].

Malhi et al. [16] stated that the exclusion of these symptoms would alter the trajectory of research and the implications of future findings.

According to this, in the research report published by Vieta and colleagues [17] more patients in the mania with depressive symptoms group had symptoms of anxiety and irritability associated with agitation than those without depressive symptoms (72.4% versus 27.1%; $P < 0.0001$). Furthermore, in Takeshima and Oka's study [19] psychomotor agitation was the manic/hypomanic symptom that was observed most frequently in both patients with BD (59.8%) and those with MDD (48.8%).

In the M.I.N.I. module for the DSM-5 MFS validation [22] psychomotor retardation was found to be the depressive symptom that patients presented least frequently during a hypo/manic episode.

The previous findings are in line with previous researchers' belief [27] that psychomotor agitation and distractibility are symptoms of particular interest because both have been identified as putative drivers in mixed episodes and are associated with poorer treatment outcomes [16, 28].

However, undoubtedly the new DSM-5 classification has helped to identify more patients suffering from a mixed state than the previous nosology and this may have clinical consequences. In fact, in McIntyre and colleagues [15] study, hypo/mania with MFS was identified in 20.4% ($n = 52$) of BDI participants of which 12.9% ($n = 33$) met criteria for a DSM-IV-TR defined mixed episode; this means that 7.5% ($n = 19$) of patients in this sample were considered not to have a mixed episode according to the previous nosology. In another study conducted by the same authors [8] between 20 and 40% (depending on symptom severity) of patients meeting criteria for DSM-5 defined mixed specifier did not meet DSM-IV-TR defined mixed features. Only Takeshima and Oka [19] found that the prevalence of DSM-5 MFS (4.3%) in the BD sample was lower than that of cooccurrence of MDE and HME (comparable with DSM-IV-TR defined mixed episode, 15.2%).

Consequently, another consideration is that it could be important to assess, in further studies, the interrater reliability between psychiatrists for the DSM-5 MFS, looking at their low rates of agreement in diagnosis of bipolar and depressive disorders in DSM-5.

As for the prognostic implications, the results are still inconclusive. McIntyre and colleagues [15] underlined the fact that individuals with MDD-MFS exhibited a significantly more severe depression than did individuals with MDD without MFS (adjusted $P = 0.0002$ and $P < 0.0002$, resp.) or BD-MDE without MFS (adjusted $P = 0.0001$ and $P < 0.0001$, resp.).

Finally, individuals with MFS exhibited a higher rate of alcohol/substance use disorder in the context of BD [15] and a younger age at onset [20, 21], as stated in previous researches based on DSM-IV-TR [29–31] meaning that some clinical presentations and disorders in comorbidity are intrinsic to the psychopathology of mixed states and do not depend on the classification used in making a diagnosis.

5. Conclusions

The effects and clinical implications associated with the use of the DSM-5 MFS have yet to be fully assessed. Most of the research reports considered in our review were retrospective or used proxies for MFS. Systematic, prospective assessment of mixed symptoms in large population-based cohorts of individuals with MDD or BD was required to understand the meaning and the utility of these symptoms in mood disorders [18]. Furthermore, it is important to ascertain which of the associated features, such as anxiety and substance abuse, are symptomatic of the mixed state itself and which might be amenable to avert poor prognostic outcomes [13].

The identification of additional patients with mixed features according to the updated DSM-5 compared to the DSM-IV-TR definition affirms that the separation of these subtypes of mood episodes from manic or depressive states is necessary in clinical settings mainly to enable the selection of the most effective treatments [8].

Even though the DSM-5 approach considers mixed states as subtypes of manic or depressive episodes [5], mixed depression and mixed mania deserve their own diagnostic identity [4]. In fact, a diagnostic category should be preferred to a specifier, because it will increase focus on mixed states [11], which should be better considered as a spectrum of states backed by the gradation from typical depressive symptoms to typical manic symptoms [19], bringing the current notion of mixed states back to what has been argued by Kraepelin [1] and Akiskal [24].

On the basis of the papers considered in this review, the authors state that the current data are not conclusive; in fact, it is not clear how this new classification can impact the bipolar-unipolar dichotomy and diagnostic reliability, mainly because of the new possibility to diagnose major depression with mixed features [7]. Consequently, further research is needed in order to better understand the implications of the new nosology for epidemiology, clinical care, prognosis, and psychopharmacological treatment of bipolar and unipolar depressed patients that show mixed states features.

It would be important to assess if manic/hypomanic or depressive episodes with mixed features would represent

homogeneous groups; maybe, the homogeneity of the different groups can be just explained by the exclusion from the MFS of those manic and depressive symptoms that overlap, such as psychomotor agitation, irritability, and distractibility. Besides, this is the major criticism to the new classification, so its validity needs to be assessed in clinical studies.

In addition, it could be useful to identify the neurobiological, neurocognitive, or neuroimaging correlates that differentiate the different episodes with or without mixed features.

For example, the possibility to separate MDD with and without MFS might help in both identifying patients with worse prognosis and prescribing a more appropriate therapy [7].

It is known that higher rates of suicidal ideation as well as higher frequencies of antidepressant use can be found in bipolar patients with mixed features [32]. As a consequence, studies need to be done in order to assess the increased suicidality in manic/hypomanic and depressed patients with MFS compared to those without MFS, both in bipolar patients and in MDD patients. In fact, this could allow for supporting the recommendation to avoid antidepressant treatment in these patients unless strictly in tandem with mood stabilisers [33] or antipsychotic medications [34].

Furthermore, mood stabilizers and atypical antipsychotics are recommended to treat mixed episodes [34] but data is limited to subanalyses or post hoc analyses of populations of patients with both manic and mixed episodes [7]. Consequently, it would be helpful to involve in randomized prospective trials homogeneous cohorts of mixed patients [34], divided according to the new DSM-5 classification, in order to assess remission rates and prophylactic benefits of the most important mood stabilizers and antipsychotics. This could be innovative mainly in consideration of the fact that patients suffering from MDD with or without MFS can be separated and this can help to distinguish patients that could respond to adjunctive antipsychotics or mood stabilizers from those who would not [7].

At the epidemiological level, the lifetime prevalence of both bipolar disorders and MDD would change and this could be due to the fact that the new MFS could decrease the prevalence of bipolar disorder not otherwise specified (BD-NOS), increasing the prevalence of the specific episodes; this data should be compared to those existing data on mixed states, based on the previous classifications, in order to evaluate the possible differences on epidemiology, morbidity, response to treatment, illness course, and outcomes. In addition, the comparison with this previous data could be useful to ascertain the validity and clinical utility of the new DSM-5 classification [7].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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