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ORIGINAL ARTICLE

Severity of panic disorder, adverse events in childhood, dissociation, self-stigma and comorbid personality disorders

Part 2: Therapeutic effectiveness of a combined cognitive behavioural therapy and pharmacotherapy in treatment-resistant inpatients

Antonin Kolek[1], Jan Prasko[1,2,3], Marie Ociskova[1], Michaela Holubova[1,4], Jakub Vanek[1], Ales Grambal[1], Milos Slepecky[2]

1 Department of Psychiatry, Faculty of Medicine and Dentistry, University Palacky Olomouc, University Hospital, 77520 Olomouc, Czech Republic.
2 Department of Psychology Sciences, Faculty of Social Science and Health Care, Constantine the Philosopher University in Nitra, Slovak Republic.
3 Department of Psychotherapy, Institute for Postgraduate Training in Health Care, Prague, Czech Republic.
4 Department of Psychiatry, Hospital Liberec, Liberec, Czech Republic.

Correspondence to: Prof. Jan Prasko, Ph.D.
Department of Psychiatry, University Hospital Olomouc,
I. P. Pavlova 6, 775 20 Olomouc, the Czech Republic
e-mail: praskojan@seznam.cz

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Abstract

OBJECTIVES: A combination of antidepressants with the cognitive-behavioural therapy showed effectiveness in treatment-resistant patients with panic disorder. This prospective study intended to establish how childhood adverse experiences, self-stigma, dissociation, and severity of psychopathology influence the effectiveness of combined cognitive-behavioural therapy and pharmacotherapy in patients with treatment-resistant panic disorder.

METHODS: One hundred and ten patients were included into the study and one hundred five subjects finished the study. After admission, the subjects were assessed during the first two days of hospitalization. Rating scales were administered before the beginning of the cognitive behavioural therapy (measurement-1) and at the end of the treatment which was after six weeks (measurement-2). Patients with panic disorder were treated using a combination of group cognitive-behavioural therapy and antidepressants. The usual antidepressant dosage range was used. Before admission to intensive cognitive behavioural therapy program, the patients were unsuccessfully treated by antidepressants for minimum 3 months, which defined them as pharmacoresistant.

RESULTS: Hospitalized pharmacoresistant patients with panic disorder improved significantly throughout the 6-week intensive CBT program in all measurements that assessed the overall severity of the disorder, the degree of general anxiety and depression and the severity of specific symptoms of panic disorder and agoraphobia.

The rate of improvement was negatively related to sexual abuse in childhood, presence of comorbid personality disorder, and positively with the severity of the disorder at the beginning, and the level of self-stigma at the beginning of treatment. Improvement in symptoms correlates significantly with decreasing of dissociation during the treatment.severity of depressive symptoms. The earlier development of the disorder is linked to higher score in childhood adverse events, higher level of dissociation and pathological dissociation, and higher level of self-stigma.

CONCLUSIONS: Our prospective study discovers importance of the role of adverse childhood experiences, self-stigma, dissociation and comorbid personality disorder in effectiveness of combined cognitive-behavioural therapy and pharmacotherapy treatment in patients with treatment-resistant panic disorder.

INTRODUCTION

Meta-analyze of 21 studies found that combination of psychotherapy and pharmacotherapy by antidepressants was more effective in acute phase of treatment to CBT or pharmacotherapy alone during the acute treatment phase (Furukawa *et al.* 2006; Furukawa *et al.* 2007). Despite effective medication and psychotherapies, almost one-third of all patients with panic disorder have persistent panic attacks with or without agoraphobia or other anxiety symptoms after the treatment (Cowley *et al.* 1997; Chen & Tsai 2016). A combination of the antidepressants with the cognitive-behavioural therapy showed effectiveness in treatment-resistant patients with panic disorder. About 40 % of the patients had reach remission (Freire *et al.* 2016, Perna *et al.* 2017, Prasko *et al.* 2005), but the rest of the patients have residual symptoms.

The model of childhood adversities is generally recognized as a predictor of psychopathology in adulthood (Safren *et al.* 2002; Widom *et al.* 2007; Rutter 2009). The patients with panic disorder describing childhood physical or sexual abuse are more probable to obtain a diagnosis of personality disorder than those who did not confirm them (Moisan et al. 1995; Ozkan & Altindag 2005). However, little is known about the connection between adverse childhood experiences and treatment effectiveness in panic disorder patients.

Dissociation is also an important trait influencing treatment results in patients with anxiety disorders (Watson *et al.* 2006, Prasko *et al.* 2009, Ociskova *et al.* 2015). Dissociative experiences are frequent in patients suffering from panic disorder and have a negative effect on medication response (Gulsun *et al.* 2007). A high level of dissociation might be one of the explanations for the treatment resistance in patients with panic disorder (Ball *et al.* 1997, Segui *et al.* 2000, Gulsun *et al.* 2007). Dissociation might also be a negative predictor in response to cognitive-behavioural therapy for patients with anxiety disorders (Spitzer *et al.* 2007). In our earlier study the level of the psychological dissociation at the beginning of the treatment negatively predicted improvement after 6 weeks of the combined CBT and antidepressant treatment (Prasko *et al.* 2016). Also, more substantial therapeutic change was associated with greater decrease of the dissociation in a total of 606 pharmacology resistant patients with anxiety or depressive disorders (Prasko *et al.* 2016).

Self-stigma can be the most critical obstacle in seeking therapeutic help (Barney *et al.* 2009, Ociskova *et al.* 2015, Cinculova *et al.* 2017). Patients' efforts to avoid stigma can lead to delay or avoid the treatment (Camp *et al.* 2002). Additionally, self-stigma is accompanied by lesser compliance with the therapeutic actions (Sirey *et al.* 2001, Padurariu 2011, Kamaradova *et al.* 2016, Cinculova *et al.* 2017). Some of our investigations have also showed that the self-stigma negatively correlates with the effectiveness of treatment in anxiety disorders (Ociskova *et al.* 2014, 2015, 2018).

A diagnosis of personality disorder frequently induces therapist´s fear of treatment complications and hard effort with little success (Grambal *et al.* 2016, Ociskova *et al.* 2017, Grambal *et al.* 2017). In our study, there was smaller yet still substantial decrease in specific panic and agoraphobic symptoms during treatment in patients with comorbid personality disorders. However, improvement was more pronounced in patients without this comorbidity (Prasko *et al.* 2005). Still, a high percentage of comorbid patients achieved significant overall improvement (Prasko *et al.* 2005).

Study objectives and hypotheses

The study aimed to find out how early childhood adverse events, self-stigma, dissociation, and comorbidity with a personality disorder affect treatment effectiveness in pharmacoresistant patients with panic disorder. According to the literature, several hypotheses were established:

(1) Patients with panic disorder who have higher scores of aversive events in childhood will report lower treatment results;
(2) Patients with a higher level of dissociation will show lower treatment results;
(3) Patients with a higher self-stigma will demonstrate lower treatment results;
(4) Patients with comorbid personality disorder will have lower outcome in the treatment than patients without comorbid personality disorder;
(5) Better treatment results will linked to a more noticeable change in dissociation.

METHOD

Patients

One hundred and ten patients were included into the study and one hundred five subjects finished the study. Two independent raters confirmed inclusion and exclu-

sion criteria. *The inclusion criteria* were the following: (a) the ICD-10 research criteria for panic disorder/agoraphobia; (b) age 18–60 years; (c) non-responders to SSRIs (at least 12 weeks treatment with SSRI without remission. *The exclusion criteria* were: (a) current depressive disorder; (b) high suicidal risk; (c) organic psychiatric disorder; (d) psychotic disorder current or anamnestic; (e) current substance abuse or dependence; (f) severe somatic illness (oncologic, cardio-vascular).

Measurements

The subjects were assessed during the first two days of hospitalization. Rating scales were administered before the beginning of the cognitive behavioural therapy (measurement-1) and at the end of the treatment, which was after six weeks (measurement-2). The following rating scales and questionnaires were used:

- **CGI** (Guy 1976, 2000) – Clinical Global Impression is an overall assessment of the severity of psychopathology by the physician (objCGI) on a scale 1–7. The second one is a self-evaluation done by patients on a scale 1–7 (subjCGI).
- **BAI** (Beck *et al.* 1988) – Beck Anxiety Inventory consists of 21 self-administered items that described anxiety symptoms in the last week. The Czech version has good test-retest reliability, validity and factor structure (Kamaradova *et al.* 2015).
- **BDI** (Beck *et al.* 1996) – Beck Depression Inventory, second edition, consists of 21 items in which patients choose how often they perceived the described depressive symptoms in the last week. The Czech version of the inventory is equivalent to the original in terms of its test-retest reliability, validity, and factor structure (Ociskova *et al.* 2017).
- **DES** (Carlson *et al.* 1991, 1993) – Dissociation Experience Scale is a self-administered 28-item inventory where patients are queried to indicate on a visual analogue scale how often they experience the symptoms of dissociation. The Czech version of the scale is equivalent to the original text in terms of its test-retest reliability, validity and factor structure (Ptacek *et al.* 2007). Pathological DES was assessed by a Dissociative Experiences Scale Taxon (DES-T) based on the DES items 3, 5, 7, 8, 12, 13, 22, 27 (Waller *et al.* 1996).
- **ISMI** (Ritsher *et al.* 2003) – Internalized Stigma of Mental Illness consists of 29 items. The scale focuses on five elements of internalized stigma – Alienation, Stereotype endorsement, Perceived discrimination, Social withdrawal, and Resistance to stigma. The scale was standardized for Czech population by Ociskova *et al.* (2014).
- **CTQ – SF** (Bernstein & Fink 1998, Bernstein *et al.* 2003; Scher *et al.* 2001; Thombs *et al.* 2009) – The Childhood Trauma Questionnaire-Short Form (CTQ-SF) is a self-report retrospective questionnaire with 28 items, which assesses five dimensions of childhood aversive experiences. The domains are (1) Physical abuse, (2) Emotional abuse, (3) Sexual abuse, (4) Physical neglect, and (5) Emotional neglect.
- **PDSS** (Shear *et al.* 1997) – Panic Disorder Severity Scale is an instrument for a specific assessment of panic disorder (Furukawa *et al.* 2009). The items evaluate the occurrence of panic attacks, distress produced by attacks, anticipatory anxiety, agoraphobic fear/avoidance, panic-related sensation of fear/avoidance, and work and social impairment (Shear *et al.* 1997).
- **Demographic data**, including age, sex, age of the onset of the disorder, duration of the disorder, and the number of psychiatric hospital admissions were obtained in an interview and using Demographic questionnaire.

Tab. 1. Time table – assessment and measurement methods

Method	Week 0	Week 6
ICD diagnostic criteria	X	
Demographic questionnaire	X	
objCGI severity	X	X
PDSS	X	X
subjCGI severity	X	X
BAI	X	X
BDI	X	X
DES	X	X
CTQ-SF	X	
ISMI	X	

ICD-10 = International Classification of the Disorders, 10th edition; objCGI = objective Clinical Global Impression scale; PDSS = Panic Disorder Severity Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory, Second version; DES = Dissociation Experience Scale; CTQ-SF = Childhood Trauma Questionnaire-Short Form; ISMI= Internalized Stigma of Mental Illness.

The *primary outcome criteria* of the therapeutic change were defined as:

- The change in objCGI severity;
- The change in PDSS.

The *secondary outcome criteria* of the therapeutic change were defined as:

- The change in subjCGI severity;
- The change in BAI;
- The change in BDI.

Treatment approach

The patients were treated by a combination of group cognitive-behavioural therapy and antidepressants in the usual range of dosages. The usual antidepressant dosage range was used. Before admission to intensive cognitive behavioural therapy program, the patients were unsuccessfully treated by antidepressants for minimum 3 months, which defined them as pharmacoresistant.

The structured CBT program contained 20 CBT group sessions, each lasting 1.5 hours. The main topics consist of education about panic disorder and its treatment, a vicious circle of panic attacks and agoraphobia, cognitive restructuring, interoceptive exposure, exposure in vivo, training in communication skills, practical problem solving, and working with cognitive schemas and self-stigma. Once a week with each patient the additional individual session was performed. There were also supplementary programs - ergo-therapy, daily relaxation and physical exercise (15 minutes).

As the patients used antidepressants at least three months before the study enrolment, the pharmacotherapy was variable. There were minimal and no significant differences between the antidepressant dosage at the beginning and at the end of the hospitalization. In order to compare different antidepressants, we converted the doses of individual drugs to the equivalents of an antidepressant (paroxetine 20 mg = citalopram 20 mg or fluoxetine 20 mg or sertraline 50 mg or fluvoxamine 50 mg or escitalopram 10 mg or venlafaxine 75 mg), or an anxiolytic (alprazolam 0.75 mg = clonazepam 0.5 mg or diazepam 15 mg or oxazepam 20 mg).

The antidepressant (n=91; 86.7 %) were the most common medication of the patients, followed by anxiolytics (n=19; 18.1 %), and antipsychotics (n=6; 5.7 %). The dosage of medication was in panic disorder prescribing guidelines range. The mean dosage of antidepressant was 33.2 ± 20.9 mg of paroxetine equivalent at beginning and 32.9 + 21.4 mg of paroxetine equivalent at the end of program, 13.8 + 14.6 mg of diazepam equivalent at beginning and 12.5 + 11.6 mg of diazepam equivalent at the end of program and in antipsychotics 3.3 ± 2.4 mg of risperidone equivalent at beginning and no antipsychotics at the end of program. This indicates that during the 6weeks CBT treatment minimal (no significant) change in antidepressant dose was done.

Statistic

Patient's demographical, clinical, and psychological data were examined using column statistics. All data are presented as the mean and standard deviation. Normal distributions of the variables were analysed using the Shapiro-Wilk W test. Parametric or nonparametric independent and dependent t-tests calculated changes among the scores gained at the start and end of the treatment and for differences according to sex, education, employment, and partnership. The chi-square tests were used for the categorical variables. Spearman Rank Correlation coefficients or Pearson correlation coefficients were obtained to examine relationships between questionnaires and rating scales. Correlations and multiple stepwise regression analysis found relationships between treatment outcome and other factors. The level of significance was set at $p<0.05$. All analyses were conducted using STATISTICA 24.0 software and Prism 8.

Ethics

The study was carried out in agreement with the latest version of the Declaration of Helsinki and ICH-GCP guidelines (International Conference on Harmonization, Good Clinical Practice) (EMEA 2002/2009). All participants signed the informed consent before the enrolment and after the nature of the procedures had been fully explained. The local ethics committee of University Hospital Olomouc approved the project.

RESULTS

Demographic variables

A total of 142 patients with panic disorder, who had been resistant to psychopharmacs in an outpatient facility services were admitted for a 6-week complex inpatient treatment program during the period from November 2015 to July 2019 (Table 2). 110 patients with mean age 37.7 + 12.0 entered the study (37 men and 74 women). Mean age of disorder onset was 27.7 + 12.4 years with a mean duration of 9.8 + 9.6 years. Another 32 patients admitted to the department were not interested in participation in the study (mean age 38.5 + 8.9). Data of another 5 (4.5 %) participants were not used because they did not complete more than half of the questionnaires. Data from 105 patients were statistically analysed (Table 2).

Comorbidities

The patients showed various comorbidities with anxiety and personality disorders. Sixty-nine patients suffered from additional comorbid neurotic spectrum disorder (65.7%). Twenty-five of them (23.8%) suffered from agoraphobia, 19 (18.1 %) generalized anxiety disorder, 8 (7.6 %) social phobia, and 17 (16.3 %) other neurotic spectrum disorders (6 with somatoform disorders, 2 with adjustment disorder, 4 with dissociative disorders, 5 with mixed anxiety-depressive disorder). The relatively frequent comorbidity was also insomnia (n=8; 7.6 %). There were no differences between groups with and without comorbid anxiety disorder at the start of the treatment in clinical, demographic, or psychosocial data.

There were 43 patients with comorbid personality disorder (41.0%): 17 (16.2 %) with borderline personality disorder, 12 (11.4 %) with mixed personality disorder, and 14 (13.3%) with other personality disorders (4 obsessive-compulsive, 4 avoidant, 3 dependent, 2 histrionic, 1 schizoid).

Results of the treatment

There were statistically significant decreases in psychopathology measured by objCGI, subjCGI, PDSS, BAI, BDI, DES, and DES-T during the six weeks combined intensive group cognitive behavioural therapy program added to ongoing pharmacotherapy (Table 2, Figures 1-5).

According to the objCGI ratings, 50.5 % of the patients improved moderately or more (decrease

Tab. 2. Patients included in study

Variable	Completers – 1st assessment (n=105)	Completers – 2nd assessment (n=105)	Statistic: Difference between the 1st and 2nd assessment
Age	37.8 ± 12.1		
Sex: male / female	33 / 72		
Age of onset of the disorder	27.7 ± 12.5		
Duration of the disorder	10.0 ± 9.8		
Heredity no/yes	39/56		
Education: basic/vocational / secondary /university	17/34/42/12		
Employment: no / yes	47/58		
Marital status: single/married/ divorces/widowed	56/35/14/3		
Partner: no(yes	52/53		
Another anxiety disorder: no/yes	77/28		
Personality disorder: no/yes	81/24		
objCGI-S	4.3 ± 0.7	2.7 ± 0.9	paired t-test: t=15.97 df=104; p<0.0001
PDSS	14.5 ± 4.1	8.6 ± 5.4	paired t-test: t=10.73 df=104; p□0.0001
subjCGI-S	4.5 ± 1.2	3.8 ± 1.4	paired t-test t=5.492 df=104; p□0.0001
BAI	28.3 ± 13.1	22.8 ± 13.8	paired t-test t=3.980 df=104; p□0.0001
BDI	25.0 ± 12.1	20.2 ± 13.5	paired t-test t=4.169 df=104; p□0.0001
DES	18.5 ± 19.5	16.3 ± 17.2	paired t-test t=1.729 df=104; ns
DES-T	14.7 ± 22.4	12.0 ± 17.4	paired t-test t=1.422 df=104; ns
CTQ-Total	49.8 ± 18.1		
Emotional abuse	11.3 ± 5.6		
Psychical abuse	8.0 ± 4.3		
Sexual abuse	6.4 ± 3.3		
Emotional neglect	15.0 ± 5.6		
Physical neglect	9.1 ± 3.6		
ISMI-Total score	62.9 ± 13.2		
Alienation	14.5 ± 4.1		
Stereotype endorsement	13.3 ± 3.6		
Perceived discrimination	9.8 ± 3.1		
Social withdrawal	13.4 ± 3.5		
Resistance to stigma	11.0 ± 2.1		
Antidepressant index	33.8 ± 20.6 (n=91)	33.3 ± 21.2 (n=93)	Mann-Whitney test: ns
Anxiolytic index	13.8 ± 14.7 (n=19)	12.5 ± 11.6 (n=19)	Paired t test: t=1.313 df=16: ns
Antipsychotic index	3.3 ± 2.4 (n=6)	0	
objCGI-change	1.6 ± 1.0		
PDSS-change	5.9 ± 5.6		
subjCGI-change	0.7 ± 1.3		
BAI-change	5.5 ± 14.2		
BDI-change	4.8 ± 11.8		
DES-change	2.2 + 13.1		
DES-T-change	2.7 ± 19.7		

BAI, Beck Anxiety Inventory; BDI, Beck Depressive Inventory, second edition; an objCGI-S, objective form of the Clinical Global Impression-Severity of the disorder; subjCGI-S, sell-rated form of the Clinical Global Impression-Severity of the disorder; DES, Dissociative Experience Scale; df, degrees of freedom; PDSS, Panic Disorder Severity Scale.

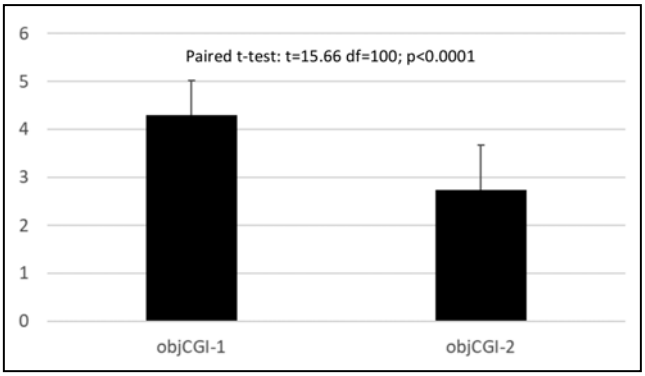

Fig. 1. Objective Clinical Global Impression before and after the treatment

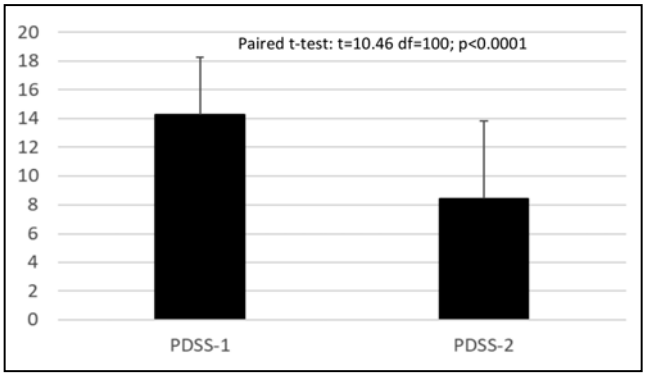

Fig. 2. Panic Disorder Severity Scale before and after the treatment

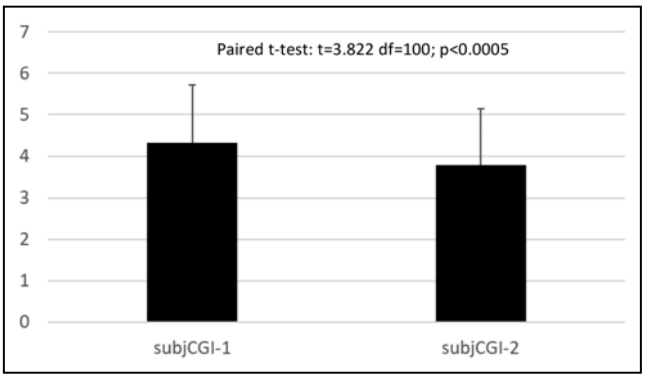

Fig. 3. Subjective Clinical Global Impression before and after the treatment

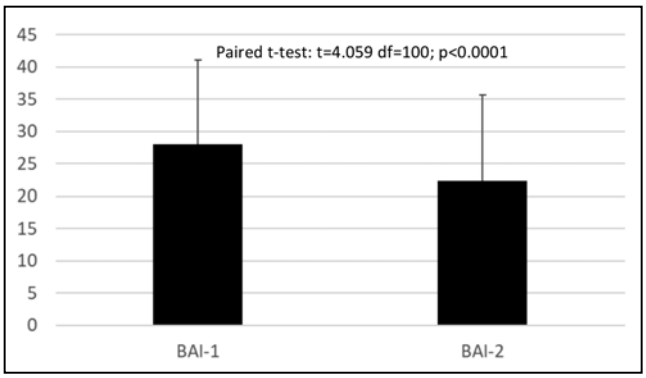

Fig. 4. Beck Anxiety Inventory before and after the treatment

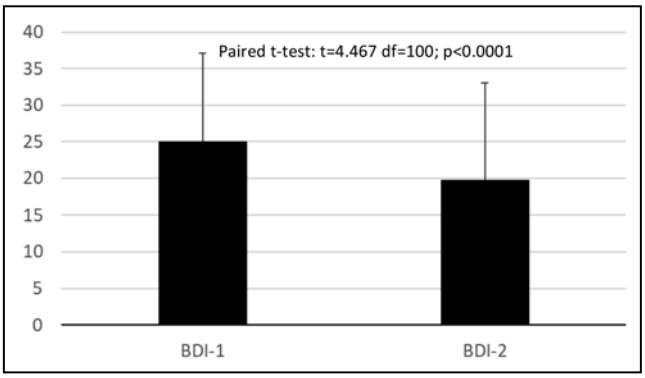

Fig. 5. Beck Depression Inventory before and after the treatment

2 points and more) and 42.6 % reached remission that was defined as a score one or two in the last measurement of objCGI-S.

According to the PDSS rating, 60.4 % of the patients showed at least 30 % decrease in the severity of the panic disorder and agoraphobia symptoms (that is considered as a treatment response), and 49.5 % reduced symptomatology at least 50 % which was thought of as a robust treatment response.

The therapeutic change and the initial measurements

Women had statistically significantly higher objCGI changes, but this did not show in other primary and secondary outcome measures (Table 3). The level of education did not have a significant influence on any outcome measures. When comparing the unemployed patients with the employed ones, there was a statistically significant difference between these groups in PDSS-change and subjCGI-change: the employed patients had larger decrease in these measures. Being in a partnership did not influence the treatment results (Table 3).

In a correlation analysis of the ***demographic data***, only the earlier onset of the disorder positively correlated with the specific panic/agoraphobic symptomatology measured by PDSS (Table 4).

The level of ***dissociation*** measured by DES decreased during the treatment non-significantly from 18.3 ± 18.7 to 15.9 ± 16.0 (paired t-test; t=1.814 df=100; ns /p=0.07) and pathological dissociation measured by DES-T from 14.5 ± 21.9 to 11.5 ± 16.1 (paired t-test; t=1.506 df=100; ns). Nevertheless, the DES change significantly positively correlated with the BAI change (Spearman r=0.36, p<0.001), the BDI change (Spearman r=0.33; p<0.001), and the PDSS change (Spearman r=0.20; p<0.05). The change of the pathological dissociation measured by DES-T positively correlated with the BAI change (Spearman r=0.31, p<0.005) and the BDI change (Spearman r=0.28; p<0.05) (Table 4).

The level of ***self-stigma*** assessed by ISMI total score did not correlate with changes in any of primary or secondary measures (Table 4).

The total score of ***adverse childhood experiences*** measured by TCQ did not correlate with the change in any of primary or secondary measures (Table 4).

The effectiveness of the therapy evaluated by the decrease of global severity of the disorder (subjCGI-change) positively correlated only with subjCGI-1 (Table 4).

The effectiveness of the therapy measured by the decrease of anxiety symptoms (BAI change) positively correlated only with BAI-1 and paroxetine-equivalent (Table 4).

The effectiveness of the treatment measured by decreasing of depressive symptoms (BDI change) positively correlated with objCGI-1, BDI-1, DES, DES-T (Table 4).

Adverse experiences in childhood according to the type of experience and their relationship with therapeutic change

The total score of adverse experiences in childhood did not significantly correlate with the therapeutic change measured by changes in PDSS, objCGI, subjCGI, BAI, and BDI (Table 5). When looking at specific types of early adversities, the emotional abuse correlated weakly negatively with the objCGI change and sexual abuse weakly negatively with the PDSS change.

Self-stigma and therapeutic change

The total score of self-stigma, measured by ISMI total, statistically significantly correlated with the therapeutic change measured by the objCGI change and the BAI change but not with the therapeutic change in panic attacks and agoraphobia (PDSS) or depressive symptoms (BDI) (Table 6). Subjects with higher self-stigma generally improved more than individuals with a lower level of self-stigma. The subscales of ISMI mirrors most but not all correlations of ISMI total with the therapeutic change, except for Perceived Discrimination and Stigma Resistance subscales which did not correlate with any of primary or secondary measures of the change (Table 6).

Comorbidity and treatment effectiveness

The patients without a comorbid anxiety disorder showed higher change in BAI during the treatment than the patients without this comorbidity. Other primary and secondary outcome measures did not show differences between these two groups (Table 7).

The treatment effectiveness did not differ with respect to the personality disorder comorbidity except for PDSS (Table 7).

Multiple regression analysis for treatment efficacy factors

Backward stepwise multiple regression analyses were performed to detect the most significant components influencing consequently primary and secondary outcome measures as dependent factors. The independent variables were regressors which were previously sig-

Tab. 3. Differences during the treatment according to sex, education, job, and partnership

Variable	Men (n=33)	Women (n=72)	Sign. $p<$	Education lower (n=49)	Education higher (n=52)	Sign. $p<$	Not employed (n=47)	Employed (n=58)	Sign. $p<$	Without a partner (n=52)	With a partner (n=53)	Sign. $p<$
objCGI-change	1.2 ±0.9	1.7 ± 1.0	**0.05**	1.7 ± 1.1	1.5 ±0.9	ns	1.6 ± 1.0	1.6 ± 1.1	ns	1.5 ± 0.9	1.7 ± 1.1	ns
PDSS-change	6.8 ± 5.8	5.3 ± 5.6	ns	5.9 ± 5.2	5.8 ± 6.1	ns	3.8 ± 5.5	7.7 ± 5.2	**0.001**	5.2 ± 5.6	6.6 ± 5.7	ns
subjCGI-change	0.8 ± 1.4	0.7 ± 1.3	ns	0.5 ± 1.4	0.6 ± 1.5	ns	0.3 ± 1.3	1.0 ± 1.2	**0.01**	0.9 ± 1.3	0.5 ± 1.3	ns
BAI-change	5.5 ± 15.4	5.5 ± 13.7	ns	6.9 ± 13.4	4.5 ± 15.2	ns	3.8 ± 13.6	6.9 ± 14.6	ns	4.3 ± 15.0	6.7 + 13.4	ns
BDI-change	5.9 ± 12.9	4.3 ± 11.4	ns	6.4 ± 10.3	4.0 ± 13.2	ns	2.6 ± 11.0	6.6 ± 12.3	ns	5.3 ± 12.8	4.4 ± 11.0	ns
DES-change	3.4 ± 18,7	1.7 ± 9.7	ns	1.8 ± 10.4	3.0 ± 15.9	ns	3.4 ± 14.7	1.3 ± 11.7	ns	0.7 ± 13.0	3.7 ± 13.2	ns
DES-T-change	0.7 ± 16.6	3.7 ± 21.0	ns	1.7 ± 12.7	4.3 ± 25.7	ns	4.5 ± 26.2	1.4 ± 12.2	ns	-0.1 ± 15.8	5.5 ± 22.8	ns

Tab. 4. Correlations of psychopathology measurements, disorder onset, and therapeutic change

Measures	objCGI change	PDSS change	subjCGI change	BAI change	BDI change
Disorder onset	-0,08	**0.21** ^{P*}	-0.03	0.01	-0.05
Disorder length	-0.13	0.01	0.16	0.16	0.12
objCGI-1	**0.43** ^{S***}	-0.17	-0.03	-0.10	**-0.19** ^{S*}
PDSS-1	-0.03	**0.41** ^{P***}	-0.18	-0.06	-0.13
subjCGI-1	0.02	-0.09	**0.36** ^{S***}	0.19	0.02
BAI-1	-0.02	0.02	**0.21** ^{S*}	**0.49** ^{P***}	0.09
BDI-1	-0.05	-0.13	**0.30** ^{S**}	0.17	**0.36** ^{S***}
DES	-0.13	-0.17	0.03	0.10	0.01
DES-T	-0.09	-0.09	0.08	**0.20** ^{S*}	0.08
DES-change	-0.04	**0.22** ^{S*}	0.06	**0.38** ^{S***}	**0.35** ^{S***}
DES-T-change	-0.04	0.14	0.05	**0.32** ^{S**}	**0.32** ^{S**}
Paroxetine equivalent	0.12	0.01	0.16	**0.24** ^{S*}	0.13

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

nificantly or almost significantly associated with the therapeutic effectiveness of each of outcome factors (Table 8).

The resulting models explained 19.5 % of the objCGI-S change variance, 22.6 % of the PDSS-change variance, 16.1 the % of subjCGI-S-change variance, 31.8 % of the BAI-change variance, and 22.1% of the BDI-change variance (all: $p < 0.001$), (Table 8).

Response to the hypotheses

(1) Patients with panic disorder who, have a higher score of aversive events in childhood. will report lower treatment results.

The total score of adversities in childhood (TPQ total) did not correlate with the therapeutic effect of the program evaluated by primary or secondary outcome criteria. There was only a weak negative correlation of emotional abuse in childhood and objCGI-change, and sexual abuse and PDSS-change.

(2) Patients with a higher dissociation will show lower treatment results.

This hypothesis was not confirmed in all outcome measures for the overall level of dissociation. The results of pathological dissociation display similar results except BAI-change, which weakly significantly positively correlated with DES-T.

(3) Patients with a higher self-stigma will demonstrate lower treatment results

This hypothesis was not confirmed in any of outcome measures. Additionally, the results showed opposite direction in objCGI change and BAI change. Patients with higher self-stigma globally improved more than people with a lower level of self-stigma.

(4) Patients with comorbid personality disorder will have worse outcome in the treatment.

This hypothesis was confirmed only for specific panic disorder scale PDSS, measured number, and severity of panic attacks and agoraphobia, not for other primary or secondary outcome measures.

(5) Better treatment results will linked to a more noticeable change in dissociation.

This hypothesis was confirmed for the changes in DES and PDSS, BAI, BDI and for DES-T and BAI, BDI, but not for objCGI and subjCGI. It seems that the decrease of dissociation is linked to the decrease of anxiety symptomatology.

Tab. 5. Correlations of childhood adverse experiences and other measurements

Measures	objCGI change	PDSS change	subjCGI change	BAI change	BDI change
CTQ total	0.13	-0.06	0.02	0.02	0.11
Emotional abuse	**-0.21** ^{S*}	-0.11	0.03	0.09	0.13
Physical abuse	0.05	-0.04	0.01	0.03	0.08
Sexual abuse	0.10	**-0.21** ^{S*}	0.03	0.02	-0.06
Emotional neglect	0.11	0.02	0.06	0.08	0.12
Physical neglect	0.07	-0.03	-0.04	0.02	0.06

* $p<0.05$; ** $p<0.01$

Tab. 6. Correlations of self-stigma and psychopathology, dissociation, and therapeutic change

Measures	objCGI change	PDSS change	subjCGI change	BAI change	BDI change
ISMI total	**0.21** P*	0.03	0.16	**0.21** P*	0.13
Alienation	**0.21** P*	0.06	**0.20** S*	**0.21** P*	0.18
Stereotype endorsement	**0.22** P*	0.02	0.11	0.17	0.15
Perceived discrimination	0.19	0.02	0.14	0.16	0.04
Social withdrawal	0.13	-0.02	**0.22** S*	**0.23** P*	0.13
Stigma resistance	-0.03	0.03	-0.03	-0.03	-0.01

* $p<0.05$; ** $p<0.01$

DISCUSSION

The study intended to explore how adverse childhood experiences, self-stigma, dissociation, and comorbidity influence the effectiveness of combined cognitive-behavioural therapy and pharmacotherapy in patients with treatment-resistant panic disorder. The importance of this study lies in the fact that approximately one-fourth to one-third of patients with panic disorder do not respond satisfactorily to pharmacotherapy (Bandelow & Ruther 2004, Perna *et al.* 2011, Chen & Tsai 2016, Freire *et al.* 2016). The procedure was carried out under typical conditions at the psychotherapeutic department for inpatients with anxiety, neurotic, mood, and personality disorders. The 6-weeks combined treatment of pharmacoresistant patients with panic disorder with or without agoraphobia was efficient. The mean scales´ scores significantly declined in all measurements. The treatment response, according to PDSS, was achieved in more than 60% of the sample, and more than 42 % of the patients reached remission according to the objCGI-S criteria. This outcome seems encouraging, especially considering genuine patients with pharmacoresistance, comorbidities, and without much selection to the study (no exclusion for patients with comorbid anxiety disorders or personality disorders). It seems that the addition of the cognitive-behavioural program to the antidepressant treatment could be a satisfying strategy in panic disorder patients. Analogous effectiveness was shown in studies of other authors (Otto *et al.* 1999, Heldt *et al.* 2003, Craske *et al.* 2005, Furukawa *et al.* 2006, Heldt *et al.* 2006, Roy-Byrne *et al.* 2006, Simon *et al.* 2009. Rodrigues *et al.* 2011) and in our previous studies of patients with anxiety or neurotic spectrum disorder (Prasko *et al.* 2005, Prasko *et al.* 2015, Prasko *et al.* 2016, Ociskova *et al.* 2015, Ociskova *et al.* 2018).

Childhood adversities

By analysing of each childhood adverse experiences subscale, we have found that only sexual abuse was negatively associated with PDSS change. It means that people with an anamnesis of sexual abuse did profit from the treatment less than people without such history. However, this correlation was weak. One possible explanation for this could be that in the psychotherapeutic program there is increasing focus on working with childhood traumas, meaning that this therapeutic step could have improved most severity measures and so minimalized the impact of childhood adversities on the treatment efficacy.

Self-stigma

ISMI total significantly positively correlated with the therapeutic change of objectively measured Clinical

Tab. 7. Differences according to the comorbidities – another anxiety disorder or a personality disorder

VARIABLE	COMORBID ANXIETY DISORDER			COMORBID PERSONALITY DISORDER		
	Absent (n=36)	Present (n=69)	Sign. *p*<	Absent (n=62)	Present (n=43)	Sign. *p*<
objCGI-change	1.7 ± 0.9	1.5 ± 1.0	ns	1.6 ± 1.1	1.6 ± 0.9	ns
PDSS-change	6.6 ± 5.2	5.6 ± 5.9	ns	7.5 ± 5.7	3.6 ± 4.7	**0.001**
subjCGI-change	0.8 ± 1.2	0.6 ± 1.4	ns	0.8 ± 1.4	0.6 ± 1.1	ns
BAI-change	9.5 ± 14.1	3.4 ± 13.8	**0.05**	6.4 ± 14.8	4.3 ± 13.2	ns
BDI-change	6.3 ± 12.1	4.0 ± 11.7	ns	3.9 ± 11.7	6.2 ± 12.0	ns
DES-change	1.0 ± 8.4	2.8 ± 15.0	ns	2.0 ± 13.6	2.6 ± 12.6	ns
DES-T-change	2.0 ± 9.5	3.1 ± 23.4	ns	1.2 ± 11.5	5.0 ± 27.6	ns

* $p<0.05$; ** $p<0.01$

Tab. 8. Multiple regression analyses of primary and secondary outcome measures

Dependent variable:	Model	Regressors	B	Std. Error	β	t	Significance
ObjCGI-S-change	6	ObjCGI-1	0.634	0.124	0.451	5.121	**0.000**
Regressors: sex, Emotional abuse, ISMI-total, Alienation, Stereotype endorsement, Perceived discrimination, objCGI-1		ANOVA: F= 26.227 df=104 ; p<0.001 Adjusted r squared = 0.195					
Dependent variable:	Model	Regressors	B	Std. Error	β	t	Significance
PDSS-change	3	Comorbid personality disorder	-3.039	1.004	-0.266	-3.025	**0.003**
Regressors: Disorder onset, Comorbid personality disorder, Sexual abuse, PDSS-1,		PDSS-1	0.503	0.121	0.365	4.149	**0.000**
		ANOVA: F= 16.159 df=104 ; p<0.001 Adjusted r squared = 0.226					
Dependent variable:	Model	Regressors	B	Std. Error	β	t	Significance
SubjCGI-S-change	5	subjCGI-1	0.465	0.102	0.411	4.574	**0.000**
Regressors: Alienation, Social withdrawal, subjCGI-1, BAI-1, BDI-1		ANOVA: F= 20.918 df=104 ; p<0.001 Adjusted r squared = 0.161					
Dependent variable:	Model	Regressors	B	Std. Error	β	t	Significance
BAI-change	6	Comorbid personality disorder	-5.315	2.785	-0.181	-1.908	0.060
Regressors: comorbid anxiety disorder comorbid personality disorder, DES-T-1, ISMI-total, Alienation, Social withdrawal, subjCGI-1, BAI-1, paroxetine equivalent		Social withdrawal	0.829	0.392	0.205	2.112	**0.038**
		subjCGI-1	-3.342	1.282	-0.280	-2.607	**0.011**
		BAI-1	0.708	0.120	0.642	5.917	**0.001**
		ANOVA: F= 11.372 df=89 ; p<0.001 Adjusted r squared = 0.318					
Dependent variable:	Model	Regressors	B	Std. Error	β	t	Significance
BDI-change	3	Heredity	2.706	1.321	0.180	2.049	**.043**
Regressors: Heredity, Alienation, objCGI-1, BDI-1		ObjCGI-1	-4.831	1.462	-0.292	-3.304	**.001**
		BDI-1	0.385	0.088	0.393	4.367	**.000**
		ANOVA: F= 11.427 df=104 ; p<0.001 Adjusted r squared = 0.221					

Global Impression (objCGI) and general anxiety (BAI). Subjects with higher self-stigma globally improved more than individuals with a lower level of self-stigma. It disagrees with our previous investigations that found that the self-stigma negatively correlates with the effectiveness of treatment in anxiety disorders (Ociskova *et al.* 2014, 2015, 2018). This result may be related to the fact that patients with higher self-stigma also had higher scores on the measurement scales at the beginning of the treatment and therefore had more space for therapeutic change. Additionally, the therapeutic program also consists of self-stigma reduction education.

Dissociation

The degree of pathological dissociation at the beginning positively affected the decline in symptoms of general anxiety - the opposite trend than hypothetically assumed. In our previous study (Prasko *et al.* 2009) in patients with OCD treated by a combination of antidepressant and cognitive behavioural therapy, the severity of dissociation negatively correlated with the results of the treatment. Also, the pharmacotherapeutic study about the panic disorder of Gulsun *et al.* (2007), found that the level of dissociation was negative predictor of the treatment response. Dissociation was also a negative predictor of cognitive behavioural therapy in anxiety disorder in the study of Spitzer *et al.* (2007). In the Spitzer´s *et al.* (2007) study, dissociation was a negative predictor of response to cognitive-behavioural therapy in anxiety disorders. How to understand this difference? There were only patients with panic disorder in our study and a mixed group of anxiety spectrum patients in Spitzer *et al.* study. In our most significant study of 640 patients with anxiety or depressive disorders, the higher initial level of dissociation predicted lesser improvement, which is in opposite to the current results in panic disorder patients (Prasko *et al.* 2015). The difference between other studies and the presented results could be attributed to the combined therapeutic program which adds cognitive-behavioural therapy to the ongoing therapy with psychopharmacs. However, the bigger therapeutic change was connected to a more significant reduction of the dissociation level, which was also confirmed in the current study. Another of our findings was that the decrease of dissociation and pathological dissociation correlated with the level of subjectively perceived anxiety symptoms. Psychotherapy focuses on the awareness of emotional states and the problems associated with them, and the decline in the rate of dissociation may be one of the processes contributing to the therapy effectiveness (Ball *et al.* 1997, Segui *et al.* 2000). In our study, the decrease in DES positively correlated with the reduction of scores in BAI, BDI and PDSS during the treatment, and the reduction in DES-T was positively associated with the reduction in scores in BAI and BDI during the treatment. And part of the treatment in psychotherapy is also to discover and manage emotions instead of avoid them.

Limitations of the study

The presented study has several limitations that should be reflected. Self-report questionnaires were used for the assessment of the symptoms, childhood adverse events, dissociation, and self-stigma. Future research should corroborate these questionnaires with clinician-rated instruments. An additional limitation of the investigation was a smaller sample size which prevented the evaluation of different subgroups of panic disorder patients (with and without agoraphobia, with fear of death or madness, etc.). The patients were medicated and at the same time treated using cognitive behavioural intensive program. That is why it is difficult to say which method of treatment was more influential.

CONCLUSION

Hospitalized pharmacoresistant patients with panic disorder improved significantly throughout the 6-week intensive inpatient CBT program in all measurements that assessed the overall severity of the disorder, the degree of general anxiety and depression, and the severity of specific symptoms of panic disorder and agoraphobia. The rate of improvement was negatively related to sexual abuse in childhood and the presence of comorbid personality disorder, and positively to the severity of the disorder at the beginning, and the level of self-stigma at the beginning of treatment. Improvement in symptoms significantly correlated with decline of dissociation during the treatment.

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