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ORIGINAL ARTICLE

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

Part 1: Relationships between clinical, psychosocial and demographic factors in pharmacoresistant panic disorder patients

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Abstract

OBJECTIVES: Little is known about the relation between severity of panic disorder, adverse events in childhood, dissociation, self-stigma and comorbid personality disorders. The aim of this study is to look for the intercorrelations between these factors.

METHOD: The study explores the relation between clinical, demographic and social factors in panic disorder using cross sectional design. The inpatients with pharmacoresistant panic disorder with and without agoraphobia were included in the study. Participants were also assessed for comorbidity with other anxiety or personality disorder. The Clinical Global Impression (CGI), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI-II), Dissociative Experiences Scale (DES), Internalized Stigma of Mental Illness (ISMI), Childhood Trauma Questionnaire-Short Form (CTQ-SF), Panic Disorder Severity Scale (PDSS) and demographic data were used as measurement tools.

RESULTS: A total of 142 pharmacoresistant patients with panic disorder with or without agoraphobia were admitted for 6-week cognitive behavioral therapy inpatient program in psychotherapeutic department between November 2015 and July 2019. One hundred and five inpatients (33 males and 72 females) with mean age 37.8 + 12.1 years were included in the study. Sixty-nine patients suffer from additional comorbid anxiety disorder and 43 had comorbid personality disorder.

Patients with comorbid personality disorder had earlier onset of the disorder, were more depressed (BDI-II), dissociated (DES; DES-T), suffered from higher self-stigma and experienced more adverse events in childhood (CTQ-total), especially higher emotional abuse and emotional neglect. According to a regression analysis, the level of dissociation and pathological dissociation were explained mostly by early onset of the disorder, social withdrawal and severity of anxiety symptoms. The severity of self-stigma was significantly explained by emotional neglect in childhood and 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: Higher rate of aversive childhood events, level of dissociation, and level of self-stigma are associated with earlier onset of the disorder. Patients with comorbid personality have earlier onset of the disorder, were more depressed, dissociated, self-stigmatized and experienced more adverse events in childhood, especially higher emotional abuse and emotional neglect.

INTRODUCTION

Panic disorder (PD) is characterized by recurring unexpected panic attacks accompanied by considerable physical, cognitive and emotional symptoms (Jacobi *et al.* 2004; Kessler *et al.* 2006; Woodward *et al.* 2009). PD affects 4-5 % of the general population (Kessler *et al.* 2005).

Adverse childhood experiences

Adverse childhood experiences are quite common and have frequently been associated with poor psychological and physical health in adulthood (Rosenman & Rodgers 2004; Pirkola *et al.* 2005, Kessler *et al.* 2010; Radford *et al.* 2013, Curran *et al.* 2016; Westermair *et al.* 2018). The related distress —such as early parental loss; parental psychopathology; parental physical, verbal, and sexual abuse; and low family income, have been recognized to disturb basic neural and biological processes during development (Nemeroff 2016).

Dissociation

Dissociation is the aptitude to separate specific psychological processes so that they seem to arise autonomously of each other (Spiegel & Spiegel 1987). The basis of dissociation is splitting of feelings, thoughts, emotions, or behaviour from ordinary unified consciousness (Zanarini *et al.* 2000). Spiegel (1994) defined it as "separation of mental events that would ordinarily be processed together – a discontinuity of memory, identity, perception, motor function, or consciousness". Dissociation proved to be the significant psychological characteristic influencing treatment outcomes in anxiety disorders (Watson *et al.* 2006, Prasko *et al.* 2009, Ociskova *et al.* 2015). Dissociation is connected with panic symptoms that happen throughout the traumatic experience (Bryant & Panasetis 2005). It is also connected with the earlier onset of the disorder (Prasko *et al.* 2016). Dissociative experiences are common in individuals with panic disorder (Gulsun *et al.* 2007). The amount of dissociation might be one of the reasons for treatment resistance in patients with panic disorder (Ball *et al.* 1997, Segui *et al.* 2000, Gulsun *et al.* 2007).

Self-stigma

The patients with panic disorder frequently struggle with both the labelling from the others and self-stigma (Prasko *et al.* 2011). Self-stigma is associated with lower adherence to medical procedures (Sirey *et al.* 2001, Padurariu 2011, Kamaradova *et al.* 2016, Cinculova *et al.* 2017). Patients' efforts to avoid stigma can lead to rejection of being mentally ill, delaying or quitting from the treatment (Camp *et al.* 2002). Self-stigma can be the most crucial block seeking for help (Barney *et al.* 2009, Ociskova *et al.* 2015, Cinculova *et al.* 2017). Thus, patients often try to find a somatic explanation for their symptoms and seek for the somatic medicine specialists (Prasko *et al.* 2011). Ociskova *et al.* (2014) showed that self-stigma was associated with the severity of anxiety, depression, and global evaluations of mental state at the start of treatment in individuals with neurotic spectrum disorders. According to some authors, self-stigma increases symptoms of anxiety (Lysaker *et al.* 2010, Drapalski *et al.* 2013). Link *et al.* (1997) also showed that self-stigma predicted severity of depressive symptoms. Self-stigma is also connected with a lower quality of life and negative coping strategies in neurotic spectrum disorders (Holubova *et al.* 2019).

Comorbid personality disorder

Other substantial features associated with the treatment results are comorbidities (Prasko *et al.* 2005, Ociskova *et al.* 2015). Particularly the comorbidity with a personality disorder. Treatment of personality disorders is commonly anticipated to be difficult, requiring significant effort with little success (Prasko *et al.* 2015). These diagnoses always disturb the therapist's conscious or unconscious approach to the patient. Most clinicians believe that the panic disorder in comorbidity with a personality disorder frequently leads to prolonged therapy, has worse prognosis, and increases the treatment costs.

Study objectives and hypotheses

Little is known about the relationship between adverse childhood events, self-stigma, dissociation, comorbid personality disorder and severity of psychopathology in adult patients with panic disorder. According to the theory and results mentioned above, several hypotheses were established:

(1) Patients with panic disorder who have higher scores of adverse events in childhood will report:

Tab. 1. Patients included in study

Variable	Completers – 1st assessment (n=105)
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	53/35/14/3
Partner: no/yes	52/53
Another anxiety disorder: no/yes	77/28
Personality disorder: no/yes	81/24
objCGI	4.3 ± 0.7
PDSS	14.5 ± 4.1
subjCGI	4.5 ± 1.2
BAI	28.3 ± 13.1
BDI	25.0 ± 12.1
DES	18.5 ± 19.5
DES-T	14.7 ± 22.4
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	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)
Anxiolytic index	13.8 ± 14.7 (n=19)
Antipsychotic index	3.3 ± 2.4 (n=6)

BAI, Beck Anxiety Inventory; BDI-II, 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;

(a) earlier onset of the disorder (Safren *et al.* 2002, Pirkola *et al.* 2005, Rutter 2009);
(b) higher self-stigma (Hazel *et al.* 2008; Keyes *et al.* 2012);
(c) higher level of dissociation (Bryant & Panasetis 2005);
(d) higher level of severity of the disorder, higher anxiety and depression.

(2) Patients with higher level of dissociation will present:
(a) earlier onset of the disorder (Prasko *et al.* 2016);
(b) higher self-stigma (Ociskova *et al.* 2015);
(c) higher level of severity of the disorder, anxiety and depressive symptomatology (Ociskova *et al.* 2015).

(3) Patients with higher level of self-stigma will demonstrate:
  (a) earlier onset of the disorder (Ociskova *et al.* 2014);
  (b) higher level of dissociation (Ociskova *et al.* 2015);
  (c) higher level of severity of the disorder, anxiety and depressive symptomatology (Ociskova *et al.* 2015);
  (d) higher proportion of comorbid personality disorder (Grambal *et al.* 2016).
(4) Patients with comorbid personality disorder will have:
  (a) earlier onset of the disorder (Friborg *et al.* 2013, Valero-Solís *et al.* 2018);
  (b) higher self-stigma (Grambal *et al.* 2016);
  (c) higher level dissociation (Prasko *et al.* 2016);
  (d) higher level of aversive childhood experiences (McFarlane *et al.* 2005).

METHOD

Patients

One hundred and five inpatients suffering from pharmacoresistant panic disorder/agoraphobia were included in the study. Patients with panic disorder with or without agoraphobia were admitted for 6-week cognitive behavioral therapy inpatient program in psychotherapeutic department between November 2015 and July 2019. The study was carried out under typical conditions at the inpatient psychotherapeutic department for anxiety, affective and personality disorders. Two independent raters confirmed inclusion and exclusion criteria.

- Inclusion criteria: ICD-10 criteria for panic disorder/agoraphobia; age 18–60 years; non-responders on SSRIs (at least 12 weeks treatment with SSRI);
- Exclusion criteria: current depressive disorder; high suicidal risk; organic psychiatric disorder; psychotic disorder current or in history; current substance abuse or dependence; serious somatic disease

Measurements

After admission, the subjects were assessed during the first two days of hospitalization. The assessment was carried out using rating scales and questionnaires:

- **CGI** (Guy 2000) – Clinical Global Impression is an overall assessment of the severity of psychopathology. The basis of assessment is a comprehensive evaluation of the severity of the disorder by the physician (objCGI) at the time of assessment, relative to the clinician´s experience with the patients who have the same diagnosis. The second one is a self-evaluation done by patients (subjCGI).
- **BAI** (Beck *et al.* 1988) – Beck Anxiety Inventory consists of 21 self-administered items based on a four-point Likert scale in which patients choose, which of the described anxiety symptoms they perceived in the last week. The Czech version of the inventory is comparable to the original form in terms of its 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, which of the described depressive symptoms they perceived in the last week. The Czech version of the inventory is equivalent to the original text in terms of its test-retest reliability, validity and factor structure (Ociskova *et al.* 2017).
- **DES** (Carlson *et al.* 1991) - Dissociative Experiences Scale is a self-administered 28-item inventory to indicate how often they experience the symptoms of dissociation (in the percentage of the time). 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 (DES-T) comprises of 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 with statements and a four-point scale measuring a level of an agreement with them. The scale focuses on five elements of internalized stigma – Alienation, Stereotype endorsement, Perceived discrimination, Social withdrawal, and Resistance to stigma. The scale was standardized in Czech by Ociskova *et al.* (2014a).
- **CTQ** (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. Bernstein & Fink (1998) described good internal consistency and test-retest reliability of the questionnaire. The Czech version of the questionnaire is equivalent to the original text in terms of its test-retest reliability, validity and factor structure (Kascaková *et al.* 2018).
- **PDSS** (Shear *et al.* 1997) – The severity of specific panic/agoraphobic symptomatology was objectively assessed using Panic Disorder Severity Scale (Furukawa *et al.* 2009). The items evaluate the occurrence of panic attacks, distress produced by attacks, anticipatory anxiety, agoraphobic fear/avoidance, panic-related sensation fear/avoidance, and work and social impairment (Shear *et al.* 1997).
- **Demographic data**, including sex, age, age of the onset of the disorder, duration of the disorder, and the number of psychiatric hospitalizations, employment status, pension income, education, the overall time of attending the outpatient department, current medication, were obtained in an interview and using Demographic questionnaire.

Treatment

Pharmacotherapy was variable because the patient used antidepressants at least three months before study enrolment prescribed by his general practitioner or outpatient psychiatrist. In order to compare antidepressants

Tab. 2. Differences according to sex, education, job and partnership

Variable	Men (n=33)	Women (n=72)	Sign.	Education lower (n=54)	Education higher (n=51)	Sign.	No employed (n=47)	Employed (n=58)	Sign.	Without partner (n=52)	With partner (n=53)	Sign.
Age	37.4 ± 12.0	38.0 ± 12.2	ns	37.0 ± 12.8	38.6 ± 11.4	ns	36.6 + 14.5	38.8 + 9.9	ns	32.9 ± 10.1	42.6 ± 12.1	**0.001**
Disorder onset	28.5 ± 12.3	27.3 ± 12.7	ns	27.9 ± 12.5	27.4 ± 12.7	ns	24.4 ± 12.0	30.3 ± 12.4	**0.05**	24.4 ± 10.3	30.8 ± 13.7	**0.01**
Disorder duration	8.9 ± 8.8	10.5 ± 10.3	ns	8.8 ± 8.8	11.2 ± 10.7	ns	11.7 ± 10.5	8.6 ± 9.1	ns	8.3 ± 9.1	12.6 ± 10.3	ns
objCGI	4.1 ± 0.8	4.4 ± 0.7	**0.05**	4.3 ± 0.7	4.3 ± 0.8	ns	4.4 ± 0.7	4.2 ± 0.7	ns	4.3 ± 0.7	4.3 ± 0.7	ns
PDSS	14.6 ± 4.0	14.4 ± 4.2	ns	14.2 ± 4.0	14.8 ± 4.2	ns	14.2 ± 4.0	14.7 ± 4.2	ns	14.2 ± 4.2	14.7 ± 4.0	ns
subjCGI-S	4.7 ± 1.2	4.5 ± 1.2	ns	4.5 ± 1.1	4.5 ± 1.3	ns	4.4 ± 1.1	4.6 ± 1.2	ns	4.6 ± 1.2	4.5 ± 1.1	ns
BAI	27.7 ± 12.5	28.5 ± 13.4	ns	27.6 ± 12.1	28.9 ± 14.1	ns	28.2 ± 13.2	28.3 ± 13.1	ns	27.7 ± 13.5	28.8 ± 12.7	ns
BDI	22.2 ± 11.3	26.3 ± 12.3	ns	24.9 ± 12.2	25.2 ± 12.1	ns	24.3 ± 13.9	25.7 ± 11.4	ns	24.6 ± 12.8	25.5 ± 11.4	ns
DES	19.4 ± 20.5	18.0 ± 19.2	ns	15.8 ± 17.9	21.1 ± 21.0	ns	20.1 ± 19.5	17.0 ± 19.6	ns	19.7 ± 17.4	17.2 ± 21.6	ns
DES-T	13.0 ± 14.9	15.6 ± 25.4	ns	12.0 ± 17.7	17.6 ± 27.0	ns	16.7 ± 27.3	13.2 ± 18.0	ns	15.1 ± 16.4	14.4 ± 27.4	ns
CTQ-Total	44.3 ± 14.9	52.3 ± 18.9	**0.05**	47.0 ± 14.7	52.8 ± 20.8	ns	52.6 ± 17.8	47.5 ± 18.0	ns	47.4 ± 16.9	52.2 ± 19.0	ns
Emotional abuse	9.8 ± 5.3	12.0 ± 5.7	ns	10.9 ± 5.1	11.8 ± 6.2	ns	12.0 ± 5.7	10.8 ± 5.6	ns	11.0 ± 5.8	11.7 ± 5.4	ns
Psychical abuse	7.7 ± 3.5	8.2 ± 4.6	ns	6.7 ± 2.9	9.4 ± 5.1	**0.001**	8.5 ± 4.9	7.6 ± 3.7	ns	7.8 ± 3.9	8.3 ± 4.7	ns
Sexual abuse	5.4 ± 1.9	6.8 ± 3.7	**0.05**	6.0 ± 2.2	6.8 ± 4.2	ns	6.8 ± 2.9	6.1 ± 3.6	ns	6.0 ± 2.4	6.8 ± 4.0	ns
Emotional neglect	13.6 ± 5.3	15.7 ± 5.6	ns	14.9 ± 5.0	15.2 ± 6.1	ns	15.9 ± 5.4	14.3 ± 5.7	ns	14.3 ± 5.6	15.8 ± 5.5	ns
Physical neglect	7.6 ± 2.4	9.7 ± 3.9	**0.05**	8.6 ± 3.1	9.6 ± 4.1	ns	9.4 ± 3.6	8.8 ± 3.7	ns	8.5 ± 3.5	9.6 ± 3.7	ns
ISMI-total	59.6 ± 12.8	63.1 ± 13.3	ns	60.9 ± 13.2	63.2 ± 13.2	ns	62.5 ± 13.4	61.6 ± 13.1	ns	60.3 ± 14.3	63.6 ± 11.9	ns
Alienation	13.5 ± 3.9	14.9 ± 4.1	ns	14.5 ± 4.1	14.4 ± 4.1	ns	14.5 ± 4.4	14.4 ± 3.9	ns	14.1 ± 4.4	14.8 ± 3.8	ns
Stereotype endorsement	12.7 ± 3.4	13.5 ± 3.7	ns	13.0 ± 3.5	13.5 ± 3.7	ns	13.3 ± 3.5	13.3 ± 3.7	ns	12.7 ± 3.9	13.8 ± 3.3	ns
Perceived discrimination	9,4 ± 3.1	10.1 ± 3.2	ns	9.6 ± 2.9	10.2 ± 3.3	ns	9.9 ± 3.4	9.8 ± 2.9	ns	9.6 ± 3.4	10.1 ± 2.9	ns
Social withdrawal	12.8 ± 3.4	13.7 ± 3.6	ns	13.1 ± 3.6	13.8 ± 3.5	ns	13.2 ± 3.5	13.6 ± 3.6	ns	12.8 ± 3.6	14.0 ± 3.4	ns
Stigma resistance	11.2 ± 2.4	10.9 ± 2.0	ns	10.7 ± 2.6	11.3 ± 2.0	ns	11.6 ± 2.2	10.5 ± 2.0	**0.05**	11.1 ± 2.4	10.9 ± 1.9	ns

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 %, mean day dosage=33.2 + 20.9 mg of paroxetine equivalent) were the most common medications of the patients, followed by anxiolytics (n=19; 18.1 %; mean day dosage = 13.8 + 14.6 mg of diazepam equivalent).

Statistic

Patient's demographical, clinical and psychological data were examined using descriptive statistics. The distribution of the data, means and standard deviations were defined. Normal distributions of the variables were analysed using the Shapiro-Wilk W test. The chi-square tests were used for the categorical variables. Relationships between specific data sets (demographic data, scores of questionnaires and scores of rating scales) were calculated using correlation coefficients (Pearson or Spearman, according to data distribution) and linear regression. Regression analysis was used to determine the significance of correlations of particular 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 informed consent before incoming to the study after the nature of the procedures had been fully explained. The local ethics committee of University Hospital Olomouc approved this project.

RESULTS

Demographic variables

A total of 142 psychopharmacological resistant patients with panic disorder with or without agoraphobia were admitted for 6-week cognitive behavioral therapy inpatient program in psychotherapeutic department between November 2015 and July 2019. (Table 1). 110 patients entered the study. 32 patients admitted to the department were not interested in participation in the study. Data of another 5 (4.5 %) participants were not used because they did not fulfil more than half of questionnaires. Eventually information of 105 patients have been statistically examined (Table 1).

When looking for differences between the main demographic factors, there were (Table 2):

- statistically significant higher scores in objCGI, CTQ-total, Sexual abuse, Physical neglect in women than in men;
- the statistically significant higher scores in Physical abuse in patients with higher education (secondary school or university group) than in patients with lower education (primary school or vocational training);
- the unemployed patients showed significantly lower age of the onset of the disorder and lower score in Stigma resistance than employed patients;
- statistically significant higher age and age of the disorder onset was shown in patients with a partner than in patients without a partner.

Comorbidities

The patients showed various comorbidities with anxiety and personality disorders. The 69 patients suffered with additional comorbid anxiety disorder (65.7 %). The most frequent comorbid anxiety disorder was agoraphobia (n=25; 23.8%), GAD (n=19; 18.1 %), and social phobia (n=8; 7.6 %). Forty-three patients suffer with comorbid personality disorder (41.0 %). The most frequent comorbid personality disorder was borderline personality disorder (n=17; 16.2 %), and mixed personality disorder (n=12; 11.4%). The differences between patient with and without anxiety disorder comorbidity were insignificant with exception of higher anxiety scores in BAI in subgroup without comorbidities (Table 3), compared to statistically significant differences between patients with or without comorbid personality disorder (Table 3). Patients with comorbid personality disorder were significantly younger, had earlier onset of the disorder, were more depressed (BDI-II), dissociated (DES; DES-T), suffered from higher self-stigma (ISMI, with all subscores except Stigma resistance) and experienced more adverse events in childhood (CTQ-total), especially higher emotional abuse and emotional neglect (Table 3).

The correlation of the level of psychopathology, onset of the disorder, level of dissociation, self-stigma and adverse childhood experiences

The onset of the disorder negatively correlated with the CTQ total, subjCGI, BAI, BDI, DES, DES-T and ISMI (Table 4). The earlier development of the disorder is linked to the higher score in childhood adverse events, the higher level of dissociation and pathological dissociation, and the higher level of self-stigma (Table 4).

The level of dissociation measured by DES and DES-T was negatively correlated with the onset of the disorder and positively correlated with the disorder duration, subjective evaluation of the severity of the disorder (subj CGI), severity of anxiety symptoms (BAI) and depressive symptoms (BDI-II) (Table 4).

The level of self-stigma (ISMI-total) positively correlated with length of the disorder, subjCGI, the severity of anxiety symptoms (BAI) , the severity of depressive symptoms (BDI-II), level of dissociation (DES), level of pathological dissociation (DES-T), the antidepressant dose (paroxetine equivalent), negatively with disorder onset (Table 4).

Tab. 3. Differences according to the comorbidities; another anxiety disorder, mood disorder, personality disorder

Variable	Heredity			Comorbid anxiety disorder			Comorbid personality disorder		
	No (n=39)	Yes (n=66)	Sign.	No (n=36)	Yes (n=69)	Sign.	No (n=62)	Yes (n=43)	Sign.
Age	38.6 ± 13.2	37.3 ± 11.5	ns	40.7 ± 13.8	36.3 ± 10.9	ns	41.6 ± 12.1	32.3 ± 10.2	**0.001**
Disorder onset	29.3 ± 14.0	26.7 ± 11.6	ns	30.1 ± 11.4	26.3 ± 12.9	ns	31.9 ± 12.5	21.6 ± 9.9	**0.001**
Disorder duration	9.1 ± 9.3	10.5 ± 10.1	ns	10.2 ± 11.7	9.9 ± 8.8	ns	9.6 ± 10.4	10.5 + 9.1	ns
objCGI	4.3 ± 0.7	4.3 ± 0.7	ns	4.2 ± 0.7	4.3 ± 0.7	ns	4.2 ± 0.7	4.3 ± 0.7	ns
PDSS	15.4 ± 3.8	13.9 ± 4.2	ns	14.3 ± 4.3	14.6 ± 4.0	ns	15.1 ± 3.9	13.5 ± 4.2	ns (p=0.052)
subjCGI-S	4.3 ± 1.3	4.7 ± 1.1	ns	4.5 ± 1.0	4.6 ± 1.2	ns	4.4 ± 1.2	4.7 ± 1.1	Ns
BAI	25.6 ± 14.0	29.8 ± 12.3	ns	32.3 ± 12.4	26.2 ± 13.0	**0.05**	26.9 ± 13.4	30.3 ± 12.5	ns
BDII	21.8 ± 11.6	26.9 ± 12.1	**0.05**	26.0 ± 13.0	24.5 ± 13.3	ns	21.1 ± 10.9	30.7 ± 11.7	**0.0001**
DES	18.0 ± 20.0	18.7 ± 19.5	ns	14.9 ± 13.4	20.2 ± 21.9	ns	15.1 ± 19.0	23.2 ± 19.6	**0.05**
DES-T	13.4 ± 19.7	15.5 ± 24.1	ns	11.3 ± 12.0	16.6 ± 26.4	ns	10.3 ± 15.8	21.3 ± 28.9	**0.05**
CTQ-Total	45.0 ± 17.2	52.7 ± 18.1	**0.05**	49.5 ± 15.8	50.0 ± 19.2	ns	46.00± 17.5	55.3 ± 17.6	**0.01**
Emotional abuse	9.9 ± 5.1	12.2 ± 5.8	**0.05**	11.3 ± 5.1	11.4 ± 5.9	ns	10.0 ± 4.9	13.3 ± 6.0	**0.005**
Psychical abuse	7.1 ± 3.4	8.5 ± 4.6	ns	7.6 ± 3.8	8.2 ± 4.6	ns	7.4 ± 3.5	8.9 ± 6.1	ns
Sexual abuse	6.3 ± 3.4	6.5 ± 3.3	ns	6.1 ± 2.0	6.5 ± 3.9	ns	6.2 ± 3.6	6.7 ± 2.9	ns
Emotional neglect	13.2 ± 6.0	16.1 ± 5.1	**0.05**	15.4 ± 4.9	14.8 ± 5.9	ns	13.8 ± 5.8	16.7 ± 4.8	**0.01**
Physical neglect	8.5 ± 3.3	9.4 ± 3.8	ns	9.0 ± 3.7	9.1 ± 3.6	ns	8.7 ± 3.8	9.6 ± 3.3	ns
ISMI-total	61.8 ± 12.0	62.1 ± 14.0	ns	62.1 ± 12.2	61.9 ± 13.8	ns	57.9 ± 11.7	67.9 ± 13.2	**0.001**
Alienation	14.4 ± 4.1	14.5 ± 4.1	ns	14.5 ± 3.8	14.4 ± 4.3	ns	13.5 ± 3.8	15.8 ± 4.1	**0.005**
Stereotype endorsement	12.8 ± 3.5	13.5 + 3.7	ns	13.2 ± 3.3	13.3 ± 3.8	ns	12.4 ± 3.4	14.5 ± 3.6	**0.005**
Perceived discrimination	9.8 ± 3.1	9.9 ± 3.2	ns	10.3 ± 3.2	9.6 ± 3.1	ns	9.0 ± 2.8	11.1 ± 3.2	**0.001**
Social withdrawal	13.6 ± 3.5	13.3 ± 3.6	ns	13.3 ± 2.9	13.5 ± 3.8	ns	12.3 ± 3.3	15.1 ± 3.3	**0.001**
Stigma resistance	11.1 ± 1.9	10.9 ± 2.3	ns	10.8 ± 2.1	11.1 ± 2.2	ns	10.7 ± 1.9	11.3 ± 2.5	ns

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

	Disorder onset	DES	DES-T	ISMI total	TCQ- total
Disorder onset		**-0.33**^{S***}	**-0.27** ^{S**}	**-0.23** ^{P*}	**-0.28** ^{P**}
Disorder duration	**-0.49**^{S***}	**0.23** ^{S*}	**0.21** ^{S*}	**0.22** ^{S*}	**0.35** ^{S***}
objCGI	-0.08	0.11	0.11	0.19	0.11
PDSS	0.07	0.05	0.05	-0.06	0.09
subjCGI	**-0.32** ^{S***}	**0.37**^{S***}	**0.38**^{S***}	**0.30**^{S**}	0.16
BAI	-0.19	**0.52**^{S***}	**0.52**^{S***}	**0.29**^{P**}	0.17
BDI-II	**-0.25**^{P*}	**0.51**^{S***}	**0.49**^{S***}	**0.58**^{P***}	**0.33**^{P***}
DES	**-0.28**^{P***}		**0.87**^{S***}	**0.24** ^{P*}	0.13
DES-T	**-0.29** ^{S**}	**0.87** ^{S***}		**0.33** ^{S**}	0.10
Paroxetine equivalent	0.08	0.21(p=0.051)	0.18	**0.38** ^{S***}	0.20(p=0.056)

* significance of correlation coefficient $p<0.05$; ** significance of correlation coefficient $p<0.01$;
*** significance of correlation coefficient r $p<0.001$, S, Spearman r; P, Pearson r

The total score of the adverse childhood experiences (CTQ-total) statistically positively correlated with the duration of the disorder, ISMI-total and BDI-II and negatively with the age of the onset of the disorder (Table 4). The adverse childhood experiences also positively correlate with BDI-II scores, which means that patients with panic disorder with higher level of adverse events in childhood have more depressive symptoms (Table 5).

Especially emotional abuse and neglect in childhood negatively correlated with the onset of the disorder, positively correlate with depressive symptoms (BDI-II), self-stigma (ISMI-total) and in case of emotional abuse also with the severity of anxiety symptoms (BAI). Also, the physical neglect was positively correlated with BDI-II and self-stigma (Table 5).

The level of self-stigma (ISMI-total) positively correlated with BAI, BDI-II, DES, DES-T and TCQ-total and significantly negatively with disorder onset. Domains of self-stigma (Alienation, Stereotype endorsement, Perceived discrimination and Social) mirrored mostly the ISMI- total (Table 6). Stigma resistance does not significantly correlate with any of measures (Table 6).

Multiple regression analysis of significant factors

Backward stepwise multiple regression analyses were performed to detect the most significant components influencing the levels of dissociation, the level of pathological dissociation, and self-stigma. The independent variables were regressors, which were significantly associated with the dependent variables in correlation analysis (Table 7).

The resulting models explained 24.7% of DES, 26.8% of DES-T, 38.6% of ISMI-total, as dependent variables with statistically significance (all: $p < 0.001$) (Table 7).

DISCUSSION

Our study examines more precisely how adverse childhood experiences, dissociation and the self-stigma are interrelated and how they relate to the severity of psy-

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

	Disorder onset	objCGI	PDSS	subjCGI	BAI	BDI-II	DES	DES-T	ISMI total
CTQ total	**-0.28** ^{P**}	0.11	-0.11	0.16	0.17	**0.33**^{P***}	0.10	0.11	**0.31** ^{P**}
Emotional abuse	**-0.38** ^{S***}	0.10	-0.17	0.19	**0.23**^{S*}	**0.38** ^{S***}	0.14	0.13	**0.31** ^{S**}
Physical abuse	-0.08	-0.01	-0.10	0.07	0.12	0.14	0.04	0.09	0.11
Sexual abuse	-0.17	0.15	-0.11	0.03	0.13	0.11	0.06	0.05	0.13
Emotional neglect	**-0.22** ^{P*}	0.11	-0.09	0.12	0.13	**0.32** ^{P***}	0.08	0.09	**0.39**^{P***}
Physical neglect	-0.13	0.09	-0.02	0.01	0.05	**0.23** ^{P*}	0.04	0.04	**0.25**^{P*}

* significance of correlation coefficient $p<0.05$; ** significance of correlation coefficient $p<0.01$;
*** significance of correlation coefficient r $p<0.001$; S, Spearman r; P, Pearson r

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

	Disorder onset	objCGI	PDSS-1	subjCGI	BAI	BDI-II	DES	DES-T	TCQ total
ISMI- total	**-0.24** P*	0.18	-0.04	**0.30** P**	**0.29** P**	**0.58** P***	**0.24** S*	**0.33** S***	**0.31**P**
Alienation	**-0.24** P**	0.18	-0.01	**0.25** P**	**0.23** P*	**0.52**3P***	0,11	**0.27** S**	**0.31**P**
Stereotype endorsement	-0.13	0.14	-0.07	**0.28**P**	**0.27** P**	**0.48** P***	**0.24** S*	**0.31** S**	**0.29**P**
Perceived discrimination	**-0.28**P*	0.12	-0.01	**0.19**P*	**0.25** P*	**0.40** P***	**0.25** S*	**0.33** S***	**0.31**P**
Social withdrawal	-0.16	0.13	-0.09	**0.23**P*	**0.28** P**	**0.58**P***	**0.30** S**	**0.35** S***	**0.23**P*
Stigma resistance	-0.16	0.19	0.04	0.16	0.08	0.17	-0.03	0.04	-0.04

* significance of correlation coefficient $p<0.05$; ** significance of correlation coefficient $p<0.01$;
*** significance of correlation coefficient r $p<0.001$, S, Spearman r; P, Pearson r

chopathology in adult patients with pharmacoresistant panic disorder with or without agoraphobia. The mean age of the patients, the mean age of the disorder onset and disorder duration are comparable with the demographic parameters in other studies looking for the self-stigma, or dissociation and therapeutic efficacy in anxiety spectrum disorders (Ociskova *et al.* 2015, Grambal *et al.* 2016, Cinculova *et al.* 2017). When comparing the mean scores of DES and ISMI in studies of neurotic spectrum disorders, the findings have shown similar figures (Prasko *et al.* 2011b, Pastucha *et al.* 2009a, Pastucha *et al.* 2009b, Ociskova *et al.* 2015, Prasko *et al.* 2015, Ociskova *et al.* 2016, Prasko *et al.* 2016, Grambal *et al.* 2016, Cinculova *et al.* 2017, Holubova *et al.* 2019).

Childhood adversities

This study found that patients with higher level of adverse experiences in childhood develop panic disorder earlier in their life and have higher self-stigma. In analysis of each childhood adverse experiences subscales, we found that:

- Emotional abuse correlates positively with general anxiety (BAI), depresivity (BDI –II), the level of self-stigma, and negatively with disorder onset. These correlations are mild to moderate. Nevertheless, this factor did not pass the regression analysis to explain level of dissociation, pathological dissociation, or self-stigma.
- Physical and sexual abuse were not correlated with any of the studied measurements.

Tab. 7. Multiple regression analyses of DES, DES-T and ISMI as dependent factors

Dependent variable: DES	**Model**	**Regressors**	**B**	**Std. Error**	**β**	**t**	**Sign.**
Regressors: disorder onset, length, comorbid personality disorder, ISMI-total, stereotype endorsement, perceived discrimination, social withdrawal, subjCGI, BAI, BDI	8	Disorder onset	-0.303	0.137	-0.193	-2.210	**0.029**
		Social withdrawal	1.228	0.494	0.223	2.487	**0.016**
		BAI	0.487	0.135	0.324	3.598	**0.001**
		ANOVA: F= 12.174 df=103; $p<0.001$ Adjusted r squared = 0.247					
Dependent variable: DES-T	**Model**	**Regressors**	**B**	**Std. Error**	**β**	**t**	**Sign.**
Regressors: disorder onset, comorbid personality disorder, ISMI-total, alienation, stereotype endorsement, perceived discrimination, social withdrawal, subjCGI, BAI, BDI-II	7	Disorder onset	-0.305	0.162	-0.169	-1.882	0.063
		Social withdrawal	1.823	0.562	0.287	3.247	**0.002**
		SubjCGI	-3.674	2.070	-0.190	-1.775	0.079
		BAI	0.727	0.183	0.417	3.969	**0.000**
		ANOVA: F= 10.408 df=103; $p<0.001$ Adjusted r squared = 0.268					
Dependent variable: ISMI-total	**Model**	**Regressors**	**B**	**Std. Error**	**β**	**t**	**Sign.**
Regressors: disorder onset, length, comorbid personality disorder, DES, DES-T, TPQ-total, Emotional abuse, Emotional neglect, Physical neglect, SubjCGI, BAI, BDI, Paroxetine equivalent	10	DES-T	0.116	0.068	0.162	1.709	0.091
		Emotional neglect	0.471	0.208	0.204	2.267	**0.026**
		BDI-II	0.383	0.109	0.371	3.512	**0.001**
		Paroxetine equivalent	0.107	0.057	0.169	1.887	0.063
		ANOVA: F= 14.857 df=88; $p<0.001$ Adjusted r squared = 0.386					

- Emotional neglect negatively correlated with disorder onset. Patients reporting higher score in Emotional neglect in childhood developed the panic disorder earlier in their life. These patients also had higher depression score and higher self-stigma at the time of measurement. These correlations are mild to moderate. In regression analysis the emotional neglect was significant regressor for ISMI-total, but nor for explaining the level of dissociation or pathological dissociation.
- Physical neglect correlated with the level of depresivity and with self-stigma. Nevertheless, in regression analysis this type of abuse was not powerful enough to reach statistical significance to explain level of dissociation, pathological dissociation, or self-stigma.

Our findings are in corellation with study by Lochner *et al.* (2010) who found out that emotional abuse in childhood play predictive role in both social anxiety and panic disorder. Also, Asselmann *et al.* (2018) confirm in their study that early childhood adversities increase the risk of developing the panic disorder. They found out that separation/loss events were powerfully connected with panic disorder pathology among persons with higher early childhood adversities.

In our study , in regression analysis, we didn't confirm that emotional abuse, physical abuse, sexual abuse and physical neglect are powerfull factors for the dissociation and self stigma. Only emotional neglect predicted positively level of self-stigma.

Comorbidity with personality disorder

In association with the occurrence of comorbidities our study showed, that patients with comorbid personality disorder have higher mean score of total childhood adversities, emotional abuse and emotional neglect.

These findings show, that higher level of childhood adversities might have stronger connection to the personality comorbidity than to the panic disorder itself.

Self-stigma

Self-stigma is the factor which positively correlated with BAI, BDI-II, DES, DES-T and TCQ-total and significantly negatively with disorder onset. Domains of self-stigma (Alienation, Stereotype endorsement, Perceived discrimination and Social) mirrored mostly the ISMI- total. Likewise, Ociskova *et al.* (2014b) recognised a significant association between the severity of anxiety symptoms and self-stigma in a mixed group of anxiety disorder inpatients. Cinculova *et al.* (2017) found a significant correlation between self-stigma and subjective assessment of the severity of the disorder in a mixed group of anxiety disorder outpatients. To the contrary of presented study, objective scales of psychopathology assessment (objCGI, PDSS) did not correlate significantly with a total score of self-stigma. After performing a regression analysis, self-stigma was predicted only by emotional neglect and depresivity, other factors were not powerful enough to pass the regression analysis and reach statistical significance.

Dissociation

The level of dissociation (DES / DES-T) was positively correlated with the early onset of the disorder, subjective evaluated of the seriousness of the disorder (subj CGI), severity of anxiety symptoms (BAI) and depressive symptoms (BDI-II), and with the disorder duration. (Table 4). In regression analysis only social withdrawal and level of anxiety reached the statistical significance. The previous study of Ociskova *et al.* (2015) on a broader population of anxiety and mood spectrum disorders presented results that were partially concordant and partially divergent - DES scores were highly negatively correlated with objCGI and the degree of dissociation affects positively the subjective measurements of psychopathology; BAI, BDI-II. Different results could be explained be the different population of patients.

Response to the hypotheses

Regarding the hypotheses proposed at the beginning of our study, we were able to state:

(1 a) *Patients with panic disorder who have higher score of adverse events in childhood will report the earlier onset of the disorder.*

The hypothesis was confirmed for CTQ total and subscales Emotional abuse and Emotional neglect.

(1 b) *Patients with panic disorder who have higher score of adverse events in childhood will report higher self-stigma.*

This hypothesis is confirmed for ISMI total and also for domains of ISMI: Alienation, Stereotype endorsement, Perceived discrimination, Social withdrawal, but not for Stigma resistance. The correlation analysis does not show the direction of causality, but very probably the childhood adversities come first in the life, therefore it is highly likely, that early traumatization influences latter self-stigma in individuals with panic disorder. From the subscales of CTQ, there was statistically significant correlations between ISMI total and Emotional abuse, Emotional neglect and Physical neglect.

(1 c) *Patients with panic disorder who have higher score of adverse events in childhood will report higher dissociation.*

This hypothesis was not confirmed. Both CTQ total and all domains of CTQ had no significant correlation with DES or DES-T. This result is surprising because theoretically it is assumed dissociation is learned by experiencing adversities during childhood (Bryant & Panasetis 2005), and additionally the patients with the panic disorder show several dissociative symptoms (Cox & Swinson 2002; Hunter *et al.* 2004, Pastucha *et al.* 2009a). Possible explanation for this discrepancy could be the low level of dissociative symptoms in our panic disorder patients, which was far from dissociative symptoms of borderline personality or dissociative disorder patients. (Pastucha *et al.* 2009a, Pastucha *et al.* 2009b, Ociskova *et al.* 2015). The insufficient number

of patients with adverse childhood experiences may limit our outcomes.

(1 d) *Patients with panic disorder who have higher score of adverse events in childhood will report higher severity of the disorder, higher anxiety and depression.*

This hypothesis was not confirmed in subjective evaluation of the severity of the disorder (subjCGI-1) but was established by the significant positive correlation of TPQ total and BDI-II, of subscale Emotional abuse with BAI and BDI-II, Emotional neglect with BDI-II, and Physical neglect also with BDI-II. The direction of causality is difficult to recognize because of the cross-sectional character of data used in these correlations. Hypothetically the adversities in childhood precede the depressive or anxiety symptoms in adulthood, but the current symptoms may also influence reminiscence of the childhood.

(2 a) *Patients with higher dissociation will show an earlier onset of the disorder.*

This hypothesis was confirmed both for DES and for pathological DES-T. Patients with higher dissociation showed earlier onset of the disorder. The direction of the relationship is not clear because of the cross-sectional character of analysed data. Individuals who dissociated firstly could develop earlier onset of the disorder, but the other way is also possible - individuals who developed disorder earlier could have developed higher dissociation afterwards. Only a long-term prospective study on a population basis may answer these questions.

(2 b) *Patients with higher level of dissociation will show higher self-stigma.*

The total score of ISMI correlated significantly with dissociation and pathological dissociation (DES and DES-T). The ISMI domains Stereotype endorsement, Perceived discrimination, and Social withdrawal correlated with the DES and DES-T. Alienation correlated with DES-T. Only Stigma resistance did not correlate with DES or DES-T, and Alienation did not correlate with DES. From the results it is obvious that patients with more dissociative symptoms stigmatize themselves more.

The connection of the severity of dissociative symptoms and self-stigmatisation is clear, However, again the direction of causality is hard to confirm because of cross-sectional data of this correlation. It is also possible that patients with higher severity of self-stigma are in such distress, that they start to dissociate. There is also the possibility of repeated increasing of both because of feedback interaction. The longitudinal studies in future need to respond to these questions.

(2 c) *Patients with higher dissociation will show higher severity of the disorder, higher anxiety and depression.*

This hypothesis was confirmed. The subjective severity of anxiety and depressive symptoms significantly positively correlates with both general and pathological type of dissociation measured by DES and DES-T. The same results were reported by studies in patients with anxiety disorders in the past (Pastucha *et al.* 2009a, Ociskova *et al.* 2015, Ociskova *et al.* 2016). Nevertheless, when looking for the objective measurements, both objCGI-1 and PDSS-1 did not correlate with DES or DES-T. It seems that a higher degree of dissociation may contribute to a more severe perception of the symptoms of panic disorder, but only in subjective evaluation. According clinical evaluations the patient's symptoms is not affected by the patient's self-stigma.

(3 a) *Patients with higher self-stigma will show an earlier onset of the disorder.*

The hypothesis was confirmed in the correlation between ISMI-total and both DES and DES-T. Patients who developed disorder earlier display higher self-stigma. This association is confirmed for DES and all domains of ISMI except Alienation and Stigma resistance, and DES-T and all domains of ISMI except Stigma resistance.

(3 b) *Patients with higher self-stigma will show higher level of dissociation*

This hypothesis was confirmed. The findings are in accordance with the study of Ociskova *et al.* (2015). It is hard to say, if the first is dissociation or the self-stigma. Since level of dissociation is negatively correlated with earlier disorder onset it could be speculated that the dissociation was preceding. Nevertheless, dissociation does not correlate with early adverse events which did not confirm the theoretical assumption, that dissociation was developed because of early adversities in this group of patients.

(3 c) *Patients with higher self-stigma will show higher severity of the disorder, higher anxiety and depression.*

Patients with a higher level of self-stigma show higher subjective severity of the disorder, general anxiety, and depresivity. This is also true for all subscales of ISMI except Stigma resistance. Many studies showed the same results (Ociskova *et al.* 2014, Ociskova *et al.* 2015, Ociskova *et al.* 2018, Grambal *et al.* 2016, Prasko *et al.* 2016). The cross-sectional design of the study limits us in evaluating causality. There is a need for longitudinal study, which repeatedly searches for self-stigma in the acute phase of treatment and remission.

However, the hypothesis is not confirmed for primary outcome measures, objective scales (objCGI and PDSS), which do not correlate with ISMI-total and most of the domains of ISMI. We have discussed above that self-stigma could influence the subjective perception of anxiety and depressive symptoms, while it is unlikely to be a to part of objective clinician evaluation.

(4a) *Patients with comorbid personality disorder will have earlier onset of the disorder.*

The hypothesis was confirmed; patients with comorbid personality disorder developed panic disorder in average nine years earlier than patients without personality disorder.

(4b) *Patients with comorbid personality disorder will have higher self-stigma;*

Self-stigma is significantly higher in patients with comorbid personality disorder than in patients without personality disorder. This difference was shown in four of five subscales of ISMI.

(4c) *Patients with comorbid personality disorder will have higher dissociation.*

This hypothesis was confirmed, the level of dissociation and pathological dissociation were higher in group of patients with comorbid personality disorder than in the group without comorbid personality disorder.

(4d) *Patients with comorbid personality disorder will have higher adverse childhood experiences than patients without comorbid personality disorder.*

The hypothesis was confirmed for total score of aversive experiences in childhood and also for subscale Emotional abuse and Emotional neglect.

Limitations of the study

Our study has substantial limitations that should be considered. First of all, assessment methods for level of symptomatology, childhood adverse events, dissociation and self-stigma, were self-reported. Despite the fact that demographic or clinical data of the patients who dropped out of the study did not differ from those who fully cooperated in the investigation, we may assume that a subset of patients who have significant problems with collaboration, which can be linked to childhood adverse events, self-stigma, or treatment efficacy. Future research should corroborate these questionnaires with clinician-rated instruments. An additional limitation of our investigation is a small sample of individuals, which made impossible the evaluation of different subgroups of panic disorder patients (with and without agoraphobia, with fear of death or madness, etc.) impossible.

CONCLUSION

It has been shown that a higher rate of aversive childhood events, the higher level of dissociation and pathological dissociation, and the higher level of self-stigma are associated with earlier onset of the disorder in patients who have panic disorder with or without agoraphobia. The level of dissociation was explained mostly by early disorder onset, social withdrawal and severity of anxiety symptoms. Patients with comorbid personality disorder were significantly younger, have earlier onset of the disorder, were more depressed, dissociated, suffered from higher self-stigma and experienced more adverse events in childhood, especially higher emotional abuse and emotional neglect.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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