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ORIGINAL RESEARCH

Personality features, dissociation, self-stigma, hope, and the complex treatment of depressive disorder

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Objective: Identifying the predictors of response to psychiatric and psychotherapeutic treatments may be useful for increasing treatment efficacy in pharmacoresistant depressive patients. The goal of this study was to examine the influence of dissociation, hope, personality trait, and selected demographic factors in treatment response of this group of patients.

Methods: Pharmacoresistant depressive inpatients were enrolled in the study. All patients completed Clinical Global Impression – both objective and subjective form (CGI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) at baseline and after 6 weeks of combined pharmacotherapy and psychotherapy (group cognitive-behavioral or group psychodynamic) treatment as an outcome measures. The Internalized Stigma of Mental Illness Scale (ISMI), Dissociative Experience Scale (DES), Adult Dispositional Hope Scale (ADHS), and Temperament and Character Inventory (TCI-R) were completed at the start of the treatment with the intention to find the predictors of treatment efficacy.

Results: The study included 72 patients who were hospitalized for the pharmacoresistant major depression; 63 of them completed the study. The mean scores of BDI-II, BAI, subjCGI, and objCGI significantly decreased during the treatment. BDI-II relative change statistically significantly correlated with the total ISMI score, Discrimination Experience (ISMI subscale), and Harm Avoidance (TCI-R personality trait). According to stepwise regression, the strongest factors connected to BDI-II relative change were the duration of the disorder and Discrimination Experience (domain of ISMI). ObjCGI relative change significantly correlated with the level of dissociation (DES), the total ISMI score, hope in ADHS total score, and Self-Directedness (TCI-R). According to stepwise regression, the strongest factor connected to objCGI relative change was Discrimination Experience (domain of ISMI). The existence of comorbid personality disorder did not influence the treatment response.

Conclusion: According to the results of the present study, patients with pharmacoresistant depressive disorders, who have had more experience with discrimination because of their mental struggles, showed a poorer response to treatment.

Keywords: depressive disorder, cognitive-behavioral therapy, pharmacotherapy, psychodynamic therapy, treatment efficacy, dissociation, personality features, hope, self-stigma

Introduction

Psychotherapeutic and biological approaches have proven their effectiveness in the treatment of depressive disorders. Approximately 40%–70% of the patients who are suffering from depression react positively to the treatment with the antidepressant for at least 2 months.[1–5] Approximately 80% of them respond to the first or second choice of a recommended antidepressant. Despite the relatively high antidepressant efficacy, the level of treatment resistance is relatively high. Approximately 15%–20% of those who do not respond to the treatment are supposed to suffer from treatment-resistant depression.[6–10]

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In addition to the biological factors, the treatment resistance issue may also be relevant to study the demographic and psychosocial factors, which influenced the patients. Based on the clinical experience, following factors are included: 1) demographic factors such as sex, occupation, partner, and marital status, the age or the disorder onset, and the duration of the disorder; 2) psychological factors such as the presence of personality traits or the comorbidity with the personality disorders, dissociation, and hope; 3) psychosocial factor such as self-stigma. It is important to study these factors and explore their clinical relevance exceptionally in patients with treatment resistance.

Personality

A common clinical experience is that personality could accelerate or hinder the outcome of the treatment of depressive disorder. A dimensional model of personality designed by Cloninger et al[11] has been repeatedly studied in patients with major depression and has been recognized to be important. Cloninger et al's[11] Temperament and Character Inventory (TCI-R) assesses four temperament dimensions: novelty seeking, harm avoidance, reward dependence, and persistence, and three dimensions of character: self-directedness (SD), cooperativeness, and self-transcendence.[11] The severity of depression positively correlated with Harm Avoidance scores in many studies.[12–23] In addition, the scores were changed by depression improvement and during the treatment with antidepressant.[13,16,17,24] In a meta-analysis of major depressive disorder and personality traits, Harm Avoidance rates displayed a definite negative change from baseline to endpoint.[25] Depressed patients also present low scores of SD. The severity of depression correlates negatively with SD in several reports.[14–22,26] Depressive patients with low scores of Harm Avoidance incline to reach relatively good results in the treatment.[27,28] Typical TCI-R scores representing a satisfactory outcome demonstrate decrease in Harm Avoidance and Self-Transcendence rates and increase in SD and Cooperativeness rates during the treatment.[29] In addition, the Harm Avoidance scores in treatment-resistant patients are significantly higher at the beginning of the treatment than the scores of the group with a favorable outcome.[28,30] Also, no significant changes in personality features were detected in patients with poor outcome.[29] Both nonresponders and responders presented higher Harm Avoidance rates and decreased SD and Cooperativeness rates on the inventory.[16]

Comorbid personality disorder

Another important factor that can affect the resistance to treatment is the presence of personality disorder. Comorbidity of depression with a personality disorder has been studied frequently. Depressive individuals with comorbid personality disorder commit more suicidal attempts and have a worse reaction to antidepressant treatment in comparison with people with depression alone.[31,32] In our previous study, it was found that there were no significant differences between these two groups in the treatment results associated with the number of depressive episodes, the duration of hospitalizations, doses of medication, or comorbid personality disorder.[33] Other studies found comparable findings suggesting that comorbidity with a personality disorder has no negative influence on the depression treatment.[12,34–37] The negative effect of comorbid personality disorder is more evident in depression comorbidity with two or more personality disorders, which was shown in some studies as taking longer time for getting to remission in these persons.[31,38,39] However, these results are not consistent with the studies of psychotherapy. Levenson et al[39] investigated depressive patients who were treated with interpersonal therapy. They found no differences in the results of treatment regarding the presence of one comorbid personality disorder (except borderline personality disorder). O'Leary and Costello found that comorbidity with a personality disorder predicts an extended time for reaching remission in the acute depression treatment, but the presence of personality disorder was not a predictor of more frequent relapses in the 18-month follow-up.[40] From the personality disorders, borderline personality disorder is recognized to be a predictor of later bipolar and unipolar depression.[41] Related to depressed patients without borderline personality disorder, the patients with a comorbid borderline personality disorder had an earlier time of onset, more depressive episodes, and a higher number of previous suicide attempts, prevalence of anxiety disorders comorbidity, and substance use disorders.[42] Different results regarding comorbid personality disorder may be due to various assessment methods (using different methods of assessment), several types of treatment (only pharmacotherapy or psychotherapy, various psychotherapeutic approaches, or different setting), and specifics of the patient (coping strategies, the rate of cooperation, personality characteristics, voluntariness of hospitalization, pharmacoresistance, etc).

Dissociation

Another factor contributing to treatment resistance in the depressive individuals is the preference of dissociation as a coping strategy. Dissociation is a defense mechanism used to cope with unbearable emotional states.[43,44] According to *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition,

dissociation is described as the deterioration of the integrative functions of consciousness, as the perception of memory, identity, and environment.[45] Usually, these experiences altogether constituted wholeness in the stream of mind.[46,47] Dissociation prevents the integration of experiences and information and can be characterized by amnesia, depersonalization, or derealization.[48] It is a strategy commonly display by the patients with dissociative disorders,[49] panic disorder,[50] OCD,[51–53] depressive disorder, and borderline personality disorder.[54,55] People perceive dissociation as a dispersion in the wholeness of a sense of self. This dispersion emerges as the disintegration of the harmony of chronological, biographic, and perceptive identity.[47,56] Dissociation is showed to be one of the essential psychological factors that influence the treatment efficacy.[57,58]

In the etiology of dissociation, traumatic experiences, such as childhood abuse, take a major place.[59–61] A history of childhood trauma is connected to psychiatric problems in adulthood, mostly to depression.[62] Van Veen et al[63] examined relations of childhood trauma, childhood life events, and recent life events in a patient with or without depressive or anxiety disorders. Strong associations were seen for emotional neglect with anhedonic depression and sexual abuse with anxious arousal. Emotional trauma in childhood has a higher impact on interpersonal problems in adults with depression than childhood physical trauma.[64] History of abuse or/and neglect during childhood is associated with a risk factor in the pathogenesis of dissociation.[65–70] In a related perspective, tension reduction theory suggests that dissociation is used to self-regulate unpleasant emotions.[71,72]

Bersani et al[73] assessed the presence of dissociative symptoms in women suffering from mood and anxiety disorders and correlated them with disorder severity and personality traits. Depressive signs positively correlated with the total rates of Dissociative Experience Scale (DES). Sar et al[74] screened the prevalence and correlates of dissociative disorders among depressive women in the general population. The prevalence of present major depressive episode was ~10.0%. Of the women, 26 (40.6%) had the lifetime diagnosis of a *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition, dissociative disorder, yielding a prevalence of 4.1% for dissociative depression. The dissociative depression group frequently reported the early termination of school education and childhood sexual abuse.

Hope

Another important element that contribute to the effectiveness of therapy is hope. The construct of hope has received increasing attention over the last three decades.[75–77] The theory is grounded on the notion that individuals are inherently goal-directed and that, in search of their goals, they involve in two related cognitive and motivational processes: 1) pathways thinking, which contains thinking about ways to reach goals and 2) agency, which involves motivation toward achieving the goals and sustaining despite frustration and failure.[78] Previous research has found that high scores of hope are positively correlated with better mood, physical health, and better ability to cope with illness.[78–84]

Stigma of mental illness

Many depressive patients have a stigma about depression, which may impede treatment seeking and treatment adherence.[85–87] Self-stigma and fear of stigmatization by others often lead to avoidance of treatment, its premature termination, and poor adherence.[87] Higher depression severity was connected with amplified self-stigma associated with the treatment and the psychiatric diagnosis. Higher self-stigma was linked with more negative beliefs about medications and more positive beliefs about psychotherapy.[86] Borecki et al[88] showed the importance of personality resources in coping with stigma in depressive patients and points to secrecy as an important hidden feature in these processes. Stigma experienced by the individual is connected not only to the external indicators of public stigmatization and the severity of depression but also to the personal features of the patients. One consequence of these accepted prejudices is reduced treatment effectiveness.[58] The effect of self-stigma to treatment efficacy in patients with depressive disorder is less clear.

Aim of the study

The objective of this research is to explore the influence of hope, self-stigma, dissociation, and personality features on the treatment efficacy of patients with depressive disorder and with or without comorbid personality disorders.

Methods

Participants

A total of 72 antidepressant treatment-resistant depressive patients from outpatient setting were enrolled in this inpatient study (Table 1). The research sample consisted of inpatients who were hospitalized in the psychiatric department and met the ICD-10 research criteria for the depressive disorder.[89] Two senior-level psychiatrists assessed patients' psychopathology by Clinical Global Impression (CGI) and Mini-International Neuropsychiatric Interview (M.I.N.I.). The diagnostic criteria of ICD-10 (1996) were used as a primary diagnostic tool; the diagnostic M.I.N.I. was used

Table 1 Inclusion and exclusion criteria

Inclusion criteria
• Diagnosis of depressive disorder according to research ICD-10 criteria (ICD-10 1996)
• Both sexes
• Age between 18 and 65 years
• Informal consent
Exclusion criteria
• Severe somatic illness
• Organic brain disease
• Bipolar affective disorder lifetime
• Schizophrenia lifetime
• Mental retardation
• Acute suicidal behavior or plan

to confirm the diagnosis and comorbidities.[90] The patients were all somatically fit and free of drug or alcohol abuse. Inclusion and exclusion criteria for the study are listed in Table 1. Patients were considered to be pharmacoresistant if they were treated for a minimum of 6 months of adequate doses of minimum two different antidepressants before being admitted to the hospital.

Measurements

The patients, who agreed to contribute to the study, signed an informed consent form and completed several scales. The following methods were completed at the start and at the end of the treatment:

- BDI-II (Beck Depression Inventory, second edition) – This scale includes 21 items – depressive symptoms – in which patients choose perceived symptoms and their severity during the last week.[91] Internal consistency of the scale is higher in psychiatric population (α=0.86) than in general population (α=0.81).[91] The Czech version was published by Preiss and Vacir.[92] The relative change in BDI-II is the main outcome criterion for the improvement in the present study. This criterion is defined as a difference between the last and the first evaluation divided by the initial assessment.
- CGI – This scale is used for global assessment of the severity of psychopathology.[93] The initial assessment is performed by the patient's psychologist or psychiatrist using the objective form of the scale (objCGI). The patient also assesses himself/herself by the subjective version (subjCGI), which includes seven levels of severity of the psychopathology. Internal consistency of the scale seems satisfactory.[94]
- BAI (Beck Anxiety Inventory) – This scale is based on 21 items – anxiety symptoms – on a 4-point Likert scale.[95] The patients choose perceived symptoms and their severity during the last week. This method has excellent internal consistency (mean α=0.91).[96] The validation of the Czech translation is currently in progress. Its Cronbach alpha is 0.92.[97]

The following methods were completed only before the treatment:

- TCI-R – This inventory measures four dimensions of temperament, three dimensions of character, and a number of their subscales.[11,19,98–100] The revised version consists of 240 items out of which five are check items. The temperament domains are Novelty Seeking, Harm Avoidance, Reward Dependence, and Persistence, and the character domains are Self-Directedness, Cooperation, and Self-Transcendence.[101] Reliability of the Czech translation of the method is also satisfactory.[102]
- ADHS (Adult Dispositional Hope Scale) – This scale consists of 12 items – four of them focus on pathway thinking (ie, the ability to find ways to achieve desired goals), another four relate to agency (ie, a sense of inner motivation and will achieve the goals), and the last four items are distractors.[76] Patients select one of the 8 points on a scale agreeing to the level of an agreement with each statement. The internal consistency of the Czech standardization of the scale is good (α=0.82 for the general population, α=0.85 for psychiatric population).[103]
- ISMI (Internalized Stigma of Mental Illness) – This questionnaire consists of 29 statements with a 4-point scale measuring the level of the agreement with them.[104] The scale measures five facets of internalized stigma – alienation, perceived discrimination, stereotype endorsement, social withdrawal, and resistance to stigma. Cronbach alpha of the method is excellent (α=0.90). The questionnaire was standardized in Czech by Ociskova et al.[105] The Czech version of the scale has a similar internal consistency (α=0.91).[105]
- DES – This method describes 28 dissociative experiences, and patients mark a spot on a 10-cm line according to the frequency of experiencing the symptoms.[106] Current modifications of the dissociation model have arrived at the difference between a dimensional, nonpathological type and a discontinuous, pathological class of dissociation, which can be recognized by a subgroup of eight items of the DES, the DES-Taxon (DES-T).[107] This subscale consists of eight out of the 28 DES items (items 3, 5, 7, 8, 12, 13, 22, and 27).[108] The Czech version of the scale is similar to the original version regarding its validity, test–retest reliability, and the factor structure.[109]

- The demographic questionnaire consists of basic information such as sex, age, age of disease onset, number of hospitalizations, employment status, education, pension status, duration of attendance at the outpatient clinic, time since last hospitalization, current medication, number of visited psychiatrists, and discontinuation of drugs in the past (recommended by a psychiatrist or arbitrarily).

The treatment response was defined as a decrease of 35% of symptomatology or more. Remission was defined as a score 1 or 2 on the objCGI-severity or <10 on the BDI-II.

Methods of the treatment

All patients were hospitalized for 6 weeks in the psychotherapeutic department of the Department of Psychiatry, University Hospital Olomouc. They were treated by the group cognitive-behavioral therapy (CBT) or brief psychodynamic therapy in combination with pharmacotherapy. Patients used antidepressants, mainly SSRIs, with mean daily dosage of 49.74±28.42 mg of paroxetine index (n=59), mean daily dosage of anxiolytics 0.82±0.89 mg (n=22) of alprazolam index, and mean daily dosage of antipsychotics 1.40±1.45 mg (n=17) of risperidone index at the beginning of the treatment. The change of antidepressant and its dosage were rare, mostly because of optimization of dosages because of side effects. At the end of the treatment, the mean daily dosage of antidepressant was 47.57±31.25 mg. There was an effort to decrease or stop medication with anxiolytics – the number of patients treated with benzodiazepines drops from 22 at the beginning to 10 at the end, with a mean daily dosage of 0.438±0.456 mg of alprazolam index. On the other hand, seven more patients were additionally prescribed antipsychotic medication during the treatment to augment the antidepressant effect, with a mean daily dosage of 1.029±0.8258 mg of risperidone index. All patients were treated with standard doses of previously used medication for depressive disorders. Patients attended the 30 group sessions (CBT or short psychodynamic therapy) and five individual sessions. The psychotherapeutic group protocol also included drama therapy, progressive muscle relaxation, mental imagery, and physical activities.

Statistics

Statistics was calculated by using statistical software SPSS 24.0 (IBM Corporation, Armonk, NY, USA) and the Prism (GraphPad PRISM version 5.0; http://www.graphpad.com/prism/prism.htm; GraphPad Software, Inc., La Jolla, CA, USA). The applied statistical procedures were descriptive statistics for the demographic data, mean scores, and a character of data distribution. Differences between scores measured at the start and the end of the treatment were calculated by parametric or nonparametric pair Student's *t*-tests. The chi-square tests were used for the categorical variables. Differences in the declines of the scores in patients with and without comorbid personality disorder and patients undergoing the group CBT or short-term psychodynamic therapy were calculated by two-way ANOVA, followed by Bonferroni's Multiple Comparison Test. Relationships between treatment outcome and other factors were considered by correlations and a multiple stepwise regression analysis. Differences were considered to be significant when *P*-values were <0.05.

Ethics statement

The investigation was performed in agreement with the latest version of the Helsinki Declaration and the Guideline for Good Clinical Practice.[110] The local ethical committee of University Palacky Olomouc, Faculty of Medicine and Dentistry, accepted the study. Written informed consent was obtained from all participants after the procedures had been fully explained.

Results

Sample description

The research was conducted from January 2012 to July 2014 in the psychotherapeutic department in Olomouc. During this period, 72 of 442 treated patients met the inclusion criteria for the study (Table 2). Nine patients dropped out from the study because of various reasons: all of them stopped the treatment in psychotherapeutic department prematurely, three of them because of dislike of the psychotherapeutic program and preferring only the pharmacotherapy, in two patients, the diagnosis was changed (one to bipolar disorder and second to organic affective disorder), two were readmitted to the other department because of severe psychotic depression, and one refused the fulfilling questionnaires.

Rating scales during the treatment

There was a statistically significant improvement in all rating scales during the treatment (Table 3, Figure 1).

Treatment response defined as >35% improvement in BDI-II reached 37 patients (58.7%), and 23 patients (36.5 %) reached remission (the last subjCGI score 1 or 2). The level of hope according to the ADHS total score was 31.56±12.57, with subscore Pathway Thinking 16.81±6.39, and Agency 14.86±6.69 (Table 2). The level of self-stigma in total score of ISMI was 68.45±14.86, with subscores: Alienation 16.11±4.17, Stereotype Endorsement 14.37±3.39,

Table 2 Demographic and clinical data

Variable	All patients (n=72)	Dropouts (n=9)	Finished study (n=63)	Statistic: dropouts vs finished
Age	41.53±13.26	36.33±16.65	42.27±12.69	Unpaired *t*-test: *t*=1.262, *df*=70; ns
Sex (M/F)	21/51	1/8	20/43	Fisher's exact test: ns
Age of the onset of the disorder	32.81±16.06	30.33±19.33	33.16±15.69	Unpaired *t*-test; *t*=0.4910, *df*=70; ns
Duration of the disorder	8.63±8.97	5.94±6.10	9.02±9.28	Mann–Whitney test: MW *U*=234.5; ns
Heredity: no/yes	38/34	5/4	33/30	Fisher's exact test: ns
Education basic/vocational training/ secondary school/university	13/16/37/6	4/2/3/1	9/16/37/6	Chi-square: ns
Employed/unemployed	34/38	4/5	30/33	Fisher's exact test: ns
No pension/pension	54/18	6/3	48/15	Fisher's exact test: ns
Marital status: single/married/ divorced/widowed	25/25/15/7	7/1/0/1	18/24/15/6	Chi-square: $P<0.05$
Without a partner/with a partner	30/42	4/5	26/37	Fisher's exact test: ns
Number of previous hospitalizations	2.18±1.36	2.67±2.00	2.11±1.25	Mann–Whitney test; MW *U*=251; ns
BDI-0	27.63±8.92	24.11±10.06	27.67±9.36	Unpaired *t*-test; *t*=1.056, *df*=70; ns
BAI-0	27.34±11.42	30.75±9.32	26.90±11.65	Unpaired *t*-test; *t*=0.8961, *df*=70; ns
objCGI-Severity-0	4.38±1.06	4.25±0.71	4.40±1.1	Mann–Whitney test; MW *U*=233; ns
subjCGI-Severity-0	4.81±1.11	4.71±0.95	4.83±1.13	Mann–Whitney test; MW *U*=210; ns
DES	17.31±14.60	18.68±17.85	17.17±14.42	Unpaired *t*-test; *t*=0.2400, *df*=70; ns
DES-T	10.74±14.05	11.99±17.94	10.62±13.79	Mann–Whitney test; MW *U*=177.5; ns
NS	96.00±13.42	93.00±11.52	96.36±13.67	Unpaired *t*-test; *t*=0.6227, *df*=70; ns
HA	125.70±18.17	123.40±11.00	126.00±18.89	Unpaired *t*-test; *t*=0.3469, *df*=70; ns
RD	94.97±13.42	95.86±16.82	94.86±13.13	Unpaired *t*-test; *t*=0.1837, *df*=70; ns
PS	98.18±22.98	93.57±12.79	98.73±23.91	Unpaired *t*-test; *t*=0.5585, *df*=70; ns
SD	120.50±17.31	123.10±15.00	120.10±17.65	Unpaired *t*-test; *t*=0.4320, *df*=70; ns
CO	123.20±14.88	120.30±21.51	123.60±14.11	Unpaired *t*-test; *t*=0.4320, *df*=70; ns
ST	66.26±13.88	65.57±9.90	66.34±14.34	Unpaired *t*-test; *t*=0.1373, *df*=70; ns
ADHS – total score	31.29±12.03	28.67±3.98	31.56±12.57	Unpaired *t*-test; *t*=0.5576, *df*=70; ns
ISMI – total score	68.47±14.39	68.63±10.85	68.45±14.86	Unpaired *t*-test; *t*=0.03183, *df*=68; ns

Note: Data are presented as mean ± standard deviation.
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CO, Cooperation; DES, Dissocative Experience Scale; *df*, degrees of freedom; F, females; HA, Harm Avoidance; ISMI, Internalized Stigma of Mental Illness; M, males; objCGI, Clinical Global Impression – Severity, psychiatrist evaluation; subjCGI, Clinical Global Impression – Severity of the disorder, patient evaluation; NS, Novelty Seeking; ns, not significant; PS, Persistence; RD, Reward Dependence; SD, Self-Directednes; ST, Self-Transcencence.

Discrimination Experience 11.24±3.14, Social Withdrawal 14.50±3.96, and Stigma Resistance 11.41±3.37.

Rating scales before and after treatment according to the demographic and clinical data

The comparison of scores on BDI-II, BAI, objCGI, and subjCGI before and after treatment did not show differences between subgroups divided according to the sex, employment, marital status, partnership, heredity, and type of psychotherapy (Table 4).

There were no significant interactions between time and comorbidity before and after treatment in a group of comorbidity with anxiety disorder and the group without this comorbidity. The same result was shown in a comparison of groups with and without a personality disorder (Table 4).

Table 3 Mean scores on rating scales at the beginning and the end of the treatment

	BDI	BAI	objCGI	subjCGI
Beginning of the treatment	27.76±9.36	26.90±11.65	4.40±1.10	4.83±1.13
The end of the treatment	21.33±11.33	23.02±13.72	2.83±1.20	3.22±1.37
Statistics	Paired *t*-test: *t*=5.603, *df*=62; $P<0.0001$	Paired *t*-test: *t*=2.767, *df*=62; $P<0.01$	Paired *t*-test: *t*=13.69, *df*=62; $P<0.0001$	Paired *t*-test: *t*=8.157, *df*=62; $P<0.0001$

Note: Data are presented as mean ± standard deviation.
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; *df*, degrees of freedom; objCGI, Clinical Global Impression – Severity, psychiatrist evaluation; subjCGI, Clinical Global Impression – Severity of the disorder, patient evaluation.

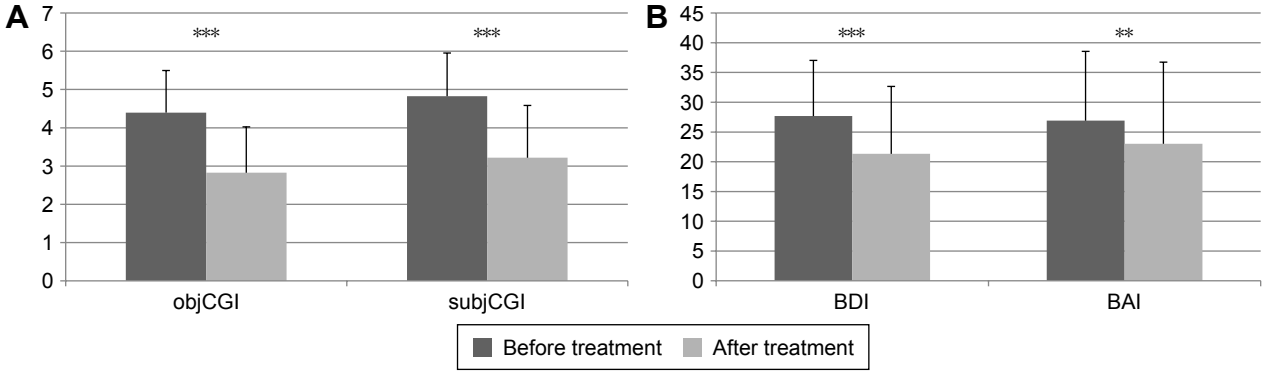

Figure 1 Mean objCGI and subjCGI (**A**) and BDI and BAI (**B**) scores before and after the treatment.
Notes: **Paired *t*-test $P<0.01$; ***Paired *t*-test $P<0.0001$.
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; objCGI, Clinical Global Impression – Severity, psychiatrist evaluation; subjCGI, Clinical Global Impression – Severity of the disorder, patient evaluation.

Table 4 Mean scores on BDI, BAI, objCGI, and subjCGI before and after treatment according to qualitative demographic parameters, comorbidity, and psychotherapeutic approach

Variable	BDI-0	BDI-L	BAI-0	BAI-L	objCGI-0	objCGI-L	subjCGI-0	subjCGI-L
Male (n=20)	25.8±8.1	17.3±10.8	23.8±10.2	19.1±14.1	4.2±1.2	2.4±1.2	4.9±1.2	2.9±1.4
Female (n=43)	28.6±9.9	23.2±11.2	28.4±12.1	24.9±13.3	4.6±1.0	3.0±1.1	4.8±1.1	3.3±1.3
Statistics	Two-way ANOVA: *F*=0.2654, *df*=40; Interaction: ns Time: $P<0.001$ Sex: ns		Two-way ANOVA: *F*=0.3705, *df*=40; Interaction: ns Time: ns Sex: ns		Two-way ANOVA: *F*=0.2089, *df*=40; Interaction: ns Time: $P<0.001$ Sex: ns		Two-way ANOVA: *F*=0.7166, *df*=40; Interaction: ns Time: $P<0.001$ Sex: ns	
Employed (n=30)	28.1±8.5	19.6±11.2	27.2±11.6	21.2±15.6	4.4±1.0	2.6±1.3	4.7±1.1	3.2±1.5
Unemployed (n=33)	27.3±10.2	22.9±11.4	26.6±11.9	24.7±14.7	4.4±1.2	3.0±1.4	5.0±1.2	3.3±1.3
Statistics	Two-way ANOVA: *F*=0.3112, *df*=60; Interaction: ns Time: $P<0.005$ Employment: ns		Two-way ANOVA: *F*=0.4238, *df*=60; Interaction: ns Time: ns Employment: ns		Two-way ANOVA: *F*=0.2671, *df*=60; Interaction: ns Time: $P<0.0001$ Employment: ns		Two-way ANOVA: *F*=0.9013, *df*=60; Interaction: ns Time: $P<0.0001$ Employment: ns	
Single (n=18)	26.8±10.4	22.7±13.7	31.1±12.6	25.4±17.0	4.4±1.3	2.8±1.3	4.6±1.4	3.1±1.4
Married (n=24)	26.3±8.4	18.8±10.7	23.7±9.4	20.0±12.3	4.3±0.7	2.7±1.2	4.7±1.0	3.2±1.5
Divorced (n=15)	30.7±10.1	23.5±10.5	26.5±10.8	24.1±13.4	4.5±1.2	3.1±1.1	5.5±0.9	3.2±1.4
Widow (n=6)	28.3±8.6	21.7±8.0	28.2±17.1	25.3±9.5	4.2±1.2	2.7±1.2	4.3±0.8	3.3±1.0
Statistics	Two-way ANOVA: *F*=0.3113, *df*=78; Interaction: ns Time: $P<0.005$ Marital: $P<0.01$		Two-way ANOVA: *F*=0.2039, *df*=78; Interaction: ns Time: ns Marital: $P<0.005$		Two-way ANOVA: *F*=0.252, *df*=78; Interaction: ns Time: $P<0.0001$ Marital: $P<0.01$		Two-way ANOVA: *F*=0.5828, *df*=78; Interaction: ns Time: $P<0.0001$ Marital: ns	
Without partner (n=26)	27.5±9.7	22.0±10.9	26.3±12.3	24.2±15.0	4.2±1.3	2.8±1.2	5.0±1.3	3.0±1.3
With partner (n=37)	27.8±9.3	20.8±11.7	27.4±11.4	22.2±12.9	4.5±0.9	2.8±1.2	4.7±1.0	3.4±1.4
Statistics	Two-way ANOVA: *F*=0.4452, *df*=52; Interaction: ns Time: $P<0.0005$ Partner: $P<0.005$		Two-way ANOVA: *F*=0.4992, *df*=52; Interaction: ns Time: ns Partner: $P<0.05$		Two-way ANOVA: *F*=0.3302, *df*=52; Interaction: ns Time: $P<0.0001$ Partner: $P<0.01$		Two-way ANOVA: *F*=0.8712, *df*=52; Interaction: ns Time: $P<0.0001$ Partner: ns	
Heredity (n=30)	29.5±7.2	21.2±10.0	27.7±12.2	23.9±12.5	4.5±1.0	2.8±1.1	4.8±1.1	3.2±1.0
No heredity (n=33)	26.3±10.8	21.5±12.6	26.2±11.3	22.2±15.0	4.3±1.2	2.9±1.3	4.8±1.2	3.2±1.7
Statistics	Two-way ANOVA: *F*=0.5118, *df*=60; Interaction: ns Time: $P<0.0005$ Heredity: $P<0.005$		Two-way ANOVA: *F*=0.6791, *df*=60; Interaction: ns Time: $P<0.05$ Heredity: $P<0.0005$		Two-way ANOVA: *F*=0.4055, *df*=60; Interaction: ns Time: $P<0.0001$ Heredity: $P<0.01$		Two-way ANOVA: *F*=0.9781, *df*=60; Interaction: ns Time: $P<0.0001$ Heredity: ns	

(*Continued*)

Table 4 (*Continued*)

	BDI-0	BDI-L	BAI-0	BAI-L	objCGI-0	objCGI-L	subjCGI-0	subjCGI-L
Comorbid anxiety disorder (n=45)	27.6±8.7	22.0±10.6	28.2±11.9	25.0±12.3	4.5±1.3	2.9±1.2	4.8±1.1	3.4±1.4
Without anxiety disorder (n=18)	27.9±11.2	19.7±13.2	23.6±10.7	18.1±16.2	4.1±1.3	2.6±1.1	5.0±1.2	2.9±1.1
Statistics	Two-way ANOVA: *F*=0.2302, *df*=36; Interaction: ns Time: *P*<0.01 Anxiety disorder: ns		Two-way ANOVA: *F*=0.3769, *df*=36; Interaction: ns Time: *P*<0.001 Anxiety disorder: ns		Two-way ANOVA: *F*=0.2073, *df*=36; Interaction: ns Time: *P*<0.0001 Anxiety disorder: ns		Two-way ANOVA: *F*=0.8814, *df*=36; Interaction: ns Time: *P*<0.0001 Anxiety disorder: ns	
Comorbid personality disorder (n=46)	30.2±10.2	23.7±11.2	28.1±10.2	24.4±11.6	4.7±1.1	3.2±1.1	5.0±1.1	3.1±1.5
Without personality disorder (n=17)	26.7±9.0	20.5±11.4	26.5±12.2	22.5±14.5	4.3±1.1	2.7±1.2	4.8±1.1	3.3±1.4
Statistics	Two-way ANOVA: *F*=0.352, *df*=34; Interaction: ns Time: *P*<0.001 Personality: *P*<0.05		Two-way ANOVA: *F*=0.6003, *df*=48; Interaction: ns Time: *P*<0.05 Personality: *P*<0.005		Two-way ANOVA: *F*=0.3, *df*=48; Interaction: ns Time: *P*<0.0001 Personality: ns		Two-way ANOVA: *F*=1.144, *df*=48; Interaction: ns Time: *P*<0.0001 Personality: ns	
Dynamic psychotherapy (n=39)	26.7±8.8	20.7±10.9	27.1±12.0	22.0±14.1	4.3±1.2	2.8±1.4	4.9±1.2	3.2±1.4
Cognitive-behavioral therapy (n=24)	29.3±10.1	22.3±12.2	26.6±11.3	24.7±13.3	4.5±0.9	2.9±0.9	4.7±1.0	3.3±1.3
Statistics	Two-way ANOVA: *F*=0.4205, *df*=48; Interaction: ns Time: *P*<0.001 Therapy: *P*<0.05		Two-way ANOVA: *F*=0.3426, *df*=48; Interaction: ns Time: ns Therapy: ns		Two-way ANOVA: *F*=0.4147, *df*=48; Interaction: ns Time: *P*<0.0001 Therapy: *P*<0.05		Two-way ANOVA: *F*=0.7135, *df*=48; Interaction: ns Time: *P*<0.0001 Therapy: ns	

Note: Data are presented as mean ± SD.

Abbreviations: -0, beginning of the treatment; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; *df*, degrees of freedom; ns, not significant; L, end of the treatment; objCGI, Clinical Global Impression – Severity, psychiatrist evaluation; SD, standard deviation; subjCGI, Clinical Global Impression – Severity of the disorder, patient evaluation.

Relative change during the therapy according to demographic and clinical data

Considering the relative change in BDI-II as a main outcome criterion for the improvement, this change does not correlate significantly with any demographic factors such as the age, the onset of the beginning of the depression, duration of the disorder, number of hospitalizations or subjectively evaluated the severity of disorder in baseline as shown in BDI, BAI, subjCGI, objCGI, not correlated with the dose of the antidepressants. However, the relative improvement in the BDI-II (more negative value means greater improvement) significantly positively correlated with the degree of self-stigma in total score of ISMI, Discrimination Experience (the subscale of ISMI), the severity of dissociation measured by DES, Harm Avoidance (HA), and negatively correlated with the duration of the disorder (Table 5).

The relative objCGI change positively correlates with the level of dissociation measured by DES, ISMI-total score, ISMI subscales Alienation, Discrimination Experience, Social Withdrawal, an overall score of hope measured by ADHS, subscore of ADHS Pathway Thinking, and negatively correlate with SD.

Personality disorders

A personality disorder was diagnosed in 17 patients (29.98%). Patients with a comorbid personality disorder were significantly younger than the patients without a personality disorder (33.06±10.23 vs 45.67±1.87 years; unpaired *t*-test: $t=3.878$, $df=61$, $P<0.001$). The differences between the subgroups were significant also in age of the onset of the disorder (24.00±13.23 vs 36.54±15.28 years; unpaired *t*-test: $t=2.992$, $df=61$; $P<0.005$), in ISMI-total score (75.47±19.23 vs 65.80±12.07; unpaired *t*-test: $t=2.371$, $df=60$; $P<0.05$), Novelty Seeking (107.1±13.5 vs 92.35±11.5; unpaired *t*-test: $t=4.184$, $df=57$; $P<0.0001$), SD (110.0±14.3 vs 123.9±17.4, unpaired *t*-test: $t=2.852$, $df=57$; $P<0.01$), DES (23.76±17.79 vs 14.68±12.24; unpaired *t*-test: $t=2.287$, $df=60$; $P<0.05$), but not in other measurements (duration of the disorder, ADHS total score and subscales, Harm Avoidance, Reward Dependence, Persistence, Cooperation, Self-Transcendence, rating scales BDI, BAI, subjCGI, and objCGI) at the beginning, but also not with main outcome measures BDI relative change (–0.158±0.403 vs –0.235±0.390, unpaired *t*-test: not significant) and objCGI relative change (–0.3013±0.249 vs –0.379±0.212, unpaired *t*-test: not significant).

Stepwise regression of the relative BDI-II change

Because of the various aspects significantly correlated to the BDI-II relative change, a multiple regression analysis (backward stepwise regression) was performed to identify the most important factors linked to the BDI-II relative change as

Table 5 Correlations of relative change in BDI-II and objCGI with demographic and clinical data

Variables	BDI-L – BDI-0 BAI-0	objCGI-L – objCGI-0
Age	–0.204	–0.07899
Onset of the disorder	–0.05437	–0.08142
Duration of the disorder	–0.2449(P=0.053)	–0.03704
Number of previous hospitalizations	0.09845	–0.1498
BDI-0	–0.1132	0.07405
BAI-0	0.1839	0.142
objCGI-0	0.05708	0.1248
subjCGI-0	0.05838	0.1445
DES	0.2403P(P=0.059)	0.2733P,*
DES-T	0.08373	0.2017
ISMI-Total Score	0.2712P,*	0.4955P,***
Alienation	0.1989	0.3294P,**
Stereotype Endorsement	0.02452	0.1555
Discrimination Experience	0.3252P,**	0.5202P,***
Social Withdrawal	0.2089	0.2748P,*
Stigma Resistance	0.1192	0.0537
ADHS-Total Score	–0.1341	–0.2646P,*
Pathway Thinking	–0.1279	–0.2705P,*
Agency	–0.1204	–0.206
Novelty Seeking	0.0453	0.2038
Harm Avoidance	0.2594P,*	0.1442
Reward Dependence	–0.1083	–0.1951
Persistence	–0.04753	–0.1062
Self-Directedness	–0.2164	–0.3356P,**
Cooperation	–0.2129	–0.1872
Self-Transcendence	0.0891	–0.05161
Antidepressant paroxetine index	–0.03514 (n=59)	0.04076
Anxiolytic alprazolam index	–0.4429P,* (n=22)	–0.2656
Antipsychotc risperidon index	–0.2167	–0.2135

Notes: *$P<0.05$; **$P<0.01$; ***$P<0.001$. P, Pearson correlation coefficient.

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; objCGI, Clinical Global Impression – Severity, psychiatrist evaluation; subjCGI, Clinical Global Impression – Severity of the disorder, patient evaluation; ADHS, Adult Dispositional Hope Scale; ISMI, Internalized Stigma of Mental Illness Scale; DES, Dissocative Experience Scale; DES-T, DES-Taxon.

the dependent variable. The independent variables that were entered were the duration of the disorder, DES, ISMI-Total Score, Discrimination Experience, Harm Avoidance, and comorbid Personality disorder (Table 6). The resultant model explained 15.1% of the dependent variables. The strongest factors connected to the BDI-II relative change are the duration of the disorder and Discrimination Experience.

Stepwise regression of relative objCGI change

Because of the several factors significantly related to objCGI relative change, a multiple regression analysis was calculated. The dependent variable was the objCGI relative change while DES, ISMI-Total Score, Alienation, Discrimination Experience, Social Withdrawal, ADHS-Total Score, Pathway Thinking, and SD were entered as independent variables. The method used was a backward stepwise regression. The resultant model explained 26.8% of the dependent variable. The strongest factor connected to objCGI relative change was Discrimination Experience (Table 7).

Table 6 Backward stepwise regression with BDI-II relative change as the dependent variable

Regressors	B	SE	β	Significance
Duration of the disorder	–0.013	0.006	–0.276	0.029
Discrimination Experience	0.045	0.015	0.363	0.005
Adjusted r^2=0.151				

Abbreviations: BDI, Beck Depression Inventory; SE, standard error.

Table 7 Backward stepwise regression with objCGI relative change as the dependent variable

Regressors	B	SE	β	Significance
Discrimination Experience	0.0388	0.0086	0.5307	0.0001
Adjusted r^2=0.268				

Abbreviations: objCGI, Clinical Global Impression – Severity, psychiatrist evaluation; SE, standard error.

Discussion

The objective of this analysis was to find the potential psychological factors related to the treatment response in

pharmacoresistant patients with the major depressive disorders, who were treated with an antidepressant and psychotherapy. The patients' ratings on all scales were reduced during the treatment. The clinical improvement was achieved in 58.7% and remission in 36.5% of patients. The improvement and remission rate is encouraging in light of the fact that these patients had been resistant to the previous outpatient treatment.

The results of the present study show that several clinical or psychosocial variables significantly influenced the treatment change in a patient with a depressive disorder during an intensive 6-week therapeutic inpatient program according to primary outcome criteria.

Looking for the results of correlations with the first outcome measure (the relative BDI-II change), no sociodemographic factor significantly correlated with the therapeutic change, the only duration of the disorder correlated with the BDI-II relative change on the border of statistical significance. However, there were psychological factors that show the correlation with the relative BDI-II change: the level of dissociation in DES, self-stigma in ISMI-total score, Discrimination Experience, and Harm Avoidance.

The second types of factors that could hypothetically contribute to the treatment resistance are psychological factors. The comorbidity with personality disorder did not appear to be an aspect contributing to the treatment efficacy in the study. The present study also showed that individuals with a comorbid personality disorder substantially improved during the treatment, and the relative change of the depressive symptoms was comparable between the groups with and without personality comorbidity.[87] Several studies published worse treatment outcomes in depressive disorders comorbid with personality disorders.[31,111] The differences between the results of these studies can be explained by different patient populations; in the present study, there were inpatients with pharmacoresistant depression. Also, this study did not follow the patients after their finishing the hospitalization. However, the small number of subjects in all these studies may distort the results.

The connection between higher dissociation and lower treatment effectiveness was also found in other studies with different diagnostic populations. It has repeatedly been shown that dissociation is one of the factors contributing to the poor treatment outcome in panic disorder[112,113] and obsessive–compulsive disorder patients.[51,57] In a previous work, dissociation was an important element influencing treatment effectiveness in the mixed neurotic spectrum and depressive disorders.[105]

The relationship between treatment efficacy and personality traits from the Cloninger theory of personality (specifically harm avoidance and SD) was studied in depression. Higher rates of neuroticism, Harm Avoidance, or lower levels of self-directedness and extraversion are associated with a worse course of the depressive disorder.[20,114] Treatment-resistant patients with unipolar depression demonstrated low scores for reward dependence and cooperativeness, using the TCI-R.[23] Both Harm Avoidance and self-directedness have been recognized as features influencing efficiency of pharmacotherapy and psychotherapy in the present study. Other five personality traits of the Cloninger's theory of personality did not relate to treatment effectiveness in the present study. It was shown that the harm avoidance trait decreases the antidepressant efficacy in depression in the study of Quilty et al.[115] Also in other studies, patients suffering from major depressive disorders with higher scores of Harm Avoidance incline to have no good results in the treatment.[27,28] Moreover, the Harm Avoidance scores in patients with treatment-resistant depression were significantly higher than the scores of patients with better results.[28,30]

Probably the most significant finding of the present study related to its primary goals is that lower treatment efficacy was associated with higher rates of self-stigma. This result is consistent with findings of other authors who examined the relationship between treatment efficacy and self-stigma in depressed patients and with the results of the study with patients with mixed neurotic spectrum and depressive disorders.[58,116] Furthermore, the present study confirmed that patients with comorbid personality disorder showed higher rates of self-stigma than those without personality disorders. Therapeutic efficacy also highly negatively correlates with the level of self-stigma in anxiety disorder patients and also in the group of the mixed neurotic spectrum and depressive disorders.[58,105] There have been several studies focusing on the relationship between self-stigma and treatment effectiveness, related to pharmacotherapy and affective disorders and psychoses.[116] It was shown that the harm avoidance trait decreases the antidepressant efficacy in depression. Thus, one of the aims of this investigation was to determine whether the self-stigma considerably contributes to the treatment efficiency of the systematic therapy of the major depressive disorders. As for the impact of self-stigma on the combined pharmacological and psychotherapeutic effectiveness, an inverse relationship was found. The firm correlation between internalized stigma and the change of the psychopathology and severity of the disorder during the treatment evaluated by a psychiatrist supports the hypothesis that patients who highly stigmatize themselves improve noticeably less during the systematic treatment than the patients with lower levels of internalized stigma. The most relevant subscale from the

self-stigma measurement by ISMI was Discrimination Experience, which was the strongest factor that correlated with the therapeutic change in both outcome measures according to regression analysis. The mediators of this association could have been the demoralization brought on the depressive symptoms, as well as the lack of Pathway Thinking caused by low levels of hope, a factor that is connected to the depressive symptoms.[104]

This study desired to determine whether self-stigma (especially subscale Discrimination Experience) is a strong predictor of the therapeutic change or whether it would be eliminated during the regression analyses because other factors would be stronger. It could happen that Harm Avoidance or Dissociation would be better suited to explain the lack of the treatment changes. After all, it is claimed to be temperamental, a largely heritable, trait, and self-stigma is learned during life. While looking at the results of backward stepwise multiple regression analysis, the Discrimination Experience was an only significant factor that influences the relative treatment change in both outcome measures. Other factors that were separately associated with treatment response were eliminated.

The self-stigma subscale Discrimination Experience is the only factor that significantly predicts the second treatment outcome measure – the relative objCGI change.

Limitations

The group of the depressive patients, who participated in the study, was relatively small and heterogeneous due to the high rate of comorbidity with personality disorders and anxiety disorders for firm conclusions about specific predictors of outcome. A particular risk might pose the prevalent use of the evaluation approaches built on self-evaluation. Some patients did not fill in the questionnaires completely; hence, they had to be excluded from some analyses. The use of these measures and inventories depends on the ability of introspection of the probands and their willingness to be open in the statements.

The diagnoses of major depressive disorder and personality disorders were evaluated by a psychiatrist based on the diagnostic criteria and confirmed by two other qualified psychiatrists. On the other hand, the objectivity of the diagnosis of personality disorders is done only by an experienced psychiatrist, not using the standard tools such as IPDE or SCID-II.

The patients were treated with various psychopharmacs and with two alternative psychotherapeutic approaches that also need to be mentioned. Despite this treatment diversity, self-stigma, especially Discrimination Experience prove to be an influential factor contributing to the treatment efficacy of the patients with depressive disorders.

Conclusion

Because the current methods of the treatment cannot help all patients with the major depressive disorder, and a high proportion of them remains resistant to the treatment, it is necessary to search for alternative therapeutic approaches for reducing the self-stigma. If further studies confirm these findings, a great perspective for increasing treatment efficacy in major depressive disorder may be strategies for the reduction of self-stigma.

Disclosure

The authors report no conflicts of interest in this work.

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