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Impulsivity in drug-naïve panic disorder as related to therapeutic intervention

Impulsywność w zaburzeniu panicznym bez uprzedniego leczenia farmakologicznego a interwencja terapeutyczna

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ABSTRACT

Objectives. Impulsivity is a key feature of several psychiatric disorders. However, the relationship between impulsivity and anxiety disorders is controversial and not well explored. The aim of this study was to compare impulsivity in healthy control and drug-naïve panic disorder patients before and after 8 weeks of therapeutic intervention.
Materials and methods. We examined 21 healthy volunteers and 15 psychotropic drug-naïve outpatients with panic disorder without agoraphobia before and after 8 weeks of treatment with escitalopram or Cognitive Behavioural Therapy (CBT). The severity of Panic Disorder was assessed based on the Panic and Agoraphobia Scale (PAS), CGI (Clinical Global Impression Scale), HADS (Hospital Anxiety and Depression Scale). Impulsivity was evaluated based on the Barratt Impulsiveness Scale, 11th version (BIS-11).
Results. The clinically significant improvement was observed with PAS, CGI and HADS-A in both treatment groups after the therapeutic intervention. That improvement was similar in both groups and both methods had equal efficacy in PD treatment. No statistically significant change in the score of total impulsivity before and after treatment was found regardless of the treatment applied (i.e. escitalopram or CBT).
Conclusions. Future research should be performed to examine the impact of impulsivity on panic disorders outcome. Higher impulsivity seems to be an independent and persistent trait in patients with panic disorder not linked with PD severity.

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KEYWORDS

- impulsivity
- escitalopram
- panic disorder
- BIS-11
- cognitive behavioural therapy
- selective serotonin reuptake inhibitors

SŁOWA KLUCZOWE

- impulsywność
- escitalopram
- zaburzenie paniczne
- BIS-11
- terapia poznawczo-behawioralna
- selektywne inhibitory wychwytu zwrotnego serotoniny

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STRESZCZENIE

Cel pracy. Impulsywność jest dominującą cechą wielu zaburzeń psychicznych. Jednakże związek między impulsywnością a zaburzeniami lękowymi jest kontrowersyjny i niewystarczająco zbadany. Celem badania było porównanie impulsywności u zdrowych osób oraz chorych z zaburzeniem panicznym bez uprzedniego leczenia

farmakologicznego, przed terapią i po ośmiu tygodniach interwencji terapeutycznej.
Materiał i metody. Zbadano 21 zdrowych ochotników oraz 15 ambulatoryjnych pacjentów z zaburzeniem panicznym bez agorafobii, którzy nie byli wcześniej leczeni farmakologicznie, przed leczeniem oraz po ośmiu tygodniach leczenia escitalopramem lub terapią poznawczo-behawioralną (CBT). Nasilenie zaburzenia panicznego oceniano przy użyciu skal: PAS (Skala Oceny Lęku i Agorafobii), CGI (Skala Ogólnej Oceny Klinicznej), HADS (Szpitalna Skala Lęku i Depresji). Impulsywność oceniania była przy użyciu skali BIS-11 (Skala Oceny Impulsywności Barrata – wersja 11).
Wyniki. Statystycznie istotna poprawa stanu klinicznego obserwowana była w skalach PAS, CGI, HADS w obu leczonych grupach pacjentów przed terapią i po interwencji terapeutycznej. Poprawa na podobnym poziomie wystąpiła w obu grupach i obie metody okazały się równie skuteczne w leczeniu zaburzenia panicznego. Nie obserwowano statystycznie znaczącej zmiany całkowitej impulsywności w grupie chorych przed leczeniem i po leczeniu (escitalopram lub CBT). Ograniczenia: Liczba badanych była stosunkowo niewielka. Badanie prowadzono w grupie pacjentów bez agorafobii, bez uprzedniego leczenia farmakologicznego.
Wnioski. Istnieje potrzeba realizacji kolejnych badań oceniających wpływ impulsywności na przebieg zaburzenia panicznego. Podwyższona impulsywność wydaje się niezależną i trwałą cechą, niezwiązaną z ciężkością objawów w grupie pacjentów z zaburzeniem panicznym.

Introduction

Negative effects of Panic Disorder (PD) on social, familial and occupational functioning are similar to those of depression (Park *et al.* 2012).

Impulsivity is a broad and multifaceted construct. There are three dimensions of impulsivity, i.e. motor, attentional and non-planning. Attentional impulsivity is defined as the inability to focus on the ongoing task and cognitive instability. Non-planning impulsivity is seen as the inability to plan and think carefully; it is characterized by orientation towards the present rather than to the future and it includes developed self-control. Motor impulsivity is expressed by acting on the spur of the moment, without inhibition or perseverance (Taylor *et al.* 2008; Vasconcelos *et al.* 2012).

Core features of anxiety disorders, such as behavioural inhibition, harm avoidance, safety-seeking or anxious apprehension (involves excessive worry about potential negative or catastrophic outcomes) may seem inconsistent with conventional 'view' of impulsivity, such as increased risk seeking, acting without forethought and decreased anticipation of the consequences of one's behaviour (Taylor *et al.* 2008; Summerfeldt *et al.* 2004).

The aim of this study was to evaluate impulsivity in patients with panic disorder before and after 8-week-long treatment with escitalopram or CBT. We hypothesized that drug-naïve patients with PD before treatment would exhibit higher impulsivity than after treatment identified as 'state-dependent impulsivity'. However, those patients might still present high residual impulsivity, even after remission, which could be identified as 'trait-dependent impulsivity'.

Methods

We examined 21 psychotropic drug-naïve outpatients with panic disorder. Out of the 21 patients included in the study, in 15 patients treatment was administrated. Therefore, the data presented refer to the 15 patients who completed the study. It was part of a bigger project, involving 21 patients and 20 healthy volunteers.

The inclusion criteria for the patients were 18–60 years of age and the diagnosis of Panic Disorder without agoraphobia, based on SCID-I (DSM-IV-TR) (First *et al.* 2002). The exclusion criteria were the presence of any chronic somatic illness and any positive history of psychotropic medication, including dietary supplements. Patients had no current diagnosis of substance abuse or other lifetime concomitant psychiatric disorders. Pregnant and breastfeeding woman were excluded. None of them was overweight. Thus, the protocol excluded individuals with any comorbidity that might influence the precipitation of panic attacks.

The severity of Panic Disorder was assessed based on the Panic and Agoraphobia Scale (PAS) and CGI (Clinical Global Impression Scale). Impulsivity was evaluated based on the Barratt Impulsiveness Scale, 11th version (BIS-11). Patients were allocated into two groups and received CBT or escitalopram treatment, being re-tested after 8 weeks. Following completion of the protocol, the patients assigned into CBT treatment had 12 sessions with a qualified CBT therapist. The patients assigned to pharmacotherapy started treatment with 5 mg of escitalopram, increasing it to 10 mg/day on day 3. The daily dose of 10 mg was maintained for the next 8 weeks. Patients were assessed by a psychiatrist at 2-week intervals and compliance with escitalopram was monitored.

The study was carried out in accordance with the Declaration of Helsinki and with the approval of the Ethic Research Committee of the Medical University of Gdańsk. For each participant, written consent was obtained.

The statistical analysis was performed using nonparametrical Spearman's rank correlation test. All analyses were conducted with Statistica v.10.0.1011 software. Normally distributed variables were compared using Student's t-test. The Wilcoxon test was used to compare the differences before and after treatment. For all tests $p < 0.05$ was considered statistically significant.

Results

Table 1 shows demographic and clinical variables in healthy controls and in PD patients. The statistically significant improvement of PD severity in PAS [p = 0.0000; 95% CI 15.6 (11.4, 19.9)], BIS-total [p = 0.0398; 95% CI 3.0 (0.2, 5.8)], HADS-A [p = 0.0005; 95% CI 5.1 (2.6, 7.5)], HADS-D [p = 0.018; 95% CI 2.8 (0.5, 4.9)] after treament was observed. The total impulsivity score was significantly higher in PD patients as compared to healthy controls [p < 0.0001; 95% CI 10.8 (6.0, 15.8)].

Table 2 shows the effect of treatment modality with respect to therapeutic approach employed. Regardless of the intervention, no statistically significant changes in PAS, HADS-A, HADS-D before and after the treatment in panic disorder patients were observed. However, BIS-total score was significantly reduced after the treatment in the subgroup receiving treatment with escitalopram [p = 0.014; 95% CI 5.8 (1.5, 10.0)].

Table 1 Demographic and psychometric characteristics of the study groups

		Controls	Panic disorder		Mean difference (CI 95%) p@
			before treatment	after treatment	
N		20	15		
Women	%	70	60		
Age (years)	Median (IQR)	31 (28, 38.5)	32.0 (27.0, 35.0)		
BMI	Mean (95% CI)	23.7 (21.9, 25.5)	23.4 (21.0, 25.8)		
WHR	Mean (95% CI)	0.81 (0.77, 0.85)	0.84 (0.78, 0.90)		
CGI-S	Median (IQR)	-	4 (4.5)	3 (3.4)	
CGI-I	Median (IQR)	-	-	2 (2, 3)	
PAS	Mean (95% CI)	-	26.5 (22.9, 30,1)	10.9 (7.0, 14.7)	15.6 (11.4, 19.9) 0.0000
HADS-A	Mean (95% CI)	2.7 (1.7, 3.7)	12.1 * (10.2, 14.0)	7.0 ### (5.0, 9.0)	5.1 (2.6, 7.5) 0.0005
HADS-D	Mean (95% CI)	1.3 (0.6, 1.9)	6,9 ** (4.4, 9.3)	4.1 $ (2.2, 6.4)	2.8 (0.5, 4.9) 0.018
BIS total	Mean (95% CI)	59.5 (56.5, 62.4)	72.6 ## (68.1, 77.1)	69.6 ^ (64.4, 74.8)	3.0 (0.2, 5.8) 0.0398

@ before vs. after, two-tailed paired t-test

* vs. Control: $p < 0.0001$, two-tailed unpaired t-test, mean difference (95% CI) = 9.4 (7.3, 11.5)

** vs. Control: $p < 0.0001$, two-tailed unpaired t-test, mean difference (95% CI) = 6.1 (3.8, 8.5)

\# vs. Control: $p = 0.006$, two-tailed unpaired t-test, mean difference (95% CI) = 3.6 (1.1, 6.1)

vs. Control: $p < 0.0001$, two-tailed unpaired t-test, mean difference (95% CI) = 10.8 (6.0, 15.8)

vs. Control: $p < 0.0003$, two-tailed unpaired t-test, mean difference (95% CI) = 4.3 (2.1,6.5)

$ vs. Control: $p < 0.005$, two-tailed unpaired t-test, mean difference (95% CI) = 2.8 (1.0, 4.7)

^ vs. Control: $p < 0.0005$, two-tailed unpaired t-test, mean difference (95% CI) =10.1 (4.8,15.5)

WHR (Waist-Hip Ratio), BMI (Body Mass Index), PAS (Panic and Agoraphobia Scale), CGI-S (Clinical Global Impression Scale – Severity), CGI-I (Clinical Global Impression Scale – Improvement), HADS-A, HADS-D (Hospital Anxiety and Depression Scale), BIS (Barratt Impulsiveness Scale)

Table 2 CBT vs. pharmacotherapy group at the baseline and after the 8-week treatment

			CBT	Pharmacotherapy	P (ANOVA: R x therapy)
N			7	8	-
Good response (CGI-I ≤ 2)	% (95% CI)		71.4 (29.0; 96.0)	32.5 (8.5; 69.4)	-
CGI-S	Mediane (IQR)	before	4 * (4; 5)	4,5 # (4; 5)	
		after	3 (3; 4)	4 (3; 4)	
PAS	Mean (95% CI)	before	26.9 ** (22.2; 31.2)	26.3 ## (19.6; 32.9)	0.389
		after	9.3 (4.1; 14.3)	12.3 (5.5; 19.0)	
HADS-A	Mean (95% CI)	before	11.4 *** (8.7; 14.3)	12.6 ### (9.4; 15.9)	0.958
		after	6.4 (3.9; 8.4)	7.5 (3.8; 11.2)	
HADS-D	Mean (95% CI)	before	6.4 (2.2; 8,1)	7.1 (3.9; 12.4)	0.888
		after	2.9 (1.1; 4.5)	5.3 (2.0; 8.5)	
BIS-11 total	Mean (95% CI)	before	75.0 (66.6; 83.4)	70.5 (64.4; 76.6)	0.020
		after	75.1 (66.8; 83.4)	64.8 ^ (59.0; 70.5)	

* vs. after: p = 0.028, Wilcoxon test

** vs. after: p = 0.001, two-tailed paired t-test**,** mean difference (95% CI) = 17.6 (10.3; 24.9)

*** vs. after: p = 0.024, two-tailed paired t-test, mean difference (95% CI) = 5.0 (0.9; 9.1)

vs. after: p = 0.028, Wilcoxon test

vs. after: p = 0.001, two-tailed paired t-test, mean difference (95% CI) = 14.0 (7.6; 20.4)

vs. after: p = 0.017, two-tailed paired t-test, mean difference (95% CI) = 5.1 (1.2; 9.0)

^ vs. after: p = 0.014, two-tailed paired t-test, mean difference (95% CI) = 5.8 (1.5; 10.0)

PAS (Panic and Agoraphobia Scale), CGI-S (Clinical Global Impression Scale – Severity), CGI-I (Clinical Global Impression Scale – Improvement), HADS-A, HADS-D (Hospital Anxiety and Depression Scale), BIS (Barratt Impulsiveness Scale)

Discussion

The clinically significant improvement was observed with PAS, CGI and HADS-A in both treatment groups after therapeutic intervention. That improvement was similar in both groups and both methods had equal efficacy in PD treatment. The most interesting finding in the present study is no statistically significant change in total impulsivity score before and post treatment in panic disorder patients comparing to the healthy control. Impulsivity seems to be a treatment independent trait for PD patients. Regardless of the therapeutic approach, impulsivity was permanently higher in PD patients comparing to the healthy volunteers. In addition, the effect of treatment on PD severity did not significantly affect the impulsivity level. We observed some insignificant decrease in impulsivity after pharmacotherapy in PD being probably associated with escitalopram serotonergic effect. Numerous studies confirmed a major role of SSRI in decreasing the impulsivity in patients with impulsive aggression. The link between serotonergic dysfunction and impulsive aggression was seen, being in line with findings on pharmacological enhancement of serotonin activity and reduced impulsive aggressive behaviour (Coccaro *et al.* 2009; New *et al.* 2004; Reist *et al.* 2003; Butler *et al.* 2010).

Studies investigating correlation between anxiety disorders and impulsivity produce confounding results. Some studies found no correlation between anxiety and impulsivity (Apter *et al.* 1993; Lecrubier *et al.* 1995; Caci *et al.* 1998; Askenazy *et al.* 2000). According to Apter *et al.* (1993), anxiety evaluated with the State-Trait anxiety scale led to reduced risk for violent behaviour. Any correlation between anxiety and impulsivity was observed in any clinical sample of adolescents (Caci *et al.* 1998). The study in a sample of violent adolescents with high impulsivity levels did not find a correlation between anxiety and impulsivity, either (Askenazy *et al.* 2000; Lecrubier *et al.* 1995).

According to Perugi *et al.* (2011), the state and trait of impulsivity are higher in patients with anxiety disorders than in the healthy control. High levels of impulsivity in patients with anxiety disorders comparing to the healthy control were also observed by other authors (del Carlo *et al.* 1998; Kashdan & Hoffman 2008; Kashdan *et al.* 2009). Kashdan *et al.* (2009) reported a high rate of impulsive behaviours and comorbid substance abuse in a subgroup of patients with Social Anxiety Disorder (SAD) characterized by high novelty seeking. It was proven in numerous studies that patients with bipolar disorder and anxiety disorder present higher levels of impulsivity in comparison to bipolar patients without such comorbidity (del Carlo *et al.* 2013). Also patients with panic disorder, social anxiety disorder (SAD) and obsessive-compulsive disorders (OCD) reported higher scores than healthy controls in total impulsivity and cognitive dimension comparing to healthy controls (Summerfeldt *et al.* 2004). Furthermore, OCD patients with tics were found to be associated with elevated levels of impulsivity comparing to OCD patients without tics only in cognitive dimension what was related to increased severity of obsessions in the tic group (Summerfeldt *et al.* 2004). Patients suffering from bipolar disorder and comorbid anxiety disorders comparing to healthy controls also seem to present higher levels of impulsivity (Taylor *et al.* 2008; Preve *et al.* 2014).

Our results are consistent with numerous studies reporting higher impulsivity in anxiety disorder patients (Summerfeld *et al.* 2004; del Carlo *et al.* 1998; Kashdan & Hoffman 2008; Kashdan *et al.* 2009). It seems that patients with anxiety disorder may engage in impulsive behaviour when they experience negative internal experiences and probably this is the impulsivity function to regulate or manage negative affect and uncertainty (Pawluk & Koerner 2013).

Study limitations

Some study limitation should be noted in elucidating the results. Firstly, the number of participating subjects was relatively small. Thus, the results should be replicated in a larger sample. Secondly, the study results apply to drug-naïve panic disorder patients without agoraphobia with short-illness duration, therefore the selection of study subjects may be reflected in the outcome limiting generalization of the results. Thirdly, it is a single dose study with escitalopram that might produce different results at higher doses. The divergent findings may be partly related to methodological differences including sample size, selection criteria, unmatched groups, sex, age, pharmacotherapy or different assessment tools (rating scales and neurocognitive tests).

Conclusion

Taken all together, there was no statistically significant change in the level of total impulsivity before and after treatment in the group of drug-naïve panic disorder patients, irrespective of pharmacotherapy or CBT comparing to controls. Higher impulsivity seems to be an independent and persistent trait in patients with panic disorder not linked with PD severity. Both escitalopram and CBT exhibit no significant effect on impulsivity in PD patients. Impulsivity and anxiety seems to be independent symptoms in PD. ■

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Conflict of interest: None to declare.

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, EU Directive 2010/63/EU for animal experiments, and Uniform Requirements for manuscripts submitted to biomedical journals. / Treści przedstawione w artykule są zgodne z zasadami Deklaracji Helsińskiej, dyrektywami EU oraz ujednoliconymi wymaganiami dla czasopism biomedycznych.

Authors' contributions / Wkład autorów: KJ-W – basic conceptual work, data collection and interpretation / zasadniczy wkład w koncepcję i project pracy, zebranie danych i ich interpretacja; JL – statistical analysis and preparation of study results for analysis, critical reviewing / analiza statystyczna i przygotowanie wyników badań do analizy, krytyczne zrecenzowanie pod kątem zawartości intelektualnej; MW – literature search, acceptance of the final manuscript version / zebranie piśmiennictwa, akceptacja ostatecznej wersji artykułu; WJC – basic conceptual work, critical reviewing / zasadniczy wkład w koncepcję i projekt pracy, krytyczne zrecenzowanie pod kątem zawartości intelektualnej; MG-W – therapeutic intervention / interwencja terapeutyczna; KG – therapeutic intervention / interwecja terapeutyczna

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