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INSTRUCTIONS FOR AUTHORS

General information

The *Archives of Clinical Psychiatry* is a peer-reviewed journal with six issues per year, published bimonthly. Consonant with its broad access policy, the Journal charges no publication fees, article processing charges, or access fees.

The Journal follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), available at www.icmje.org.

Submissions

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All submissions must be accompanied by a cover letter, to be uploaded as a supplementary file under this name during the submission process. The cover letter should summarize the essence of the work, describing main results and potential impact for the field of research. For additional information about the contents of an adequate cover letter, please click here.

In addition to the cover letter, submissions (except letters to the editor) must include an abstract. Both the cover letter and the abstract should respond to the following questions: (i) Why this study has been done?; (ii) How this study has been done? (literature reviews: consulted databases, number of articles found, number of articles included, inclusion and exclusion criteria, meta-analysis or descriptive work; original articles: study design, number of subjects included, study duration, etc.); (iii) What are the key findings?; and (iv) What significance do your results have for the field and for the broader community?

The abstract must not exceed 200 words and should be structured as follows: Background, Objectives, Methods, Results, and Discussion/Conclusion.

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Conflicts of interest

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Peer review

Upon receipt, manuscripts are evaluated by the journal editor and/or assistant editors for their originality, structure, and relevance of contents and conclusions. Manuscripts with insufficient quality or priority for publication are promptly rejected at this point.

After the initial evaluation, submissions are forwarded to an area editor according to their field of knowledge. The area editor then assigns at least two independent reviewers for the submission. In special cases, the area editor may increase or decrease the number of reviews or make a recommendation to the Editor-in-chief based on his own appraisal of the submission. Once all reviews have been received, the area editor makes a recommendation to the editor-in-chief. The area editors' recommendations are standardized and include the options "Accept", "Reject", Minor Review", and "Major Review". The editor-in-chief receives the recommendation and has the last word on all submissions.

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The *Archives of Clinical Psychiatry* publishes (a) original articles; (b) brief communications; (c) review articles; and (d) letters to the editor. Case reports will be considered for publication if submitted according to the guidelines for letters to the editor (below).

ORIGINAL ARTICLES

Typically, original articles contain new data derived from a sizable and representative sample of patients or subjects.

Original articles should not exceed 3,500 words and include a maximum of 6 tables and/or figures and 30 references. The word count includes only the main body of the text (i.e., not tables, figures, abstracts or references).

The main text should follow the typical structure of scientific articles, namely, Introduction, Methods, Results, Discussion, Conflicts of interest statement, Acknowledgments (if available), and References.

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Brief reports are short manuscripts with a maximum of 1,500 words, organized according to the same structure of original articles and with a maximum of 2 tables and/or figures and 15 references.

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Letters to the editor are considered for publication if they do not contain material submitted to other publications. They should not exceed 500 words, contain a maximum of 1 figure or table, and 10 references. Letters with comments on previous publications of the *Archives of Clinical Psychiatry* should be submitted within three months of the original publication.

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Preparation of Manuscripts

I. TITLE PAGE: The first page should include only the title of the manuscript.

II. AUTHORS AND AFFILIATIONS: The second page, which will not be sent to the reviewers, should include: (a) full authors' names (first name, middle initials, and family name) and main affiliations (no academic titles); (b) name and address of the institution where the study was conducted; (c) complete address of the corresponding author, including phone, fax, and e-mail.

III. ABSTRACT: The third page should include the abstract, followed by up to five relevant key words.

IV. REFERENCES: Citations in the text should be organized in the Vancouver style, i.e., followed by the appropriate reference Arabic number in parentheses. References should be numbered and listed by their order of appearance in text. Reference lists should be double-spaced.

V. TABLES: Tables should be restricted in size, consecutively numbered with Arabic numbers in the text, and presented in separate pages after the reference list (one page for each table). Refer to every table in the text in numerical order. Indicate within angle brackets < > its preferred location in the main text. Legends should provide a complete understanding of the tables without the need to go back to the text. Tables should be restricted to information that has not been already included in the text.

VI. FIGURES: Figures should be restricted both in number and size to the strictly necessary in order to clarify the text contents. Color illustrations are accepted, but additional costs may have to be covered by authors. Figures should be presented after the reference list in separate pages (one page for each figure). Refer to every figure in the text in numerical order. Indicate within angle brackets < > its preferred location.

VII. LEGENDS: Each table and figure should include a legend with the necessary information for its thorough understanding. For that purpose, a short title followed by a concise explanation of the table or figure should be provided. However, legends should not replicate contents in the text. Abbreviations and symbols that appear in tables or figures should be referred to, even though already cited in the text.

VIII. PATIENT PHOTOGRAPHY: The *Archives of Clinical Psychiatry* does not encourage the publication of photography of patients. Whenever indispensable for the comprehension of the article, written informed consent must be signed by the patient or respective caregiver, and patient details must be removed from the illustration.

A call to action for publishing study designs and preliminary results in the *Archives of Clinical Psychiatry*

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"*There is more than one way to skin a cat*", an old proverb says. Scientists know this well (metaphorically speaking, of course), as they often face complex challenges that require creative, out-of-the-box thinking, and are usually praised for their problem-solving skills.

The issue, however, is when these creative minds are faced with non-significant findings of their meticulously performed research; and, then, after ingenuity and art, obtain positive findings: in some cases, outliers are "rightfully" excluded and replaced by new data; in others, dozens of tests are run until, "out of serendipity", that association (never thought before) suddenly fits with the mainstream theory. Some data just needed to be handled more carefully, treated more softly, discussed more thoughtfully, to stand a chance in this wild world of peer reviewing and publishing. In fact, although "*God loves the [p=]0.06 as much as the 0.05*"[1], editors, reviewers and grant committees still love the latter much, much more[2].

The result of this mixed bag of controversial approaches to the data, driven by academic pressures and collectively described as "p-hacking"[2], has been detrimental to both basic and applied science, as it leads to an overinflation of false-positive – and, hence, non-replicable – findings. In psychology, a consortium of several research groups recently aimed to replicate 100 highly representative studies published in leading journals. The authors found that only one third of the replication studies had significant findings (*vs.* 97% of original studies) and the mean effect size of the replication studies was half the magnitude of the original studies[3]. Research that uses statistical methods to detect excess significance is also revealing. In a systematic review of meta-analyses investigating brain volume abnormalities, the mean effect size of each meta-analysis was employed to estimate the power to detect an alpha at 0.05 and then to estimate the number of expected positive datasets. The author found that there were too many studies with statistically significant results in the literature on brain volume abnormalities[4], which strongly suggests publication bias and/or p-hacking. A similar approach was used in psychotherapy studies, showing that the effect sizes of the psychotherapy interventions were overestimated, and that the literature had an unexpected high number (excessive) of positive findings according to the obtained evidence[5].

In another approach, Head *et al.*[2] used the p-curve to assess the reliability of published research. When the true effect of an investigated phenomenon is zero (true negative), each p value has an equal probability to occur (i.e., p = 0.04 is as likely as p = 0.03), whereas in true positive findings the p-curve right skews (i.e., has more smaller values) as the effect increases. In both cases, the p-curve shape will be changed if there is evidence of p-hacking. The typical pattern is an increased frequency of p-values just below 0.05, when researchers stop their efforts to obtain significant findings. The authors used text-mining techniques to extract p values from all open access papers available in PubMed, finding strong evidence for p-hacking across all disciplines. For instance, approximately 50% and 60% of studies in the medical and psychological sciences, respectively, had p-values between 0.045 and 0.05, "just in the limit" of significance. They concluded that p-hacking is widespread in scientific literature[2].

What can scientists do, therefore, to mitigate the p-hacking plague from our fields? Unfortunately, there is no single solution for this complex problem. There is still too much emphasis in the p-value, whereas more informative statistics, such as the effect size and its surrounding confidence interval, are usually neglected. In fact, the p-value only informs the probability of obtaining an equal or more extreme effect, *given the null hypothesis is true*. In fact, the pre-test probability (i.e., prior likelihood of the phenomenon) is the main determinant for rejecting a false negative finding[6]. Nonetheless, and in spite of having or not theoretical knowledge, editors, authors and policy-makers often simplify the p-value as being the probability of a true effect (i.e., of neglecting the null hypothesis). On the other hand, p-values > 0.05 are also informative in studies that were well-designed, powered, and robust to biases regarding sample selection, masking, performance and attrition[7].

Therefore, results should be contextually interpreted and, hence, a detailed description of the study design is crucial to critically assess its methodology. Interestingly, although the CONSORT statement emphasizes this need[8], studies are still insufficiently described in most fields[9]; possibly due to editorial restrictions regarding article size. Thus, publications of only study protocol and design are useful, which also allow assessment of study methodology separately and independently of the obtained results. Most importantly, though, is the *a priori* statement of the main research question, the primary and secondary hypotheses, and the planned statistical analyses. Authors are naturally not impeded to perform *post hoc* analyses, which also have its exploratory and hypothesis-generating value. In addition, new and important research questions might arise during an ongoing study that were not initially planned – for instance, a new neuroimaging analysis method that was not at first available or simply did not exist at study start. Researchers should and must explore novel research tracks – and also be transparent regarding *a priori* and *post hoc* hypotheses, a goal that study design publication can help to accomplish.

Considering these challenges, the *Archives of Clinical Psychiatry* issues a call to action for authors to publish the design, protocol and preliminary findings of their studies in the journal. We believe that this is one of the necessary steps to increase transparency, decrease p-hacking and tackle the reproducibility issues that ravage clinical neuroscience and psychiatry. The *Archives of Clinical Psychiatry*, an open access, peer review journal, welcomes authors to share their study protocols and methodology. Therefore, dear author, please let us know, in excruciating details, how you plan to skin your next cat.

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The relationship between eating attitudes and distress tolerance in obsessive compulsive disorder

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Abstract

Objective: The main purpose of this study is to investigate the eating attitudes of obsessive compulsive disorder (OCD) patients, while the secondary purpose is to examine the relationship between eating attitudes and distress tolerance. **Methods:** The study included 60 OCD patients and 60 healthy individuals as a control group. The data of the study were collected using the Padua Inventory (PE), Eating Attitudes Test (EAT-26), Distress Tolerance Scale (DTS) and Beck Depression Inventory (BDI). **Results:** In comparison to the control group, the EAT-26 ($p = 0.001$) and BDI ($p = 0.001$) scores of the patient group were significantly higher, while the DTS total score ($p = 0.001$) was significantly low. The patients were divided into two groups based on the EAT-26 cutoff score. In the group with EAT-26 ≥ 30; the total PI score ($p = 0.035$), rumination ($p = 0.010$), impulses ($p = 0.001$) and sub-scale scores and BDI scores ($p = 0.038$) were significantly higher, while the DTS total score ($p = 0.005$), tolerance ($p = 0.000$), regulation ($p = 0.013$) and self-efficacy ($p = 0.009$) sub-scale scores were significantly lower. **Discussion:** Our study found that the eating habits of the OCD patients were more irregular than those of the healthy individuals. Further, the distress tolerance of the patients with irregular eating attitudes was significantly lower.

Ay R et al. / Arch Clin Psychiatry. 2018;45(6):139-42

Keywords: Obsessive compulsive disorder, eating attitude, distress tolerance.

Introduction

The relationship between eating disorders and OCD was proposed about 80 years ago[1]. Some researchers claimed that some symptoms seen in ED are obsessional and called eating disorders, or "modern obsessive-compulsive syndromes"[2]. It was suggested that the symptoms seen in ED, such as repeated checking/seeking for reassurance and ritualistic eating behavior, may have obsessive-compulsive characteristics[3]. In ED, noticeable and regular thoughts about food, body image, and the desire to lose weight are likened to obsessions, while avoiding foods, excessive exercising, ritualistic eating attitudes are liked to compulsions[4].

The life-long OCD prevalence in patients monitored with an ED diagnosis was found vary from 9.5% to 62%[5]. Similarly, the life-long ED prevalence in patients monitored with OCD diagnosis was found vary from 11% to 42%[6]. It was argued that the biological mechanism of OCD and ED comorbidity may be serotonin dysregulation that is found in both diseases[7]. In a public study with 407 people, researchers found relationships between neuroticism, and checking and binge eating behavior, while neuroticism was also related to perfectionism and checking, washing, and restrictive eating behavior. As a result, it was suggested that similar clinical symptoms arising from similar personality traits may lead to OCD and ED comorbidity[8]. According to a large-sample genetics study, while the risk of anorexia nervosa (AN) increases 16 folds in female patients with OCD, it increases 32 folds in male patients with OCD. In the study, significantly increased AN risk was also found in first-degree and second-degree relatives of OCD patients, and it was argued that shared, common genes play a role in OCD and ED development, rather than disease-specific genes[9]. However, these findings are not sufficient to explain the relationship between ED and OCD.

Distress tolerance is defined as the capacity for tolerating negative situations. Distress tolerance capacity has mostly been accepted as the capacity for coping with emotional situations[10]. Some studies found that the distress tolerance capacity of OCD patients was lower than individuals without OCD[11]. There are also studies that found a relationship between a reduced distress tolerance capacity and ED[12,13]. This information raises the question of whether reduced distress tolerance is a mediator in the etiology of the eating disorders seen in OCD patients. The main purpose of this study is to investigate the eating attitudes of OCD patients, while the secondary purpose is to examine the relationship between eating attitudes and distress tolerance.

Methods

The study included 60 patients visited the Psychiatry Policlinic of Training and Research Hospital between November 2016 and April 2017, underwent monitoring and treatment, diagnosed with OCD based on the DSM-5 criteria, and complied with the criteria of the study, and 60 healthy volunteers who showed similar sociodemographic characteristics. The research project was approved by the Clinical Practices Ethics Board of Malatya, and written consent was taken from the participants.

While literate OCD patients of age 18 to 65 who volunteered were included in the study, the study excluded patients who had an additional psychiatric disease diagnosis other than OCD, or any neurological or systemic disease that might affect cognitive functions.

Healthy volunteers who were 18-65 years old without a psychiatric diagnosis any neurological or systemic disease that might affect cognitive functions were taken as control group.

Instruments

Sociodemographic Data Form

This is a questionnaire developed by the researchers to determine the sociodemographic characteristics of the participants. They were about age, sex, marital status, educational status, work status, place of residence, weight, height, BMI, past psychiatric illness, presence of psychiatric illness in the family. The BMI is then calculated by dividing the subject's weight by the square of his/her height.

Padua Inventory (PI)

The PI is a self-report scale developed by Sanavio[14] in 1988 with the purpose of measuring the distribution and severity of obsessions and compulsions in OCD patients and healthy individuals. While the

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original scale consisted of 60 items, shortened forms consisting of 39 and 41 items were developed later. Each item of the 5-point Likert-type scale is scored in the range of 0-4. The reliability and validity study of the 41-item version of the scale in Turkish was carried out by Besiroglu *et al.*[15]. The scale has five sub-scales as cleaning, impulses, checking, rumination, and precision.

Eating Attitudes Test (EAT-26)

The EAT-26 is a self-report scale designed to investigate potential disorders in the eating behaviors of individuals who have been diagnosed with an ED and those who have not[16]. An adaptation of the scale into Turkish was achieved by Savasır and Erol[17]. EAT-26 is a 40-item, 6-point Likert-type scale, and its cutoff score is 30.

Distress Tolerance Scale (DTS)

The Distress Tolerance Scale was developed in 2005 by Simons and Gaher[10]. The items are scored in the range of 1-5 with the total score in the range of 15-75. High scores indicate high levels of emotional distress tolerance. Sargın *et al.*[18] conducted the Turkish standardization work of the scale. There are three sub-scales (1) tolerance, (2) regulation and (3) self-efficacy in the Turkish form of the scale.

Beck Depression Inventory (BDI)

The BDI is a 4-point Likert-type self-report scale that consists of 21 statements of self-evaluation, developed in 1961 by Beck[19]. The items are scored in the range of 0-3, and amount to a total score of 0-63. The validity and reliability study of the scale in Turkish were carried out by Hisli[20], and the cutoff point of the scale adapted into Turkish was determined as 17.

Measurement, analysis, statistical analysis methods

The analysis of the data collected from the patient and control groups was conducted using the "SPSS for Windows 22" statistical package software. The data collected by counting were indicated as percentages, and the data collected by measurement were indicated as means and standard deviations. Categorical data were compared by a chi-squared test, numerical variables of the groups were compared by the parametric test of independent t-test and the non-parametric test of Mann-Whitney U test, and the relationship between non-parametric numerical variables was analyzed by the Spearman correlation test. In all analyses, the level of significance was taken as 0.95 ($p < 0.05$).

Results

The 60 OCD patients and 60 healthy individuals as a control group included in the study were compared. No statistically significant difference was found between the groups in terms of age, sex and BMI. In comparison to the control group, the EAT-26 ($p = 0.000$) and BDI ($p = 0.000$) scores of the patient group were significantly higher, while the patients' DTS total score ($p = 0.000$), tolerance ($p = 0.000$), regulation ($p = 0.000$), and self-efficacy ($p = 0.000$) sub-scale scores were significantly lower (Table 1).

The patients were divided into two groups based on their EAT-26 scores as 47 EAT-26 < 30 patients (72.4%), and 13 EAT ≥ 30 patients (27.6%), and compared. There was no significant difference between the groups in terms of age, sex, BMI, and the PI sub-scales of washing, checking and precision. In the group with EAT-26 ≥ 30; the total PI score ($p = 0.035$), rumination ($p = 0.010$), impulses ($p = 0.001$) sub-scale scores and BDI scores ($p = 0.038$) were significantly higher, while the DTS total score ($p = 0.005$), tolerance ($p = 0.000$), regulation ($p = 0.013$) and self-efficacy ($p = 0.009$) sub-scale scores were significantly lower (Table 2). There was weak correlations between the EAT-26 score and the scores of the rumination sub-scales of PI (r: 0.277) and there were medium-level correlations between the EAT-26 score and the PI total score (r: 0.430), the sub-scales of the impulses (r: 0.370), and BDI scores (r: 0.467), and the self-efficacy sub-scale of DTS (r: -0.456), and there were strong correlations between the EAT-26 score and the DTS total score (r: -0.729), tolerance (r: -0.670) and regulation (r: -0.555) (Table 3). Partial correlation analysis was carried out to examine the effects of distress tolerance on eating attitude independently of the scores of depression and obsessive-compulsive symptoms. It was seen that, independently of the PI total score, sub-scale scores and BDI scores, the strong negative correlation between the DTS total scores and EAT-26 scores continued (r: -0.580).

Table 1. Sociodemographic and clinical characteristics according to OCD patients and healty controls

	OCD (n: 60)	Control (n: 60)	p
Age	31.33 ± 9.44	31.10 ± 6.92	0.878
Gender	31/29	31/29	1.000
BMI	25.55 ± 3.01	24.99 ± 2.28	0.253
EAT-26	21.21 ± 13.39	11.80 ± 4.80	0.000
DTS total	37.25 ± 9.43	51.36 ± 9.38	0.000
Tolerance	19.7 ± 7.17	31.25 ± 8.04	0.000
Regulation	8.81 ± 3.06	11.38 ± 2.86	0.000
Self-efficacy	8.65 ± 1.58	10.06 ± 2.15	0.000
BDI	18.53 ± 9.39	10.15 ± 5.80	0.000

OCD: obsessive compulsive disorders; EAT-26: Eating Attitudes Test; DTS: Distress Tolerance Scale; BDI: Beck Depression Inventory.

Table 2. Sociodemographic and clinical characteristics according to the EAT-26 < 30 and EAT-26 ≥ 30 groups

	EAT-26 < 30 (n: 47)	EAT-26 ≥ 30 (n: 13)	u	p
Age	30.40 ± 9.39	34.69 ± 9.21	222.000	0.133
BMI	25.42 ± 3.24	26.01 ± 2.03	274.500	0.578
DTS total	40.02 ± 8.56	27.23 ± 4.28	59.000	0.000
Tolerance	21.68 ± 6.87	12.92 ± 2.62	61.000	0.000
Regulation	9.38 ± 2.81	6.76 ± 3.13	167.500	0.013
Self-efficacy	8.95 ± 1.38	7.53 ± 1.80	163.000	0.009
PI total	59.85 ± 33.07	79.07 ± 33.53	188.500	0.035
Rumination	18.85 ± 8.59	29.38 ± 12.28	162.000	0.010
Cleaning	15.10 ± 10.86	15.38 ± 9.03	288.500	0.760
Checking	14.27 ± 7.84	16.61 ± 8.36	268.000	0.499
Impulses	3.80 ± 3.85	9.76 ± 5.68	119.500	0.001
Precision	6.10 ± 5.47	7.92 ± 7.96	285.500	0.718
BDI	17.14 ± 8.74	23.53 ± 10.30	190.000	0.038

OCD: obsessive compulsive disorders; EAT-26: Eating Attitudes Test; BMI: body mass index; DTS: Distress Tolerance Scale; PI: Padua Inventory; BDI: Beck Depression Inventory.

Table 3. Correlations between Eating Attitudes Test, Padua Inventory, Distress Tolerance Scale

	EAT-26	
	r	p
DTS total	-0.729	0.000
Tolerance	-0.670	0.000
Self-efficacy	-0.456	0.000
Regulation	-0.555	0.000
PI total	0.430	0.001
Rumination	0.277	0.032
Cleaning	0.044	0.740
Impulses	0.370	0.004
Precision	0.209	0.109
Checking	0.303	0.018
BDI	0.467	0.000

EAT-26: Eating Attitudes Test; DTS: Distress Tolerance Scale; PI: Padua Inventory; BDI: Beck Depression Inventory.

Discussion

The main purpose of this study is to investigate the eating attitudes of OCD patients, while the secondary purpose is to examine the relationship between eating attitudes and distress tolerance. In our study, eating attitude and depression scores were higher and DTS total scores and sub-scale scores were lower in the patient group. According to the EAT-26 cutoff score, the total PI score and the rumination and impulses sub-scale scores were higher, and the DTS total and sub-scale scores were lower in the group with EAT-26 ≥ 30. There was a medium-level negative correlation between distress tolerance and eating attitudes even when the effects of depression and obsessive-compulsive symptoms were statistically controlled.

The first hypothesis of our study is that the eating attitudes of OCD patients will be more irregular than healthy controls. In a study with 30 OCD patients, the rate of eating disorder comorbidity was found as 16.7%[21]. In another study conducted with 100 OCD patients, EAT-26 was used to reach the conclusion that the ratio of patients with disordered eating behaviors without an ED diagnosis complying completely with the DSM-5 criteria was 11%[22]. Çelikel *et al.*[23] studied 55 OCD patient and healthy controls and found that EAT-26 scores were significantly higher in the patient group. In a study by Tyagi *et al.*[3] which used the SCOFF questionnaire, it was found that 22.9% of 135 patients may have an eating disorder. A clinical analysis based on ICD 10, reported that four of the 135 people fulfilled the criteria for an eating disorder diagnosis. It was reported that, while the ritualistic eating behavior and food-related perfectionism in OCD patients might not fit the diagnosis criteria based on ICD 10, they may be the cause of the ED symptoms found in the questionnaire. In contrast to these studies, there are also studies that did not find eating attitude disorders in OCD patients. EAT-26 was applied on to 16 non-medicated OCD patients, no patient exceeded the cutoff score of 30, and eating disorders accompanying OCD were discussed in a more easily detectable fashion with standardized diagnostic interviews[24]. In our study, using the Eating Attitudes Test, we found that the eating attitudes of the OCD patients were significantly more disordered than those of the healthy controls. Thought-action fusion (TAF) is a condition in which, individuals overvalue their adverse ideas, and it is a cognitive bias, which is thought to have a role in the misinterpretation of such ideas. TAF consists of two dimensions, which are TAF-Morality and TAF-Probability[25]. A study by Garcia Soriano *et al.*[26] identified obsession-like intrusive thoughts in both obsessive compulsive disorder (OCD) and eating disorders. TAF has been identified as a common cognitive bias, causing emotional disturbances created by intrusive thoughts, in both of these diagnostic identities. In the light of this information, comorbid pathological eating attitudes might have been identified in patients who is included in our study and who use TAF as a cognitive bias. Preventive interventions towards comorbid eating disorders can be performed by working through TAF and by utilizing the results of studies with larger sample sizes, involving assessments with scales specific to TAF. These contradictory results may be explained by the relatively smaller sample, different severity of the disease in the participating OCD patients, symptom patterns, medication, and differences in medication.

The relationship between the presence of eating disorder comorbidity and obsessive-compulsive symptomatology is also an interesting issue. In a study of patients with eating disorders, it was found that AN patients gained higher scores from Padua rumination and Padua impulses sub-scales in comparison to the control group[27]. A study with 100 OCD patients, revealed that, among the dimensions of obsessive-compulsive symptoms, impulse obsessions predicted anorexic eating behavior and ruminations predicted bulimic eating behavior. Items containing impulse obsessions are found to be related to the anxiety of losing control over motor behavior. Items containing rumination are seen to be related to thoughts that the person cannot obstruct even if they want to, difficulty in decision making, and excessive mental effort about situations that are unlikely to happen. Fears of losing control resembles avoidance of food in anorexic patients, while rumination indicates not being able to stop something, therefore not being able to stop episodes of binge eating[22]. In a study with a non-clinical sample of 270 prospective nurses, it was found that eating attitude is related to obsessive-compulsive symptoms (checking, slowness, rumination sub-scales), and as eating behavior became more disordered, the prevalence of obsessive-compulsive symptoms increased[28]. The symptoms that are commonly seen in eating disorders, include intense thoughts about body image, long eating times and ritualistic eating behaviors such as dividing the food into small pieces, show similarities to obsessive compulsive symptoms. In our study, a significant relationship was found between eating attitude disorders and the sub-scales of rumination and impulses. This agrees with most of the literature. Some cognitive bias similar to TAF-probability may be associated with findings questioned by The Eating Attitudes Test, such as "I have gone on eating binges where I feel that I may not be able to stop", and "I feel that food controls my life", which are the subscales questioning the thought shifting and impulsivity. Pathological eating attitudes and progression to comorbidities with eating disorders can be prevented by interventions towards TAF in individuals with higher thought shifting and impulsivity subscale scores. Different results in studies may be explained by differences among scales used to measure obsessive-compulsive symptoms, or differences regarding whether the samples are clinical or not.

The second hypothesis of our study is that OCD patients with a low distress tolerance will have an eating attitude disorder. To the best our knowledge, based on the literature review, there is not a study concerning this issue with an OCD sample. In a study with a non-clinical sample of 200 participants, it was asserted that deficits in distress tolerance play an important role in the etiology and continuation of bulimic symptoms[29]. Lavender *et al.*[30] studied on 93 substance-addicted individuals, and reported that distress tolerance and the expectancy that eating relieves negative effects predicted the development of bulimic symptoms. In a recent study monitoring 206 adolescents for six years the distress tolerance capacity was found to be related to eating disorder symptoms in initial stages, while the risk of developing an eating disorder in later stages was found to be related to basal anxiety, depression and distress tolerance levels[12]. In agreement with most of the literature, our study showed that distress tolerance in the group with eating attitude disorder was significantly lower. However, there are also studies that do not support these findings. In a study on 186 young women, as opposed to expectations, distress tolerance was not found to be related to binge eating behavior. It was discussed that this result may have been caused differences in the sample or differences in evaluation of the symptoms of eating disorder[31]. Different results may have been caused by assessment of eating disorders with different characteristics such a AN, bulimia nervosa and binge eating, and conduction of studies with non-clinical samples. In the future, it may be suitable to plan studies with larger samples where all eating disorder symptoms are investigated on this issue.

Some studies found a significant relationship between increased obsession level and low distress tolerance level[11,32-34]. It is seen that low emotional distress tolerance has a significant role in the process of resorting to compulsions in neutralizing obsessions that occur by misperception and misinterpretation of sensations. Distress tolerance has a critical role in misinterpretation of threat that is seen in obsessive-compulsive disorder. In contamination obsession, the person perceived microbes as a threat and an anxiety against the possibility of contamination starts to appear. There are negative emotions that accompany anxiety, such as disgust and fear. With these emotions, the person may think they will get ill or make someone ill. At this point, individuals with low distress tolerance levels may resort to more compulsion to neutralize these negative emotions, or show more tendency to avoid situations with possibility of contamination[32]. Low tolerance for negative emotions caused by OCD-like intrusions, leads people with lower levels of distress tolerance to use incompatible strategies to cope with the distress related to the intrusion that they think is unbearable. Additionally, all sub-scales of the Distress Tolerance Scale were found related to neutralization and post-neutralization anxiety[35]. A study of 79 OCD

and 177 ED patients, concluded that similar intrusive thoughts are found in both disorders, but coping mechanisms are different[26]. In our study, the distress tolerance was determined to be lower in OCD patients with pathological eating attitudes. In these patients, low distress tolerance might have increased the extent of neutralization against intrusive thoughts, by the development of pathological eating attitudes as a way of neutralization. Cognitive interventions to increase distress tolerance in patients with OCD can prevent the development of the pathological eating attitudes.

Based on all this information, low distress tolerance may be one of the mutual etiological reasons for OCD and ED. It may be argued that different clinical pictures are seen due to different coping mechanisms for coping with intrusive thoughts in people with low distress tolerance.

Our study has some limitations. Eating attitude was evaluated by a self-report scale only, and eating disorder diagnosis was not made via clinical interview. However, the eating attitude test used here is a test analyzed for validity and reliability by Garner and Garfinkel[16]. Another limitation is that the test used here investigated anorexia symptoms and did not contain questions about other frequently seen eating disorders such as bulimia and binge-eating disorder; however, the EAT-26 was selected as the most frequently seen ED comorbidity in OCD patients is AN. Another limitation of the study is the non-exclusion of the OCD patients with comorbid conditions such as eating disorders and depression, all of which might be associated with eating attitudes. Additionally, our sample was smaller than those of some studies with non-clinical samples, which may be considered a limitation.

Despite its limitations, our study may contribute to the literature as the first study that investigated the relationship between eating disorders seen in OCD and low distress tolerance. However, OCD and ED are complex clinical situations. The reasons for the prevalence of the comorbidity of these two conditions have not yet been made clear. However, cognitive interventions towards increasing the distress tolerance of OCD patients in the light of these findings, will not only improve the clinical outcomes in OCD, but also prevent ED comorbidity development.

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Metabolic syndrome in bipolar disorder: prevalence, demographics and clinical correlates in individuals with bipolar I, bipolar II, and healthy controls

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Abstract

Background: The metabolic syndrome is a growing global public health problem and highly prevalent in patiens with bipolar disorder. There are a few studies about relationship between metabolic syndrome and bipolar disorder subtypes. **Objective:** The aim of this study was to investigate the prevalence of metabolic syndrome (MS) and its individual components in subjects with bipolar I (BD I) and bipolar II (BD II) disorder compared with non-psychiatric controls, and to determine the variables affecting MS. **Methods:** A total of 210 individuals (mean age 42.5 ± 11.87, 58.1% female) of whom 70 had BD I, 70 BD II, and 70 controls, were included in this study. MS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the adapted ATP III (ATP III-A) and the International Diabetes Federation (IDF) criteria. **Results:** Participants with BD I had a significantly higher prevalence of MS when compared to individuals BD II and non-psychiatric controls according to the NCEP-ATP III, ATP III-A, and IDF criteria (ps < 0.01). In individuals with MS, increased waist circumference was the most common abnormality. Logistic regression analysis revealed that the presence of physical illness, age and number of cigarettes smoked significantly predicted the presence of MS. **Discussion:** This study showed that MS was more prevalent among BD I individuals compared to BD II and controls, and highlighted the importance of regular screening for MS in individuals with BD.

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Keywords: Bipolar disorder I and II, metabolic syndrome, prevalence.

Introduction

Bipolar disorder (BD) is a chronic disorder that usually starts in adolescence and early adulthood, and is characterized by significant changes in the affective state and by impaired social and/or neuropsychological development[1]. According to the epidemiological field study in the United States of America (USA), the lifetime prevalence rate is 0.8% for bipolar I disorder (BD I), and 0.5% for bipolar II disorder (BD II)[2]. The World Health Organization (WHO) estimates that BD is currently the sixth leading cause of disability worldwide among adults. Depending on unhealthy lifestyle models such as high calorie diet, cholesterol intake, smoking and physical inactivity, 38% of individuals with BD suffer from cardiovascular disease (CVD). Life expectancy compared to the general population is 13.6 years shorter for male patients, and 12.1 years shorter for female patients[3]. In addition, the long-term use of some antipsychotics (AP) or mood stabilizers for treatment may be associated with an increased risk of developing obesity, dyslipidemia, diabetes mellitus, and metabolic syndrome (MS)[4].

MS leads to an increase in central obesity, fasting blood glucose (FBG), blood pressure (BP), and arteriosclerosis associated with deteriorating lipid profiles. Insulin resistance (IR) plays a role in its pathogenesis. It is becoming increasingly common all over the world. The risk of MS increases with age[5,6]. The prevalence of MS varies between 6% and 70%[7]. According to the results of the Metabolic Syndrome Research (METSAR) conducted across Turkey, the prevalence of MS was 35% among adults 20 years of age and over[8].

In studies conducted in different countries, it has been reported that the prevalence of MS in patients with BD varies between 22.4% and 67%[9-11]. Although there are not many studies undertaken on MS in Turkey, the prevalence of MS ranges from 24.7% to 36.7%[12,13]. It has been shown that unhealthy lifestyle habits (smoking, alcohol use, malnutrition, and lack of exercise) are frequently present in individuals with BD, and that these variables increase the risk for the development of MS. The relationship between BD and MS remained unchanged even after adjustments for age, race, smoking, physical inactivity, carbohydrate intake, and alcohol use[4]. Obesity is frequently associated with MS, and it is common among individuals with BD. In these patients, obesity has been associated with bad eating habits, lack of exercise, and the use of some psychotropic drugs leading to weight gain[14]. In obese people, the hypothalamic pituitary adrenal (HPA) axis may be disrupted due to increased leptin and other hormones released from the adipose tissue, which affects normal mood regulation, and consequently leads to significant and/or rapid mood fluctuations such as depression, mania, or the mixture of both mood states[15]. In individuals with BD, the presence of MS has also been found to be associated with a decrease in treatment response, a more adverse course of illness, increased frequency of manic and depressive episodes, and increased suicide tendency[16].

Therefore, in the current study, our first aim was to investigate the prevalence of MS in individuals with BD I, BD II, and non-psychiatric controls, and to compare patients with BD with the control subjects in terms of their demographics and clinical variables. The second aim of the study was to determine which of the individual MS components were associated with BD. We also aimed to identify the clinical correlates of MS in BD.

Methods

Participants

This study was carried out between 01.03.2016 and 01.07.2016 in the Department of Psychiatry at Tokat Gaziosmanpasa University Faculty of Medicine (Tokat, Turkey). A total of 210 subjects (age range: 18-65 years) consisting of 140 euthymic patients diagnosed with either BD I or BD II according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[17] and 70 non-psychiatric control

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subjects were enrolled in the study. The control group consisted of healthy volunteers who did not have any psychiatric diagnoses, and who presented to the outpatient clinic of the physical therapy department. Participants who suffered from comorbid alcohol- and drug-related disorders (except for smoking) were not included in the study (because of the low number of alcohol and substance users among the participants with BD during their remission period), and participants who had mental retardation (MR) and/or pervasive developmental disorders were excluded from the study.

Instruments of assessment

A demographic and clinical data form, which was prepared to assess the demographic and clinical features of the participants, was completed by the interviewer. Additionally, the Young Mania Rating Scale (YMRS)[18,19], the Bipolar Depression Rating Scale (BDRS)[20,21], the Beck Depression Inventory (BDI)[22,23] were used to assess the severity of the mood episodes of the participants. To calculate the amount of cigarettes smoked, we asked the participants how many packs of cigarettes they smoked daily and how many years they were smoking and the number of packs/year was recorded, the International Physical Activity Questionnaire Short Form (IPAQ-SF)[24] was used to assess the level of their physical activity. The Turkish versions of all these scales were used in the study[25].

Procedure

Face to face interviews were held with all of the participants. The questionnaires and scales used in the study were filled out by the interviewer, and the participants during these interviews. These questionnaires and scales were later rated by the interviewer. The groups (BD I, BD II, BD I+BD II, total participants) were divided into two groups: a) current cigarette smokers (yes = 1) and b) non-smokers (no = 0). Firstly the relationship between cigarettes smoking and the duration of illness was assessed. Secondly it was assessed whether there is a relationship between the amount of cigarettes and the duration of illness. Body weight, height, and waist circumference (WC) were measured to investigate the diagnostic criteria for MS in the participants and healthy controls. The participants also underwent blood tests to identify MS parameters. Biochemical findings [FBG, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG)], and BP measurements, which are examined routinely for MS, were recorded for all three groups. MS was diagnosed according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the adapted ATP III (ATP III-A)[26,27], and the International Diabetes Federation (IDF)[28].

Statistical analyses

Independent samples' t-test, Pearson's chi-square and one-way analysis of variance (ANOVA) were used to determine whether there was a statistically significant difference between the means of the variables in the different groups. For group comparisions involving ANOVA, post-hoc Tukey analyses were performed to identify where the group differences were. Binary logistic regression analyses were used to assess the proposed relationship between the demographic and clinical variables and the presence of MS. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using a statistical software package (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Ethical approval

The study was approved by the Clinical Trials Ethics Committee of Tokat Gaziosmanpasa University Faculty of Medicine. The participants were also informed about the study. Then, written informed consent was obtained from the participants who voluntarily agreed to participate.

Results

Group comparisons according to demographic and clinical characteristics

A total of 210 participants (18-65 years) including 70 participants with BD I, 70 participants with BD II, and 70 non-psychiatric controls were enrolled in the study. The mean age was 43.51 (±11.75) years for the BD I group, 43.17 (±12.97) years for the BD II group, and 40.83 (±10.78) years for the control group. There was a significant difference among non-psychiatric controls and the other groups in terms of age ($p < 0.001$). The number of female participants in the BD II group was higher and there was a significant difference compared to the other groups ($p = 0.003$). Non-psychiatric controls were more successful in terms of work status than participants with BD ($p < 0.001$). The demographic characteristics of the participants are presented in Table 1.

The groups were compared with each other in terms of their clinical characteristics. In the BD I group YMRS score (± standard

Table 1. Demographic characteristics of the participants

Variables		Groups			χ^2/F	*p*
		BD I	BD II	Control		
Age (years)		43.51 (11.75)	43.17 (12.97)	40.83 (10.78)	11.773	< 0.001
Sex	Female	33 (47.1)	52 (74.3)	37 (52.9)	11.775	0.003
Marital status	Single	15 (21.4)	21 (30)	9 (12.9)	22.634	0.004
	Married	46 (65.7)	34 (48.6)	56 (80)		
	Divorced	7 (10)	6 (8.6)	4 (5.7)		
	Separated	2 (2.9)	3 (4.3)	0 (0)		
	Widow	0 (0)	6 (8.6)	1 (1.4)		
Level of education	Illiterate	2 (2.9)	6 (8.6)	1 (1.4)	22.420	0.013
	Primary school	33 (47.1)	21 (30)	21 (30)		
	Secondary school	9 (12.9)	10 (14.3)	3 (4.3)		
	High school	14 (20)	13 (18.6)	26 (37.1)		
	University	12 (17.1)	20 (28.6)	18 (25.7)		
Income level (TL)		974.54 (1021.73)	879.71 (1060.74)	1495.71 (951.60)	1.124	0.327
Employment *status*	Employed	29 (41.4)	22 (31.4)	53 (75.7)	30.212	< 0.001
Pack/year of cigarette smoking		5.75 (9.85)	3.94 (8.23)	3.53 (8.05)	2.156	0.118

Note. Results are presented as mean (standard deviation), or frequency (percentage). BD I: bipolar disorder I; BD II: bipolar disorder II; TL: Turkish Lira.

deviation (SD) was 0.26 (±0.97), BDRS score (±SD) was 3.1 (±3.05), BDI score (±SD) was 4.9 (±4.7), in the BD II group YMRS score (±SD) was 0.04 (± 0.36), BDRS score (±SD) was 3.5 (±3.03), BDI score (±SD) was 6.66 (±4.78), in the control group BDI score (±SD) was 4.9 (±4.7), and there was no significant difference between the groups in terms of these scale scores. The mean number of depressive episodes [± standard deviation (SD)], and the mean total number of mood episodes (±SD) were 4.94 (±2.48), and 8.66 (±3.69), respectively. In the BD II group, the mean number of depressive episodes (±SD), and the mean total number of mood episodes (±SD) were 5.49 (±2.67), and 8.67 (±4.27), respectively. There was a significant difference between the BD I group and the BD II group in terms of the mean number of depressive episodes, and mean total number of mood episodes (both p values 0.024). In the BD I group, the mean number of manic episodes (± SD), and the mean hypomanic episodes (± SD) were 3.0 (± 1.77), and 0.78 (± 1.48), in the BD II group, the mean hypomanic episodes 3.21 (±2.19 SD), respectively. The groups did not differ from each other on the mean number of manic/hypomanic episodes (p = 0.804). The cigarette smokers were twenty-one (30.%) participants for the BD I group, nineteen (27.1%) participants for the BD II group, and fourteen (20.%) participants for the control group. According to the results of statistical analysis, there was not found a significant relationship between smoking and duration of illness between groups (BD I (χ^2 = 0.258, df = 66, p = 0.79), BD II (χ^2 = 0.073, df = 68, p = 0.472), BD I+BD II (χ^2 = 0.320, df = 136, p = 0.50), total participants (χ^2 = 0.001, df = 208, p = 0.30). The mean amount of cigarettes (±SD) were 5.75 (±9.85) packs/year in the BD I group, 3.94 (±8.23) packs/year for the BD II group, and 3.53 (±8.05) packs/year for the control group, respectively. Additionaly, there was not a significant correlation between the amount of cigarettes and the duration of illness for BD I (correlation coefficient) r = 0.202, p = 0.094) and BD II (r = 0.151, p = 0.212). Mood stabilizers and combination therapies were significantly more frequently offered in the BD I group. There was a significant difference in the use of mood stabilizers and combination therapy (AP + mood stabilizers) between the BD I group and the BD II group (p = 0.002, p < 001).

Prevalence of metabolic syndrome and the presence of metabolic syndrome components according to the groups

In participants with BD who met the diagnostic criteria for MS, the prevalence of the individual diagnostic components was as follows: 93.4% for abnormal WC, 82.4% for low HDL, 74.7% for hypertriglyceridemia, 50.5% for high systolic BP, 48.4% for high FBG, 29.7% for high diastolic BP.

There was a statistically significant difference between the BD I group, and the BD II and control groups in terms of body mass index (BMI), WC, diastolic BP, triglycerides, and FGB (all p values < 0.001). On all these parameters, the BD I group had higher levels than the other two groups. On the same parameteres, there were no statistically significant differences between the BD II group and the non-psychiatric controls. Systolic BP was statistically significantly different between the BD I group and the non-psychiatric controls, and the BD I group had higher levels. There was a statistically significant difference in the HDL-cholesterol levels between the BD II group, and the non-psychiatric controls and the BD I group (p < 0.001), and the BD II group had higher levels than the other groups.

There was a statistically significant difference between the groups in terms of the prevalence of metabolic syndrome according to different diagnostic criteria (all p values < 0.01). According to the diagnostic criteria of the NCEP-ATP-III, the ATP-III-A, and the IDF, the prevalence of MS was higher in the BD I group than the BD II group and the non-psychiatric controls. The prevalence of MS did not differ from each other in the BD II group and the control group. Mean scores of the MS components and the prevalence of MS according to the groups are presented in Table 2.

Factors associated with metabolic syndrome

The effect of the independent variables sex (coded as female = 0/ male = 2), age, duration of psychiatric illness, presence of comorbid physical illness (coded as yes = 1/no = 2), total number of mood episodes, total number of hospitalizations, number of cigarette smoking (packs/year), total BDRS scores, and exercise status (MET (min/week (1 MET = 3,5 mL/kg/dk) on the presence of MS according to the IDF criteria was assessed by a binary logistic regression model. Because it was the most recent among other MS diagnostic criteria. There was a significant relationship between the presence of MS and the presence of comorbid physical illness, age, and the number of cigarettes smoked (p = 0.001, p = 0.037, p = 0.044, respectively).

Discussion

MS has also been known as Syndrome X, insulin resistance syndrome, Reaven syndrome, and the metabolic cardiovasculer syndrome[29]. MS was associated with a poor course of illness and prognosis in individuals with BD, suggesting that MS still is an important issue in clinical psychiatric practice[30,31].

In the present study, participants were assessed for MS according to the NCEP-ATP III, ATP III-A, and IDF criteria. According to the NCEP-ATP III criteria, the prevalence of MS was 57.1% for the

Table 2. Mean scores of the metabolic syndrome components according to the groups and prevalence of MS

	BD I		BD II		HC		χ^2	Post-hoc comparison	
	M	SD	M	SD	M	SD		(Tukey HSD)	*p*
BMI (kg/m²)	31.59	6.62	29.06	5.69	27.58	4.4	43.57	BD I>BD II=HC	< 0.001
WC	111.69	14.28	104.23	13.4	103.56	11.57	54.78	BD I>BD II=HC	< 0.001
Diastolic BP	79.43	8.49	75.21	8.18	76.71	9.59	18.56	BD I> BD II=HC	< 0.001
Systolic BP	124.14	13.13	121.0	11.05	118.49	14.74	21.07	BD I> HC=BD II	< 0.001
HDL-c	42.94	14.35	53.14	13.13	47.73	13.1	52.22	BD II>HC=BD I	< 0.001
TG	169.54	118.17	140.64	95.73	133.33	74.79	42.22	BD I>BD II=HC	< 0.001
FBG	110.53	49.26	96.83	24.07	93.57	17.96	13.48	BD I>BD II=HC	< 0.001

	BD I	BD II	HC	X^2	p
ATP-III	40 (57.1)	21 (30)	25 (35.7)	11.855	**0.003**
ATP-III-A	40 (57.1)	24 (34.3)	25 (35,7)	9.399	**0.009**
IDF	41 (58.6)	24 (34.3)	26 (37.1)	10.045	**0.007**

BD I: bipolar disorder I; BD II: bipolar disorder II; HC: healthy control subjects; M: mean score; SD: standard deviation; F: one-way ANOVA; HSD: highly significant difference; BMI: body mass index; WC: waist circumference BP: blood pressure; HDL-c: high-density lipoprptein; TG: triglycerides; FBG: fasting plasma glucose; ATP-III: National Cholesterol Education Program Adult Treatment Panel; IDF: Internal Diabetes Federation.

BD I group, 30% for the BD II group, 35.7% for the non-psychiatric controls, according to the ATP III-A criteria 57.1% for the BD I group, 34.3% for the BD II group, 35.7% for the non-psychiatric controls and according to the IDF criteria 58.6% for the BD I group, 34.3% for the BD II group, 37.1% for the non-psychiatric controls. According results of previous MS prevalence in participants with BD studies, MS prevalence ranged from 17% to 53%[27,32-34]. MS prevalence has been reported to be 18-26% in European countries[10,35,36], and 30-49% in the USA[4,36-38]. The lower prevalence rate in European countries has been attributed to differing eating habits, ethnicity, and lifestyle[4]. The studies we use in relation to MS prevalence are presented in Table 4.

Focusing specifically on studies of MS in BD, in a study conducted in Taiwan where the participants with BD I (n = 15), BD II (n = 16), major depressive disorder (MDD) (n = 141), and anxiety disorders (n = 36) were compared in terms of the prevalence of MS, it was reported that 46.7% BD I, 25% BD II, 22% MDD, and 18.4% anxiety disorder participants suffered from MS[34]. In another study, which was conducted in New Zealand, the prevalence of MS was reported to be 50% for participants with BD, and 32% for healthy controls[16]. In a study in which participants with BD II without treatment (valproate acid and fluoxetine were used if needed) were monitored for 12 weeks in terms of their MS parameters, it was reported that only the BMI increased during the observation period. Therefore, the authors concluded that BD II was more moderate in terms of metabolic dysregulation, and that the prevalence of MS in BD II was similar to the general population[35]. In our study, the prevalence of MS was lower in the BD II group and the non-psychiatric controls than in the BD I group.

Not many studies were conducted in Turkey in this area of research, and in one of these studies, which consisted of 125 participants, the prevalence of MS was reported 32%[8]. In another study, evaluating the efficacy of agents used for MS treatment in BD, 60 participants were reported to have MS, with a prevalence rate of 36.7%[13]. We obtained a higher MS prevalence for BD I participants

Table 3. Summary of logistic regression analysis predicting the diagnosis of metabolic syndrome

	B	S.E.	OR	95 % CI	Wald	*p*
Sex	-.357	0.405	0.70	[0.317, 1.546]	0.77	0.37
Age (years)	-.038	.018	0.963	[0.929, 0.998]	4.33	**0.037**
Disorder duration (years)	0.004	0.026	1.004	[0.954, 1.056]	0.019	0.89
Presence of comorbid medical disorder	-1.572	0.474	0.208	[0.082, 0.526]	10.98	**0.001**
Total number of depressive episodes	0.051	0.099	1.052	[0.867, 1.277]	0.267	0.605
Total number of manic episodes	-0.253	0.191	0.776	[0.533, 1.130]	1.746	0.186
Total number of hypomanic episodes	-0.036	0.109	0.985	[0.779, 1.196]	0.106	0.745
Total number of hospitalizations	-0.002	0.201	0.998	[0.673, 1.479]	0.00	0.991
Exercise status (MET)	-0.169	0.494	0.844	[0.321, 2.222]	0.117	0.732
Number of cigarettes smoked (packs/year)	0.083BB	0.040	0.920	[0.850, 0.996]	4.248	**0.039**
BDRS total score	0.124	0.084	1.132	[0.961, 1.335]	2.195	0.138
BD I	-0.358	1.123	0.699	[0.077, 6.321]	0.101	0.750
BD II	-0.280	1.081	0.756	[0.091, 6.287]	0.067	0.796

Note: Comorbid medical disorder (1: yes, 2: no), Exercise status [1: 600-3000 MET (min/week (1 MET = 3,5 mL/kg/dk)], 2: > 3000 MET min/week). BD I: bipolar disorder I; BD II: bipolar disorder II; BDRS: Bipolar Depression Rating Scale.

Table 4. Summary of studies documenting the rate of metabolic syndrome in bipolar disorder

Author/year	Sample size		Location MS	MS Definition	Rate of MS	Rate of general population
Fagiolini *et al.* (2005)	171 BD, BD I-71%, BD II-26%, BD NOS-3%		USA	NCEP-III	30%	23.7%
Cardenas *et al.* (2008)	98 BD I/II		USA	NCEP-III	49%	
Birkenaes *et al.* (2006)	103 Sch, 83 BD I/II		Norway	NCEP-III	30%	
Fiedorowicz *et al.* (2008)	60 BD, BD I-59%, BD II-34%, BD NOS-7%		USA	NCEP-III	50%	27.3%
Sicras *et al.* (2008)	178 BD		Spain	NCEP-III	24.7%	14.4%
Yumru *et al.* (2007)	125 BD I		Turkey	NCEP-III	32%	
Salvi *et al.* (2008)	99 BD		Italy	NCEP-III and IDF 30% (IDF)	25.3% (NCEP-III),	16-17.8%
Correl *et al.* (2008)	74 BD		USA	NCEP-III	43.2%	23.7%
Garcia-Portilla *et al.* (2008)	194 BD		Spain	NCEP-III	22.4%	17.9%
Elmslie *et al.* (2009)	60 BD and 60 Controlled		New Zealand	NCEP-III	BD 50%	
	BD I-40,BD II-18, BD NOS-2				Control 32%	
Chang *et al.* (2009)	117 BD		Taiwan	IDF 2005	33.9%	M-20.4%, F-15.3%
van Winkel, de Hert (2008)	60 BD		Belgium	NCEP-III, Adapted NCEP III	16.7% (NCEP-III)	
				IDF	18.3% (adapted)	
					30.0% (IDF)	
	BD I	BD II		Cyclothymia	Hypomania	
Prevalence of BD (Lifetime)	0.2-4	0.3-4.8		0.5-6.3	2.6-7.8	

NCEP-III: National Cholesterol Education Program Adult Treatment Protocol; IDF: International Diabetes Federation, BD: bipolar disorder.

in our study. Previous studies have reported that the use of lithium, valproic acid and atypical antipsychotics (e.g. olanzapine, clozapine) contributed to obesity and MS in the BD group, mainly due to their effects on appetite and glucose and lipid metabolism[32,39]. The higher prevalence of MS in BD I group in our study may be related to the higher use of AP and mood stabilizers in this group. It also differs from other studies since BD II participants and non-psychiatric controls were also included. Although this finding may have been somewhat affected by the geographic differences, these differences might also indicate that additional factors, including genetic vulnerability and environmental (lifestyle) effects, may have played a role in modifying MS prevalence rates in patients with BD[33]. At this point, it should be emphasized that abdominal obesity is one of the main causes for the occurence of all the components of MS, because adipose tissue plays an important role in lipid and glucose metabolism, and because it is responsible for the production of various cytokines influencing the development of the syndrome[40]. In studies evaluating the prevalence of obesity in Turkey, the prevalence was reported 25 % in Trabzon[41], 28% in Ankara[42] and Kocaeli[43], and 29% in Mersin[44]. The prevalence of obesity in Tokat was higher than these cities, and it was reported 33.6 % for women, and 12.9 % for men[45]. Therefore, the difference of MS prevalence reported in these studies may be due to the differences in the prevalence of obesity, which is the major component of MS in the general population.

According to the IDF criteria, the prevalence of MS was 58.6% for the BD I group, 43.3% for the BD II group, and 37.1% for the non-psychiatric controls. In a study that investigated the prevalence of MS with different diagnostic criteria in participants with BD, it was determined that the prevalence of MS was 25.3% according to the ATP-III criteria, and 30% according to the IDF criteria[4]. Similarly, a higher prevalence of MS was detected with the IDF diagnostic criteria in our study.

The mean values for WC, BMI, systolic BP, diastolic BP, FBG, and TG levels were found to be higher in the BD I group compared to the BD II group and the control group. These values were similar in the BD II group and the control group, there was no significant difference between these two groups. In a recent study that compared participants with BD with participants with MDD and non-psychiatric controls in terms of MS parameters, it was reported that the mean values of WC, triglycerides, systolic BP, diastolic BP, and FBG levels were higher in participants with BD than in participants with MDD and in non-psychiatric controls, and there were also differences between the MDD group and the control subjects, where the levels were higher in the MDD patients than in the non-psychiatric controls[46]. Our study compared euthymic participants with BD I and BD II with non-psychiatric controls, which differs from other studies. Hence, these results are a novel addition to the literature.

In our study, the mean HDL-cholesterol levels were found to be the highest for the BD II group, and the lowest for the BD I group. These findings were in line with the prevalence of MS in our study. In a study that compared participants with BD with participants with MDD and non-psychiatric controls in terms of their HDL-cholesterol levels, the mean HDL-cholesterol levels were significantly the highest in non-psychiatric controls and was the lowest in BD I. In this study, an inverse relationship was found between the HDL-cholesterol levels and MS prevalence, which was similar to our findings[46]. Therefore it may be hypothesized that in patients with BD, HDL-cholesterol levels are a predictor for MS frequency, but surely there is a need for further studies to confirm this finding.

When analysing the prevalence of each of the components of MS in our population, we found that increased WC was the most common abnormality (93.4%), followed by abnormalities in low HDL-cholesterol levels (82.4%), increased triglyceride levels (74.7%), increased systolic BP measurements (50.5%), increased FBG (48.4%) levels, and increased diastolic BP measurements (29.7%). The majority of studies undertaken in participants with BD indicate that increased WC was the most[9,10,38,47-49], and increased FBG was the least frequently encountered abnormality[4,10,38,47,49-52], and our findings are also, to a great extent, in line with these previous reports.

Daily exercise time was found to be lower in the BD I group compared to the BD II group and the control group. In a study that examined the relationship between eating and lifestyle habits and metabolic disorders in participants with BD, unhealthy eating habits and lack of exercise were found to be higher in participants with BD than in healthy participants. In the same study, it was reported that unhealthy eating habits and lack of exercise were associated with weight gain and obesity[53].

Additionaly, relationship between participants smoking behavior and duration of illness was examined; there was not found a significant relationship between smoking and duration of illness and there was not a significant correlation between the amount of cigarettes and the duration of illness in our study. However, Medeiros *et al*., found a significant relationship between smoking and duration of illness, severity of manic symptoms in bipolar subjects[54]. Our study results were different, this discrepancy can be related to the fact that participants were in clinical remission.

The participants were assessed in terms of variables affecting MS, and there was a significant relationship between MS and the presence of comorbid physical illness, age and number of cigarettes smoked. The diagnostic categories of BD I or BD II were not associated with the presence of MS. In a study involving participants with BD I and BD II in which factors affecting the development of MS were assessed, it was reported that there was a relationship between the development of MS and age, BD I diagnosis, use of AP or mood stabilizers[55]. Our results are very similar to those reported by Van Winkel *et al*., in which patients with BD and MS were older than those without[36]. Aging is commonly accompanied by a loss of muscle mass and by an increase in body fat, especially in the abdomen, and both of these changes can increase IR and finally lead to MS[28]. Additionally, the meta-analysis by Sun, Liu and Ning[56], based on data from prospective studies concluded that active smoking was associated with the development of MS. In another study that examined the relationship between smoking and metabolic disorders, it was reported that smoking was higher in patients diagnosed with MS[57]. On the other hand, another study reported that there was no relationship between MS and smoking[4]. The results of our study add to the literature that there might be a significant relationship between MS and smoking.

The findings of the current study suggest that active and early screening of metabolic parameters, including triglycerides, and HDL-C levels, WC measurements, and lifestyle interventions, including dietary changes and physical activity are absolutely essential to managing MS among patients with BD and the general population. The Mediterranean diet (MD) is a dietary pattern first presented by Ancel Keys in the 1960s[58], and it is characterized by a high intake of fruits, vegetables, legumes, fish, whole grains, nuts, and olive oil; moderate consumption of dairy products and wine; and low intake of red and processed meats and foods that contain high amounts of added sugars[59]. The beneficial role of the MD with regard to mortality from all causes, cardiovascular disease (CVD) and cancer, as well as obesity and type 2 diabetes[60,61] has already been reported from the results of many epidemiological studies and clinical trials. Similar recommendations should proactively be pursued for the physical health status of patients with BD, and a closer follow-up regarding the metabolic parameters should be part of their routine clinical management program.

When the results of the current study are evaluated, it is necessary to consider the limitations of the study. The fact that participants were evaluated cross-sectionally, and that they were not followed up longitudinally, and that all of the patients were in an euthymic period might limit the generalizability of the results. Other limitations of the study are (i) there was no definitive causal relationship in the outcomes, (ii) the study results could not be compared, or were only suboptimally compared, with other studies in the literature due to lack of similarly designed studies in similar clinical populations, (iii) it was not possible to compare the groups which were offered psychopharmacological treatment with those who were not, which

might be a contributing factor for the development of MS, and (iv) did not evaluate the role of comorbid alcohol and substance use.

In light of the high rates of MS observed in all settings, we propose that minimum monitoring for all individuals, even those with normal baseline tests, should include WC or BMI at these time points. Optimal monitoring should also include assessments of FBG, triglycerides, HDL-c and BP. Patients treated with drugs with potential for weight gain and metabolic side effects should be evaluated more frequently in terms of weight and metabolic parameters. For the medical treatment of MS, lifestyle changes such as weight loss, regular exercise, smoking cessation, healty eating are also important. The MD is one of the healthiest dietary patterns, and it may help with the prevention and treatment of cardiovascular disase, diabetes, hypertension and MS.

In conclusion, this article aimed to draw attention to MS, which not only affects patients with BD, but also increases in frequency in healthy individuals all over the world, and to emphasize the importance of necessary measures to be taken. BD is relatively highly comorbid with MS, and appropriate interventions should be prioritized against the development of MS in BD.

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Original article

Evaluation of body image, sexual dysfunctions and quality of life in female patients with generalized anxiety disorder

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Abstract

Objective: This study aimed to compare the patients with GAD in terms of SD, body perception and quality of life with healthy controls. **Methods:** The study included 41 female patients and 40 healthy female individuals with an aged between 18-50 years, regular sexual life and married. The Arizona Sexual Experiences Scale(ASEX), Short Form 36(SF-36), Body Cathexis Scale(BCS) and Beck Anxiety Inventory were used in the subjects. Patients with chronic illness, comorbid psychiatric, endocrine, alcohol or substance use disorder, drug use that could impair sexual function, pregnant, lactation, were not included in the study. **Results:** In ASEX, high scores were found in 44% of GAD patients and 17.5% of the control group in terms of SD. Sexual desire, arousal, lubrication, and orgasm scores of ASEX correlated with the body dissatisfaction in GAD patients. Physical function, general health status, mental health scores of SF-36 were found lower in the GAD group. **Discussion:** As a result of these findings, it can be suggested that sexual function, body image and quality of life are negatively affected in GAD patients and that deterioration of them should be questioned as well as symptomatic relief in patients' follow-up and treatment.

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Keywords: Generalized anxiety disorder, sexual dysfunction, body image, quality of life.

Introduction

Generalized anxiety disorder (GAD) is a disorder characterized by symptoms such as excessive anxiety and worry about the events and activities, difficulty in controlling the worry, restlessness, easy fatigue, muscle tension and sleep disorder[1]. The lifetime prevalence of GAD is around 5% and is more common in women than in men[2]. The disorder is generally characterized by chronic features, with periods of exacerbation and recovery. For this reason, patients may need to use long-term medication[3]. In addition, GAD may have negative effects on the quality of life[4,5].

Sexual dysfunctions (SD) are defined as disorders in desire, arousal and orgasm phases and painful sexual disorders in DSM-5 (American Psychiatric Association 2013). Symptoms related to SD are not often questioned on psychiatric examination. Although the frequency of psychiatric disorders associated with GAD has been assessed in many studies, the majority of large-scale studies have not been questioned SD[2,6,7]. SD frequency varies among societies. In a study conducted in Turkey, 48.3% of women had sexual dysfunction; it was reported that 48.3% of the participants of the study had deterioration in desire level, 35.9% in arousal level, 40.9% in lubrication level, 42.7% in orgasm level and 45.0% in satisfactory level[8].

Sexual functions can affect many diseases. It has been reported that anxiety disorders increase the symptoms of SD[9-11]. Stress and anxiety cognitive processes can affect different endocrine and neurotransmitter systems and may cause negative effects on sexual function[12]. Anxiety has a repressive effect on sexual arousal and inhibits other stages of sexual functioning from occurring in a healthy way[13]. Medication used in the treatment of GAD also causes SD[3]. SD affects people's quality of life, interpersonal relations and self-esteem negatively[14] and SD are one of the important factors affecting the general health status and quality of life of women.

Body image is a multidimensional concept involving the image, attitude, thoughts, feelings, and behaviors of one's body[15,16]. Body image has a decisive influence on one's self-esteem, eating behavior, anxiety levels, sexual behavior, functioning, social relations and emotional state. Body image is related to mental health[17]. Deterioration in mental health can cause someone not to like their own body[18]. As far as we know, no study has evaluated the relationship between SD, body image, and quality of life in GAD patients. In this study, it was aimed to compare patients with GAD with healthy controls in terms of SD, body image/perception and quality of life, and to investigate whether there is a relationship between these parameters in patients.

Methods

Forty seven female patients who applied to the Practice and Research Hospital Psychiatry Outpatient Clinic, were diagnosed as GAD by 2 different specialists (ÖK, YH) according to the DSM-5 diagnostic criteria[1] included to this study. 6 patients who were not fully filled in the scales were excluded from the study. At the end of the study, 41 female patients and 40 healthy female volunteers evaluated in statistical analysis. All participants were married. Patients whose age were ranging between 18 to 50, who had regular sexual life included in the study. Patients with chronic illness, comorbid depression or other psychiatric illnesses, endocrine disorder (thyroid dysfunctions, diabetes, hypogonadism), local genital problems (vaginitis, pelvic infections), cardiovascular disease, renal and hepatic disease, neurological disorder, drug use that could impair sexual function or oral contraceptive, pregnant and lactation, physical disease or undergone surgery that could impair the physical appearance, alcohol or substance use disorder were not included in the study. This study was approved by the Ethics Committee of Yozgat Bozok University (2017-KAEK-189_2017.08.24_11), and a written consent form was obtained from all of the individuals prior to the study.

Instruments and materials

Sociodemographic Information Form

This form was prepared by the physicians who conducted the study in order to question the sociodemographic characteristics of the people taken into the study and their knowledge about the disease. Information about the age, marital status, education level, monthly income, working status of the people took place in the form.

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Arizona Sexual Experiences Scale (ASEX)

This is a Likert type scale consisting of 5 questions developed by McGahuey *et al.*[19] Turkish validity and reliability of the scale were assessed by Soykan (2004) in patients who received dialysis treatment due to end-stage renal failure[20]. There are two forms of ASEX as for women and men. Sexual desire, arousal, penile erection/vaginal lubrication, orgasm and satisfaction of the orgasm are evaluated. Each question is scored between 1 and 6 and the total score is between 5-30. High scores indicate that the severity of the SD is high. A total score of 17 or above or 5 or more points from any question is considered as the SD.

Short Form-36 (SF-36)

This form, which is often used to measure the quality of life, was developed in 1992[21]. Scale was defined as physical function (10 items), social function (2 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items) and general health perceptions (5 items); total of 36 items. Scores from 0 to 100 are used in the scale evaluating the last 4 weeks and high scores indicate good health. Turkish validity and reliability study was conducted by Koçyiğit *et al.*[22].

Body Cathexis Scale (BCS)

BCS was developed by Secord and Jourand[23] and Turkish validity and reliability were made by Hovardaoğlu[24]. The scale consists of 40 items and aims to measure the levels of satisfaction of various parts of the body and body functions. There are 5 different responses for each item in the scales from 1 to 5 in the form of 'I do not like at all', 'I do not like', 'I am indecisive', 'I like it' and 'I like it very much', and the total score of the scale varies between 40-200. The high score indicates the level of satisfaction of the individual's body. The cut-off score of the scale was 135, and scores below that were defined as the low-level group.

Beck Anxiety Inventory

This is a Likert type scale, consisting of twenty-one questions, and it is the scale of self-assessment used to determine the severity of anxiety symptoms experienced by an individual. Each question has 4 options and is rated with a score between 0 and 3. The high score on the scale indicates the severity of the anxiety of the person[25]. The validity and reliability of our country were made by Ulusoy *et al.*[26].

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. When the study data were evaluated, descriptive statistical methods (mean, standard deviation, median, 1. quartile, 3. quartile, minimum, maximum), as well as normal distributions of quantitative data, were tested with the Shapiro-Wilk test and graphical examinations. Independent groups t-test was used for the comparison of the two groups of normal distribution quantitative variables, Mann Whitney U test was used for the comparison between the two groups of quantitative variables without normal distribution. Pearson correlation analysis and Spearman correlation analysis were used to evaluating the relationships between quantitative variables. Statistical significance was accepted as $p < 0.05$.

Findings

The study was conducted with a total of 81 patients who applied to the Practice and Research Hospital Psychiatry Outpatient Clinic between October 2017 and January 2018. The ages of the cases ranged from 19 to 47 years with an average of 33,05 ± 6,81 years. The duration of education of the cases ranged from 5 to 16 years with an average of 9.33 ± 3.88 years (Table 1). High scores for SD were found in 18 (44%) of GAD patients and in 7 (17,5%) of the control group.

There was no statistically significant difference between the study and control groups in terms of age and duration of education ($p > 0.05$). In the study group, it was determined that the score for SD desire, arousal and orgasm subscale and scale total scores were statistically significantly higher than the control group scores ($p = 0.007$; $p = 0.049$; $p = 0.002$; $p = 0.005$ respectively) (Table 2). There was no statistically significant difference between groups in terms of SD lubrication subscale scores ($p > 0.05$) (Table 2). The BCS scores of the patient group were found to be statistically significantly lower than the control group scores ($p < 0.001$). The Beck anxiety scale scores of the study group were found to be statistically significantly higher than the control group scores ($p < 0.001$) (Table 2).

Table 1. Distribution of descriptive properties (all participants)

	Min-Max	Mean ± SD
Age (years)	19-47	33.05 ± 6.81
Duration of education (years)	5-16	9.33 ± 3.88
Sexual dysfunction		
Desire	1-6	3.07 ± 1.19
Arousal	1-6	3.05 ± 1.09
Lubrication	1-6	2.78 ± 0.99
Orgasm	1-6	3.26 ± 0.98
Satisfaction	1-6	3.00 ± 0.97
Sexual dysfunction total	7-26	15.16 ± 4.21
Body Cathexis Scale	97-198	147.77 ± 21.84
BECK Anxiety	4-59	22.21 ± 14.01
SF-36		
Physical Function	10-30	22.33 ± 5.19
Physical Role Difficulty	4-8	6.02 ± 1.41
Pain	2-11	9.10 ± 1.84
General Health	13-25	20.80 ± 3.27
Vitality	0-24	18.85 ± 4.47
Social Function	2-10	6.49 ± 2.04
Emotional Role Difficulty	3-6	4.53 ± 1.01
Mental Health	5-30	17.77 ± 5.30

SF-36: Short Form-36.

Table 2. Inter-group evaluations

	Control (n = 40)	Study (n = 41)	p
Occupation Work Unemployed	 26 (%65) 14 (%35)	 23 (%56) 18 (%44)	
	Median (25% per-75% per)	Median (25% per-75% per)	
Age (years); mean ± sd	33.23 ± 6.70	32.88 ± 6.98	0.820[a]
‡ Duration of education (years) ‡ Number of Children	10.5 (5, 12) 2 (2, 3)	8 (5, 12) 2 (1, 3)	0.369[b] 0.932[b]
‡ Sexual dysfunction – Desire	3 (2, 3)	3 (3, 4)	0.007[b],**
‡ Sexual dysfunction – Arousal	3 (2, 3)	3 (2.5, 4)	0.049[b],*
‡ Sexual dysfunction – Lubrication	3 (2, 3)	3 (2, 4)	0.315[b]
‡ Sexual dysfunction – Orgasm	3 (2, 3)	4 (3, 4)	0.002[b],**
‡ Sexual dysfunction – Satisfaction	3 (2, 3)	3 (3, 4)	0.054[b]
Sexual dysfunction – Total	13.85 ± 3.58	16.44 ± 4.41	0.005[a],**
Body Cathexis Scale; Mean ± sd	158.65 ± 17.64	137.15 ± 20.40	<0.001[a],**
Beck Anxiety Scale	12 (8.25, 13)	33 (22.5, 41.5)	<0.001[b],**

[a] Independent groups t-test; [b] Mann Whitney U test; ‡ Relevant data is presented in median (1st quartile, 3rd quartile); * $p < 0.05$; ** $p < 0.01$.

There was a statistically significant correlation in a negative way between the BCS score of the cases and SD desire, arousal, lubrication, orgasm subscale scores and scale total scores (r:-0.305, p:0.006; r:-0.259, p:0.019; r:-0.285, p:0.010; r:-0.348, p:0.001; r:-0.305, p:0.002, respectively). No statistically significant relationship was found between the scores of the body cathexis scale and the sexual dysfunction - satisfaction subscale of the cases ($p > 0.05$) (Table 3). There was a statistically significant correlation between the duration of education and sexual dysfunction-satisfaction subscale scores at a negative level (r:-0.225, p:0.043).

In the study group, SF-36 physical function, general health and mental health subscale scores were found to be statistically significantly lower than control group scores ($p = 0.001$; $p = 0.014$; $p = 0.001$, respectively). In the study group, SF-36 energy subscale scores were not statistically significantly lower but they were almost significantly lower than the scores of the control group ($p = 0.056$; $p > 0.05$) (Table 4).

Table 3. Assessing the relationship levels between body image and sexual dysfunction

	Body Cathexis Scale	
	r	p
Sexual Dysfunction – Desire	-0.305	0.006[c],**
Sexual Dysfunction – Arousal	-0.259	0.019[c],*
Sexual Dysfunction – Lubrication	-0.285	0.010[c],*
Sexual Dysfunction – Orgasm	-0.348	0.001[c],**
Sexual Dysfunction – Satisfaction	-0.208	0.063[c]
Sexual Dysfunction – Total	-0.338	0.002[d],**

[c] Spearman correlation analysis; [d] Pearson correlation analysis. * $p < 0.05$; ** $p < 0.01$.

Table 4. Inter-group evaluations

	Control (n = 40)	Study (n = 41)	p
	Median (25% per-75% per)	Median (25% per-75% per)	
SF-36 – Physical Function‡	24 (22, 27.5)	20 (15.5, 24)	0.001[b],**
SF-36 – Physical Role Difficulty‡	6 (5, 7)	6 (5, 7)	0.761[b]
SF-36 – Pain‡	9.1 (9, 10.4)	9 (8, 10.40)	0.467[b]
SF-36 – General Health‡	22 (20, 24.40)	20 (18, 22)	0.014[b],*
SF-36 – Energy (Vitality)‡	20 (18, 22)	20 (16, 20)	0.056[b]
SF-36 – Social Function‡	7 (5, 8)	6 (5, 8)	0.398[b]
SF-36 – Emotional Role Difficulty‡	5 (4, 6)	4 (4, 5)	0.093[b]
SF-36 – Mental Health‡	20 (16.25, 25)	15 (12, 17)	< 0.001[a],**

[a] Independent groups t-test; [b] Mann Whitney U test. ‡ Relevant data is presented in median (1st quartile, 3rd quartile).* $p < 0.05$; **$p < 0.01$.

Discussion

In this study, sexual dysfunction, quality of life and body image of the female, drug-free GAD patients who applied for an outpatient therapy to a psychiatric clinic of a university hospital and healthy individuals were compared. In the study, there was a significant deterioration in the sexual desire, arousal, orgasm levels in the GAD group compared to the control group. As the duration of education increased in all cases, the satisfaction related disorders decreased.

A number of psychological factors can be mentioned in the etiology of SD[13]. Anxiety disorders can be effective in the emergence of SDs[27]. In an epidemiological study, moderate and high anxiety values in women were reported to be associated with the risk of developing sexual problems by inhibition of stimulation, orgasm, and satisfaction[28]. In the study of Dèttore *et al.*[10], panic disorder (PD), GAD, and a control group were compared; and it was found that there was no difference in sexual function between PD and GAD. When compared with the group containing PD and GAD to the control group; significant deterioration was found according to arousal, orgasm, satisfaction and general sexual functioning in comparison with the control group. In women with PD or GAD, a negative correlation was found between state and trait anxiety and subjective arousal. Anxiety can cause negative effects on sexual function with different mechanisms. It can be suggested that an increase in anxiety leads to cognitive interference, followed by decreased attention to sexual stimuli and misinterpretations of these stimuli[11]. Anxious people perceive physiological sexual stimulation as anxiety-provoking and tend to concentrate their attention on threatening. As a result, they are reported to have more anxiety and less subjective reactions to sexual arousal.

Anxiety at the physiological level is highly stimulating rather than inhibiting sexual functions. This is the result of stimulation of the sympathetic nervous system[29] For this reason, anxiety in healthy individuals does not adversely affect sexual stimulation[30].

The frequency of SD accompanying psychiatric diseases varies. In the study of Kendurkar *et al.*[31], the incidence of sexual dysfunction was 30% in healthy controls and 64% in GAD. In the same study, there was a significant increase in desire, arousal, orgasm and total points in the women with GAD as compared to the control group, namely sexual dysfunction. The deterioration in the desire, arousal, orgasm and total scores of sexuality, which was also determined in our study, was matching with the results of the study of Kendurkar *et al.*[31]. In our study, 44% of the GAD patients and 17.5% of the control group had high scores for SD.

It has been reported that a low level of education increases the risk of having sexual dysfunction in the studies[32,33]. It has been argued that the low level of education may prevent the information given to the individuals from being implemented in a satisfactory manner and may cause sexual problems to increase[33]. In our study, as the duration of education increased in all cases, satisfactory related disorders were reduced. This result shows that education has a positive influence on sexuality.

In GAD cases, the body cathexis scale scores were found to be lower than the control group scores. This shows that GAD patients are more dissatisfied with their bodies. There is a significant relationship between body sensation and mental health[17]. Deterioration in mental health also results in less admiring of one's body[18]. The deterioration of the body image of GAD patients can also be explained by this situation. As dissatisfaction with the body sensation increased in our study group, the sexual dysfunction increased in the areas of desire, arousal, lubrication, orgasm. Deterioration in body image leads to avoidance of sexual activities in both genders[34]. In addition, it has been reported that women who received a diagnosis of SD found themselves less attractive than non-diagnosed women[35]. The findings of the SD in GAD patients may be due to impairment both from anxiety and body image. As a result, it can be said that anxiety, sexual functions, and body image are mutually influential factors.

SF-36 physical function, general health, mental health scores were lower in the GAD group than the control group. Anxiety symptoms and the chronic nature of the disease in GAD may lead to deteriorations in the quality of life. Anxiety disorders such as panic disorder[36] and GAD[4,37] have been reported to impair quality of life. The results of our study are consistent with literature data.

In conclusion, this study found that there was a significant deterioration in sexual function of GAD patients and that this disorder was almost in all areas of sexuality. GAD appears to be adversely affecting the quality of life due to its chronic nature. In addition, it was decided that the increase in body dissatisfaction in these patients affects sexual functions negatively. From these results, it is important to not only improve the symptoms of the illness in the follow-up and treatment of the patients but also to question the deterioration in these areas and to arrange the treatment plan accordingly.

There are limitations in the study such as the fact that only married and female gender has been evaluated, the number of cases is low, a cross-sectional study has been carried out, a detailed

psychiatric evaluation of sexual dysfunction has not been made and sexual orientation, sexual activity and sexual partnership data has not been asked at sexual history. Another limitation is that the scale used in the study is the self-report assessment. Patient and control group were selected from participants with similar sociodemographic factors and physical disorders. Nevertheless sexual functioning is affected by many factors, so it is not possible to provide similarity of groups. Follow-up studies in which both genders are evaluated together and the effect of treatment on the larger number of cases is assessed with comprehensive scales will contribute to the acquisition of consistent scientific data in this area.

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Original article

Optical coherence tomography findings in conversion disorder: are there any differences in the etiopathogenesis of subtypes?

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Abstract

Background: Optical coherence tomography is a contactless and fast neuroimaging method. Previous Studies have observed thinning of the ganglion cell layer and inner plexiform layer in many neurodegenerative diseases. **Objective:** The aim of this study was to compare the layers of ganglion cell complex in conversion disorder. **Methods:** This study involved 50 conversion disorder patients and 50 healthy volunteers as the control. The parameters were measured and recorded automatically by a spectral optical coherence tomography device. **Results:** There was no difference in the retinal nerve fiber layers between the conversion disorder group and the control group ($p > 0.05$). The left and right choroid layer thickness acquired from three regions of the choroid layer was higher in patients compared with controls ($p < 0.05$). The ganglion cell layer and inner plexiform layer volumes were also significantly lower in the patient group ($p < 0.05$). **Discussion:** These ganglion cell layer and inner plexiform layer findings suggest that neurodegeneration occurs during the course of conversion disorder especially in subtype involved motor component. The choroid seems to be more related to the sensory component and it may be used to determine the active stage of the disease and to monitor inflammatory process like other inflammation markers used in systemic inflammatory diseases.

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Keywords: Conversion disorder, ganglion cell layer, inner plexiform layer, neuron degeneration, optical coherence tomography

Introduction

Conversion Disorder (CD) "involves unexplained symptoms or deficits affecting voluntary motor or sensory function" that cannot be attributed to an organic neurological cause. The symptoms of CD are thought to be generated unconsciously, arising from trauma, daily stressors, or conflict[1]. Symptoms suggest a medical condition with a behavioral presentation mimicking various types of neurological symptoms. 30% of neurological patients have neurological symptoms that cannot be explained medically[2]. The psychiatric approach to conversion movement disorder and the neurological approach to the psychogenic movement disorders are both problematic. Neither neurology nor psychiatry has yet made a clear interpretation of the possible mechanisms underlying this disorder. For this reason, a number of neurobiological and neuroimaging studies have been conducted in recent years to explain the etiopathogenesis of CD[3].

Cellular, molecular, and structural pathologies of the limbic regions, amygdala, thalamus, and their interactions with different motor areas have been most commonly studied. These studies indicate abnormalities outside the core motor network, including the prefrontal cortex and anterior cingulate cortex. The results support the hypothesis of abnormal inhibition of motor systems by limbic regions or impairments of motor conceptualization. In addition, reduced thalamic, caudate, basal ganglia, and lentiform nuclei volume, increased amygdala activation have been reported in the cases of the CD. The studies suggested that patients with CD have smaller mean volumes of the right and left basal ganglia and smaller right thalamus, with a trend toward to smaller left thalamus compared to healthy controls. It is emphasized that this reduction may be important in understanding the pathophysiology of the CD. Brain volume loss has been observed in patients with CD, and these findings suggest that neurodegeneration accompanies with CD[4]. Another device that can be used to evaluate neurodegeneration is optical coherence tomography.

Optical coherence tomography (OCT) is a novel imaging method that can capture biological tissue layers by acquiring high-resolution sections. This technique measures the delay time and intensity of infrared light, which is transmitted to and reflected from different tissue layers. It gives cross-sectional images of tissues similar to, but with much higher resolution than ultrasonography. The OCT method was first described by Fujimoto et al. from the Massachusetts Institute of Technology. Then, its use in ophthalmology and in neurology was described. Its use increased rapidly because it is a non-invasive and rapid method that can assess the macula thickness (MT), volume (MV) and retinal layers. Because OCT technology significantly enhances the imaging resolution, the segmentation of retinal layers, such as the ganglion cell layer (GCL), inner plexiform layer (IPL), and retinal nerve fiber layer (RNFL), is now possible. The RNFL involves axons of ganglion cells, the ganglion cell layer (GCL) involves bodies of ganglion cells, and the IPL involves dendrites of ganglion cells[5,6].

Another parameter that can be measured with OCT is choroidal thickness. The choroid is among the most vascularized tissues in the human body, and it plays important roles in providing oxygen and nutrition to the outer retina, temperature regulation of the retina, disposition of waste products from the retina, and the release of growth factors. Thus, any vascular pathology can cause choroidal thinning. More recently, its use was expanded to neurodegenerative diseases because the retina is an anatomical extension of the brain, and retinal changes may occur in parallel with inflammation and CNS degeneration[7,8]. OCT has shown retinal changes in neurodegenerative diseases, such as multiple sclerosis[8], Alzheimer's disease[9], Parkinson's disease[10], and restless leg syndrome[11] which correlated with the severity of clinical disease. A demonstration of retinal neuronal loss using OCT provides great evidence for degeneration. Research on multiple sclerosis patients has repeatedly shown an association between retinal thinning and gray matter damage in the brain. Therefore, the thickness of the retinal layers has become an important anatomical parameter to track neurodegeneration[12].

More recently OCT was used to detect neuronal degeneration in psychiatric disorders. Using time domain OCT Cabezon *et al.*[13] reported a significant reduction in the overall and superior quadrant RNFL thickness in schizophrenia patients compared with controls. The Spatial resolution of OCT devices increased with new spectral

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domain OCT and this enabled separation of other retinal sublayers such as GCL and IPL was shown to have better structure-function correlation in neurodegenerative diseases such as multiple sclerosis then RNFL[14]. Our group demonstrated reduced GCL and IPL volumes in schizophrenia patients compared with controls using spectral OCT[15]. We also detected significant negative correlations between disease severity parameters and GCL and IPL volumes. In our another study, it is suggested that the neurodegeneration occurred during the course of bipolar disorder may be demonstrated by decreased GCL at early stages, and as the disease progresses, the involvement of other retinal layers, such as the RNFL and IPL, maybe observed[16]. Again, our research team demonstrated that OCT finding of decreased GCL and IPL volumes supports previous research suggesting degeneration in major depressive disorder. According to this study, considering RNFL to be the latest layer that will be affected during the course of degeneration, GCL and IPL volumes appear to be better parameters follow. In addition, choroid may be an important structure to detect acute attack period and to follow the inflammatory process in major depressive disorder like in systemic inflammatory diseases[17]. To the best of our knowledge, no study has assessed the OCT parameters (RNFL, GCL, IPL, and choroidal thickness) in patients with CD.

Although not a subtype classification based on Diagnostic and Statistical Manual of Mental Disorders (DSM), some authors preferred to distinguish conversion disorder according to symptoms[18-20]. In these studies, there was information that conversion symptoms may have emerged with different etiopathogenesis. Our hypothesis was that the symptoms of conversion disorder could be separated with the structures of eye. The aim of this study was to compare the RNFL, GCL, IPL, and choroidal thickness of patients with motor CD (M-CD, abnormal movements such as tremor, dystonia or weakness such as paraplegia) with somato-sensorial CD (SS-CD, represents the symptoms of sensory loss such as not seeing, not hearing) with sensori-motor CD (SM-CD) and controls to assess the usefulness the usefulness of these measurements to demonstrate neurodegeneration in CD.

Material and methods

Study sample

This case-control study compared patients with CD who were followed in the Psychiatry Department at our University Medical School with a control group. The patients with CD were consecutive patients who were being followed at our outpatient clinic at least for the last 6 months. The CD group consisted of 50 patients (10 males and 40 females). In terms of subtypes; there were 19 M-CD patients, 20 SS-CD patients, and 11 SM-CD patients. After being seen during the baseline visit by the treating psychiatrist, each patient's eligibility for the study was evaluated, and if they were eligible, they were invited to participate in the study. The control group consisted of 50 healthy volunteers without a history of a CD who were recruited from the hospital staff. OCT measurements were made in the Ophthalmology Department at our University Medical School. All OCT measurements were made between 10 am – 14 pm due to the operating time of the device. Local ethics committee approval was obtained, and all study participants provided written informed consent (Protocol Number: 2016/2-7).

Inclusion and exclusion criteria

Patients with CD who were between 18 and 65 years of age and who were diagnosed according to the DSM-IV-TR criteria[1] were included. Patients who had comorbid first axis diagnosis, hypertension, diabetes mellitus, severe neurological, immunological or systemic diseases (glaucoma or retinal diseases) were excluded. Patients with refraction errors ≥ 1 prism dioptre were also excluded. Both the patient and the control groups were examined in the ophthalmology clinic and best corrected visual acuity, intraocular pressure, slit lamb bio-microscopy, and fundus examination by eye dilatation was measured. Patients and controls with normal eye findings were included. The group of healthy controls did not have any first axis diagnosis, hypertension, diabetes mellitus, severe neurological, immunological or systemic diseases which may affect the results.

OCT measurements

A spectral-OCT device (SpectralisTM OCT, Version 6.0, Heidelberg Engineering, Germany) was used to assess the RNFL and choroid thicknesses and GCL and IPL volumes in both eyes. The RNFL includes temporal (T), nasal (N), temporo-superior (TS), temporo-inferior (TI) and global (G) segments. Therefore, 7 measurements were made for each eye (i.e., N, NS, NI, T, TS, TI, G) (Figure 1).

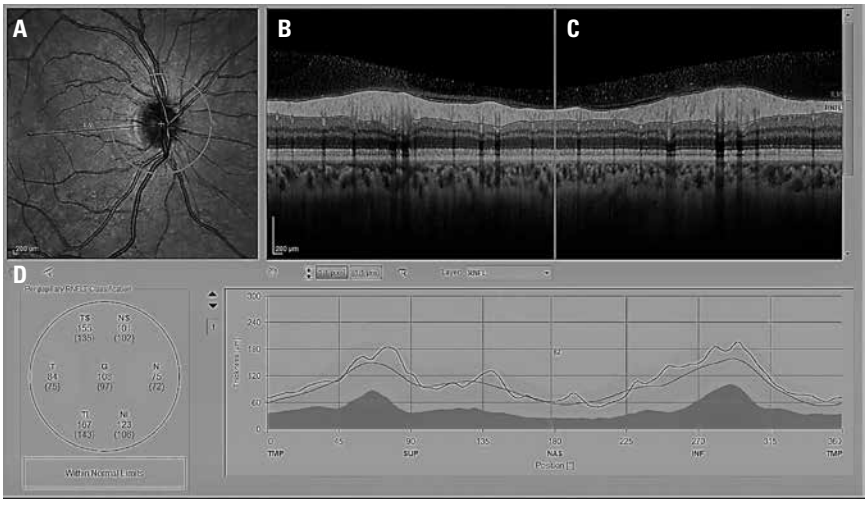

Figure 1. Measurement of RNFL thicknesses with spectral OCT.
A. The circle is drawn around the optic disc to measure peripapillary RNFL thickness. **B.** Demonstration of RNFL. **C.** Seven measurements are performed for each eye, providing the RNFL thickness of the TS, TI, T, NS, NI, N, and G sectors. **D.** RNFL thickness map.
OCT: Optical Coherence Tomography; RNFL: Retinal Nerve Fiber Layer; TS: Temporo-Superior; TI: Temporo-Inferior; T: Temporal; NS: Nasal Superior; NI: Nasal Inferior; N: Nasal; G: Global.

The choroid structure was also measured with OCT. The choroidal thickness was measured manually. A perpendicular line was drawn subfoveal from the outer edge of the retinal pigment epithelium to the choroid-sclera junction. Two additional lines were drawn at the nasal and temporal sides at 500 μm intervals from the subfoveal line. The mean value of these 3 measures was accepted as the choroidal thickness. All measurements were performed by the same author (ASK) who was blinded to the diagnoses of the patients. The choroidal measurement method used with the spectral-OCT devices has been previously explained.

Lastly, we measured the GCL and IPL volumes with an OCT device. Segmentation of the retina into 6 layers (GCL, IPL, RNFL, inner nuclear layer, outer plexiform layer, outer nuclear layer) was performed automatically with the device (Figure 2). Because the between-group comparisons provided similar results for the right and left eyes, only the results of the right eye are provided in the tables and discussed to decrease the complexity of the tables.

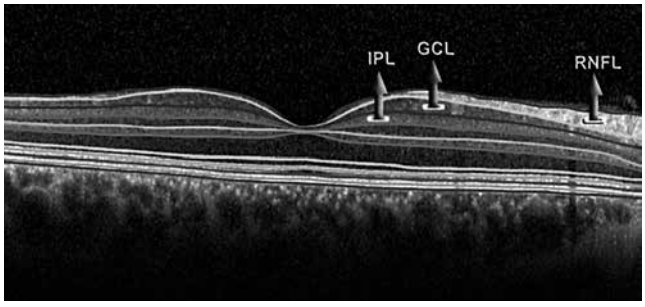

Figure 2. Measurement of the GCL and IPL thicknesses with spectral OCT. GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; RNFL: Retinal Nerve Fiber Layer; OCT: Optical Coherence Tomography.

Statistical analyses

Statistical analyses were performed using SPSS 22.0 package program (IBM Corp). The mean ± standard deviation and percentages were used as descriptive statistics. The Chi^2 test was used to compare categorical variables. The normality of the data was tested using the Kolmogorov-Smirnov test. An independent samples t-test was used to compare 2 normally distributed variables and the Mann-Whitney U test was used to compare 2 non-normally distributed variables. ANOVA and post-hoc Tukey's B test were used to compare more than two normally distributed variables. The Kruskal-Wallis test was used to compare more than two non-normally distributed variables. $P < 0.05$ indicated statistical significance.

Results

Socio-demographic data

The mean patient ages in the CD group and control groups were 35.68 ± 12.03 and 37.96 ± 15.88 years, respectively and it was not significant ($p = 0.420$). The socio-demographic features of the patients and controls are shown in Table 1. There were no statistically significant differences between the groups, according to sex, marital status, and smoking. Education was significantly higher in the control group than in the patient group ($p < 0.05$). Occupation status was also significantly higher in the control group than in the patient group ($p < 0.05$). In the CD group, there were a family history in 9 (%18) patients and 41 (%82) not. The mean disease duration was 10.52 ± 9.10 in the CD group. Number of hospitalizations; none: 41 patients (%82), < 3: 6 (%12), and > 3: 3 (%6). When we divide the conversion patients into 3 subtypes according to the predominant symptom clusters. The number of M-CD patients was 19 (38%), the number of SS-CD patients were 20 (40%) and the number of SM-CD patients was 11 (22%).

OCT findings

When all the lower layers of RNFL were evaluated in both eyes; there was no difference in the RNFL layers between the CD group and the control group ($p > 0.05$) (Table 2).

The mean choroidal thickness, which is the mean value of the measurements from three regions, was significantly increased in the patients with CD compared with the controls ($p < 0.05$) (Table 2). The choroidal thickness of right eye in patients diagnosed with SS-CD was significantly higher than M-CD and SM-CD, but not significant for left eye's choroid thickness (Figure 3).

The GCL and IPL volumes were significantly decreased in the patients with CD compared with the controls ($p < 0.05$) (Table 3). We found significantly lower GCL and IPL volumes in M-CD and SM-CD patients ($p < 0.05$). But, GCL and IPL volumes were not significantly lower in SS-CD patients when compared with M-CD and SM-CD patients (Table 4). There was no a significant decrease in GCL and IPL volumes in SS-CD patients when compared with control group ($p < 0.05$) (Table 5) (Figure 4).

Discussion

We found 3 main findings in imaging studies done with OCT device in the CD patients. One of the most important findings of our study was the lower volume of GCL and IPL volumes in CD patients compared with the controls for both eyes. Somas of the ganglion cells form GCL, dendrites of ganglion cells form IPL, and their axons form RNFL[12,13]. So our finding implies degeneration in somas and dendrites of the neurons in the retina. Axonal degeneration can be responsible for decreases in the gray matter volume and also the thinning of the RNFL. Nerve axons in the retina make synapses at the mesencephalon, lateral geniculate nucleus, pretectum, and hypothalamus. We wanted to investigate the retina by OCT method to find clues for neurodegeneration. Because the retina is accepted as an extension of the brain by many anatomists due to the embryological development and cellular structure[7,21].

Table 1. Sociodemographic features of the patients and the control groups

	Patient		Control		P value
	N = 50	%	N = 50	%	
Sex					0.483
Male	10	20	14	28	
Female	40	80	36	72	
Education					**0.026**
No	5	10	5	10	
Primary school	21	42	7	14	
Secondary school	6	12	11	22	
High school	11	22	20	40	
University	7	14	7	14	
Occupation					**0.000**
No	17	34	18	36	
Worker	2	4	19	38	
Public servant	1	2	9	18	
Farmer	1	2	1	2	
Other (Housewife)	29	58	3	6	
Marital Status					0.641
Married	38	76	34	68	
Single	10	20	14	28	
Divorced	2	4	2	4	
Smoking					0.125
Yes	6	12	13	26	
No	44	88	37	74	

Table 2. Mean values for RNFL and choroid thickness

	Patients (Mean ± SD)	Controls (Mean ± SD)	P value
Right nasal superior/Left nasal superior	116,18 ± 23,51 µm/122,86 ± 27,91 µm	112,60±19,49 µm/124,88±20,43 µm	0.409/0.681
Right nasal inferior/Left nasal inferior	130,08 ± 23,40 µm/132,52 ± 25,24 µm	127,78 ± 27,32 µm/123,84 ± 27,11 µm	0,652/0.146
Right nasal/Left Nasal	84,40 ± 17,85 µm/83,28 ± 18,68 µm	83,54 ± 15,88 µm/78,02 ± 14,69 µm	0.800/0.121
Right temporal/Left temporal	72,86 ± 14,53 µm/71,54 ± 13,47 µm	75,34 ± 8,62 µm/73,348 ± 9,16 µm	0.302/0.402
Right temporal inferior/Left temporal inferior	147,60 ± 22,87 µm/149,12 ± 26,33 µm	154,70 ± 17,55 µm/154,24 ± 20,16 µm	0.085/0.278
Right temporal superior/Left temporal superior	145,52 ± 25,96 µm/144,68 ± 20,19 µm	145,76 ± 14,77 µm/146,78 ± 14,16 µm	0.955/0.548
Right global/Left global	106,32 ± 11,09 µm/106,94 ± 11,15 µm	107,32 ± 8,82 µm/106,92 ± 10,25 µm	0.619/ .993
Right choroid mean/Left choroid mean	310,60 ± 54,11 µm/298,90 ± 55,31 µm	249,16 ± 31,67 µm/247,66 ± 37,02 µm	**0.000/0.000**

RNFL: Retinal Nerve Fiber Layer, SD: Standard Deviation.

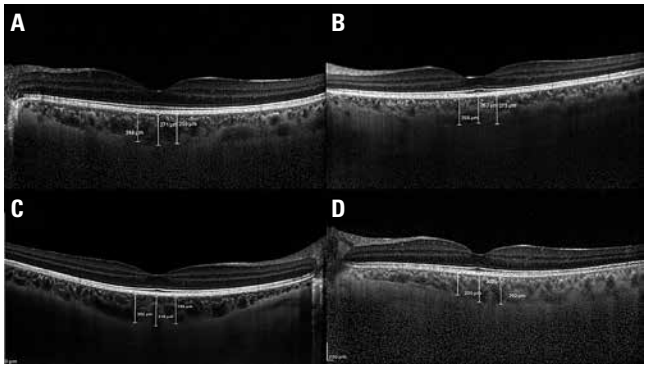

Figure 3. Comparison of choroidal thickness of CD subtypes.
Comparison of choroidal thickness of a patient with M CD (**A**), a patient with SM-CD (**B**), a patient with SS-CD (**C**), and a control (**D**) (CD: Conversion Disorder; M CD: Motor Conversion Disorder; SM-CD: Sensori-Motor Conversion Disorder; SS-CD: Somato-Sensorial Conversion Disorder).

In this study, we found a retinal nerve cell damage and neuronal degeneration in patients with CD. There are some studies that point to the findings of neurodegeneration in CD patients. Volumetric MR studies have found evidence for neurodegeneration in the brains of patients with CD[4]. Atmaca *et al.*[4] suggested that patients with CD have significantly smaller mean volumes of the left and right basal ganglia and smaller right thalamus, with a trend toward to smaller left thalamus compared to healthy controls. The demonstration of decreased activity in some areas of the brain in single photon emission computed tomography (SPECT) and functional magnetic resonance imaging studies is important in supporting neuropathological processes in the brain. In one of the studies related to cerebral blood flow, Czarnecki *et al.*[22] compared conversive tremor with essential tremor using SPECT at rest and during a tremor-inducing motor task (to bring a cup from a table to the face). During the motor task, patients with functional tremor had decreased regional cerebral blood flow in the ventromedial prefrontal cortex consistent with abnormalities of the default mode network, which were not observed in essential tremor. According to the study of Schrag *et al.*[23], psychogenic dystonia was associated with greater basal ganglia and cerebellar and decreased primary motor cortical blood flow, compared with healthy volunteers and patients with organic dystonia.

The second remarkable finding of our study is differences between subtypes of CD in terms of GCL and IPL. We found significantly lower GCL and IPL volumes in M-CD and SM-CD patients. But, GCL and IPL volumes were not significantly lower in SS-CD patients when compared with motor and SM-CD patients. There was no a significant decrease in GCL and IPL volumes in SS-CD patients when compared with control group. So; Neuronal degeneration in M-CD and SM-CD patients were found to be significantly higher than the control group, but no neuronal loss

Table 3. Mean GCL and IPL volumes of left and right eyes

	Patient (Mean ± SD)	Control (Mean ± SD)	P value
Right GCL	1.12 ± 0.99 µm	1.20 ± 0.47 µm	0.000
Left GCL	1.11 ± 0.97 µm	1.20 ± 0.47 µm	0.000
Right IPL	0.91 ± 0.73 µm	0.96 ± 0.50 µm	0.000
Left IPL	0.91 ± 0.75 µm	0.96 ± 0.50 µm	0.000

GCL: Ganglion Cell Layer, IPL: Inner Plexiform Layer, SD: Standard Deviation.

in SS-CD was found. This finding suggests that a more destructive etiopathogenesis is responsible for neuronal damage in the motor component dominant CD. Indeed, in the study of Voon *et al.*[24], some neurological findings were pointed out in CD patients with psychogenic movement disorder. The studies reveal abnormalities outside the core motor network, including the anterior cingulate cortex and prefrontal cortex. These findings support the hypothesis of impairments of motor conceptualization or abnormal inhibition of motor systems by limbic regions[25,26]. The result of all these studies suggests that neurological deficit is predominant in M-CD.

The third important finding of our study is changes in choroid thickness in CD patients. The choroid is one of the most vascularized tissues of the human body and it plays important roles in nutrition and oxygenation of outer retina, disposal of waste products out of retina and secretion of growth factors[27]. Choroid tissue is affected by any inflammatory or autoimmune conditions affecting blood flow. Research in some autoimmune diseases with retinal involvement (e.g. Behçet's disease) also demonstrated that choroid thickness increases during acute attack periods due to increased inflammation but then decreases with progressing disease[28]. We detected a significant increase in choroid thickness in CD patients who did not have any systemic disease that can disturb the vascular structure of affect blood flow when compared with. In addition, the choroidal thickness of right eye in patients diagnosed with SS-CD was significantly higher than M-CD and SM-CD, but not significant for left eye's choroid thickness. We suggest that an increase in choroid thickness results from the inflammatory process in the CD. Inflammatory process has been demonstrated in many psychiatric disorders such as obsessive compulsive disorder and depression. Because CD occurs in response to psychosocial stress, neural plasticity promises hope in explaining the effect of stress on brain[29]. One candidate mechanism that has been proposed as the site of possible flaw in signal transduction from monoamine receptors is the target gene for brain-derived neurotrophic factor. Deveci *et al.*[30] demonstrated that the serum BDNF level of the healthy control group was statistically higher than the level of the CD group. Inflammation in the central nervous system is known to cause glial degeneration and this process is blamed in the etiology of Alzheimer's disease, and Parkinson's disease. Studies in psychoneuroimmunology yielded strong evidence that the nervous and immune systems are in interaction reciprocally[31]. These intercorrections are mainly mediated by hormones, neural activations, and cytokines. Tiyekli *et al.*[32] suggested that lower TNF-α levels were found during acute conversion phase. They stated that stress associated with CD may suppress immune function in acute

Table 4. Comparison of GCL, IPL, and choroidal thickness in right and left eyes in conversion subtypes

	Subtypes (I)	Patient (Mean ± SD)	Subtypes (J)	Mean Difference (I-J)	P value
Right GCL	M-CD* (n = 19)	1.06 ± 0.42 µm	SS-CD	-0.14726	**0.000**
			SM-CD	-0.01254	0.645
	SS-CD* (n = 20)	1.21 ± 0.82 µm	M-CD	0.14418	**0.000**
			SM-CD	0.13777	**0.000**
	SM-CD* (n = 11)	1.07 ± 0.54 µm	SS-CD	-0.13473	**0.000**
			M-CD	0.01254	0.645
Left GCL	M-CD (n = 19)	1.05 ± 0.63 µm	SS-CD	-0.14418	**0.000**
			SM-CD	-0.00641	0.856
	SS-CD (n = 20)	1.20 ± 0.47 µm	M-CD	0.10242	**0.000**
			SM-CD	0.09491	**0.000**
	SM-CD (n = 11)	1.06 ± 0.12 µm	SS-CD	-0.13777	**0.000**
			M-CD	0.00641	0.856
Right IPL	M-CD (n = 19)	0.87 ± 0.65 µm	SS-CD	-0.10242	**0.000**
			SM-CD	-0.00751	0.724
	SS-CD (n = 20)	0.97 ± 0.21 µm	M-CD	0.09363	**0.000**
			SM-CD	0.09282	**0.000**
	SM-CD (n = 11)	0.87 ± 0.34 µm	SS-CD	-0.09491	**0.000**
			M-CD	0.00751	0.724
Left IPL	M-CD (n = 19)	0.87 ± 0.50 µm	SS-CD	-0.09363	**0.000**
			SM-CD	-0.00081	0.972
	SS-CD (n = 20)	0.97 ± 0.47 µm	M-CD	0.09363	**0.000**
			SM-CD	0.09282	**0.000**
	SM-CD (n = 11)	0.87 ± 0.50 µm	SS-CD	-0.09282	**0.000**
			M-CD	0.00081	0.972
Right Choroid	M-CD (n = 19)	288.94 ± 37.16 µm	SS-CD	-41,45263	**0.016**
			SM-CD	-23,05263	0.247
	SS-CD (n = 20)	330.40 ± 23.25 µm	M-CD	41,45263*	**0.016**
			SM-CD	18,40000	0.350
	SM-CD (n = 11)	312.00 ± 54.17 µm	SS-CD	-18,40000	0.350
			M-CD	23,05263	0.247
Left Choroid	M-CD (n = 19)	295.57 ± 57.34 µm	SS-CD	-7,92105	0.663
			SM-CD	-0.69378	0.974
	SS-CD (n = 20)	303.50 ± 32.74 µm	M-CD	7,92105	0.663
			SM-CD	7,22727	0.734
	SM-CD (n = 11)	296.27 ± 58.12 µm	SS-CD	-7,22727	0.734
			M-CD	0.69378	0.974

M-CD*: Motor Conversion Disorder; SS-CD*: Somato-Sensorial Conversion Disorder; SM-CD*: Sensori-Motor Conversion Disorder; SD: Standard Deviation; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer.

Table 5. Comparison of GCL and IPL Volumes of Somato-Sensorial Conversion Disorder Patients with Control Group

	SS-CD Patient (Mean ± SD)	Control (Mean ± SD)	P value
Right GCL	1.21 ± 0.54 µm	1.20 ± 0.47 µm	0.540
Left GCL	1.20 ± 0.97 µm	1.20 ± 0.47 µm	0.474
Right IPL	0.97 ± 0.52 µm	0.96 ± 0.50 µm	0.522
Left IPL	0.97 ± 0.60 µm	0.96 ± 0.50 µm	0.606

SS-CD: Somato-Sensorial Conversion Disorder; SD: Standard Deviation; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer.

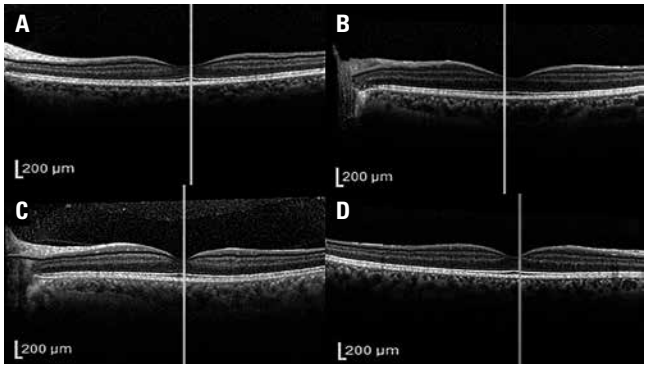

Figure 4. Comparison of GCL of CD subtypes.
Comparison of GCL volumes of a patient with M CD (A), a patient with SM-CD (B), a patient with SS-CD (C), and a control (D) (GCL: Ganglion Cell Layer; CD: Conversion Disorder; M CD: Motor Conversion Disorder; SM-CD: Sensori--Motor Conversion Disorder; SS-CD: Somato-Sensorial Conversion Disorder).

conversion phase and may have diagnostic and therapeutic value. We think that inflammatory process is active in patients with CD in symptomatic phase causing increased blood flow and increasing choroid thickness. Furthermore, the more significant increase in choroidal thickness in the somato-sensorial CD suggests that the inflammatory etiopathogenesis may play a more prominent role in the somato-sensorial subtype. The choroid thickening of the somato-sensorial CD and the direct retinal neuron damage of the motor CD and sensori-motor CD suggests the question of whether the subtypes differ in terms of etiopathogenesis. These results have led to the impression that the different clinical patterns of conversion disorder behave differently in terms of neurobiology. The cells involved in degeneration are mainly macrophages. Molecular inflammatory mediators such as cytokines, transcription factors, complement system, arachidonic acid metabolites, and oxidative stress parameters are also known to play a role in this mechanism[33]. Oxidative stress is mostly related to the increased formation of reactive oxygen and nitrogen species (ROS and RNS), which transmogrify the phospholipids and proteins leading to lipid peroxidation. These changes are considered to the change membrane permeability and configuration in addition to producing functional modification of various cellular proteins. Oxidative stress can cause to some cellular defects such as decreasing of the sarcolemmal Ca^{+2} ATP-ase pump and Na^{+}-K^{+} ATP-ase activities. These alterations lead to a decrease in the Ca^{+2} effluxes and an increase in the Ca^{+2} influxes, respectively. Oxidative stress has also been reported to suppress the sarcoplasmic reticulum Ca^{+2} ATP-ase pump and thus inhibits Ca^{+2} sequestration from the cytoplasm. ROS change the activity of Ca^{+2} regulatory mechanisms and this results in intracellular Ca^{+2} overload and cell death[34]. In these findings from different part of literature, somatic subtypes were thought to use more inflammatory processes, whereas motor subtypes were thought to use mechanisms that could lead to more direct neuronal damage. Though there is no significant difference in GCL and IPL volumes between the motor subtype and the sensori-motor subtype, the sensorimotor subtype was less affected than the motor type, suggesting that the thinning probably originated only from the motor component.

When all the lower layers of RNFL were evaluated in both eyes; there was no difference in the RNFL layers between the CD group and the control group. We have one possible explanation for this. Previous studies have found that RNFL damage can be detected by ophthalmologic examination only after 50% of the ganglion cells were damaged[35,36]. Therefore, RNFL damage may be expected to occur after more ganglion cell damage takes place. To detect such a process longitudinal studies should be performed in CD patients involving early-stage patients.

In conclusion, the findings of this study suggest that there is neuronal degeneration in CD and that it can be characterized by the thinning of the GCL and IPL. This thinning is more significant in CD patients involve motor component. Moreover, choroid may be used to determine the active stage of the disease and to monitor inflammatory process like other inflammation markers used in systemic inflammatory diseases.

Limitations

The major limitation of this study is its cross-sectional design. A prospective design starting from early periods of disease with regular follow-up OCT measurements would yield more convincing results about progressive degenerating nature of CD. There is a need for study that equals male and female subjects and control numbers. Another limitation of our study is lack of control measurements to increase validity and reliability of OCT to detect inflammation and degeneration. The inclusion of other neuroimaging methods such as magnetic resonance imaging to detect neurodegeneration and inflammatory markers such as interleukins or acute phase reactants to detect inflammation in future studies will provide better clues about the utility of OCT as a tool in neuropsychiatric disorders. Separation of patients into subgroups is another limitation because there is no classification system, since it is connected to the psychiatrist. The OCT application time can be clearer. Deep chamber, thick lens and axial length parameters are considered to be able to influence the measurements made and their absence is considered as a limitation. The fact that the medical treatment of the patient group is not known clearly is a limitation of this study. Effects of psychotropic medications on OCT measurements has not been studied in detail previously. Direct effects of psychotropic medications on the retina cannot be excluded and this should be assessed in further studies.

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Conflict of Interest

The authors declare that they have no competing interest.

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The outcomes of psychotherapy in mixed features personality disorders: a systematic review

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Abstract

Mixed features personality disorders (PDs) are highly prevalent and associated with significant burden of disease. Despite that, it has been an overlooked diagnostic category with respect to clinical research. This study aims to review empirical evidence about psychotherapy delivery available for these patients. We present a systematic review of clinical trials investigating the outcomes of psychotherapeutic interventions in adults with a primary diagnosis of mixed features PDs. Data were obtained from Medline/PubMed, Embase and PsycINFO. Seven studies met inclusion criteria; in one of them the whole sample was of this diagnostic group; two studies analysed psychotherapeutic intervention outcomes in this population, among other types of PDs, yet drawing specific conclusions on mixed features PDs patients; remaining studies addressed patient samples with different PDs types, mixed features included, where specific findings in this group of patients were not described – nonetheless, they included representative numbers of subjects with the diagnosis of interest. Available studies suggest that mixed features personality pathology *per se* does not seem to be an impediment to benefit from psychotherapeutic treatment, and improvement in different areas of life is possible for patients undergoing psychotherapy. The extant literature is marked by multiple challenges and inconsistencies across studies.

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Keywords: Personality disorder, psychological treatment, psychotherapy.

Introduction

Psychotherapy is the treatment of choice for personality disorders (PDs). This can be concluded from clinical guidelines, meta-analyses, and systematic or critical literature reviews[1]. Other treatments, such as pharmacological interventions, have received less empirical support[1,2].

According to the DSM-IV-TR, the category of Personality Disorder Not Otherwise Specified (PDNOS) can be used for "disorders of personality functioning that do not meet criteria for any specific personality disorder (…), the presence of features of more than one specific personality disorder that do not meet the full criteria for any one personality disorder (mixed personality), but that together cause clinically significant distress or impairment in one or more important areas of functioning"[3]. Recently, with the DSM-5, this category does not appear under this heading. The category of Other Specified Personality Disorder applies to similar presentations but is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific personality disorder (…) by recording Other Specified Personality Disorder followed by the specific reason (*e.g.*, "mixed personality features")[4].

Some of the structured diagnostic interviews have included directions for assigning a PDNOS diagnosis mixed type. In different approaches, it should be applied when the subject is one criterion below the diagnostic threshold for 2 or more PDs; it requires the presence of at least 10 criteria from the specific PDs; or it only requires that the subject meets traits from more than one specific PD, in addition to the general PD criteria[5]. On the other hand, Verheul *et al.* reported that a cut-off of 5 criteria yielded an additional group of PDNOS patients with a similar level of functional impairment as groups defined according to cut-offs of 10 or 15 PD criteria[5,6]. The assessment methods tend to produce different PDNOS prevalence rates[7].

Numerous studies suggest that PDNOS is one of the most prevalent mental disorders in clinical practice[8]. A meta-analysis on the prevalence and use of PDNOS diagnoses showed that 3%-6% of the general population and 8%-13% of clinical samples met the diagnostic criteria for a PDNOS diagnosis. The relative prevalence, defined as the prevalence of PDNOS divided by the overall axis II percentage without PDNOS, was estimated at 21%-49%[7]. As is the case for patients with specific PD, the burden of disease of patients with PDNOS is high, and, in terms of quality of life, patients report a quality-of-life score on the EuroQol (EQ-5D) comparable to patients with haemodialysis, rheumatic disease, lung cancer, Parkinson's disease or diabetes type II. The diagnosis is associated with high costs for society[8].

In a general population study, Johnson *et al.* found that adolescents and young adults in the general population diagnosed with PDNOS may be as likely as those with Cluster A, B, or C PDs to have axis I psychopathology and to have behavioural, educational, or interpersonal problems that are not attributable to co-occurring psychiatric disorders[9]. In contrast, the multicenter study of Verheul *et al.* found that PDNOS took an intermediate position between cluster A, B, or C PDs and no PD, regarding severity of personality pathology, symptoms, and functional impairment[6]. Another clinical study by Karterud *et al.* also found that PDNOS was associated with less severe psychopathology and better treatment response compared to patients with specific PDs[10]. Moreover, a few case reports of patients with a PDNOS diagnosis have been published[11-13].

Mixed features PDs have been an overlooked diagnostic category with respect to clinical research. Treatment studies typically focus on formal PDs and do not report results for these groups separately even when they are included in trials. According to our knowledge, there are very few treatment studies on mixed features PD patient groups, despite their high prevalence and high burden of disease, reasons why we took an interest in the subject.

Psychotherapeutic treatments can be delivered in various formats, settings, modalities, and dosages. This study aims to review the level of empirical evidence for different formats and settings that are available for psychotherapy delivery in mixed features personality disorders.

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Methods

This review was performed according to the PRISMA guidelines[14], thus providing a comprehensive framework which objectively assesses indicators of quality and risk of biases of included studies.

All original studies investigating the outcomes of psychotherapeutic interventions in adults (age between 18 and 65 years) with a primary diagnosis of mixed features personality disorders were eligible for this systematic review. Further criteria adopted were: (1) publication date in the last decade, between January 2007 and June 2017, (2) empirical study, and (3) written in English, Portuguese or Spanish language. Additionally, studies were excluded from review if they were: (1) single-case report, (2) review articles, (3) repeated study population, or (4) too small sample size (less than one-third of the total sample studied in cases where specific findings in mixed features PD are not described).

As this review focused on efficacy and effectiveness of interventions, naturalistic/non-controlled studies were included.

Studies were identified by searching relevant papers via PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed), PsycINFO and Embase using the following keywords in combination: "personality disorders"; "psychological treatment", and "psychotherapy". Finally, reference lists of retrieved studies were hand searched to identify any additional relevant studies.

After performing the initial literature searches, each study title and abstract was screened for eligibility by the first author. Full texts of all potentially relevant studies were subsequently retrieved and further examined for eligibility. The PRISMA flow diagram (Figure 1) provides more detailed information regarding the selection process of studies. Information from the included studies was then analysed and recorded in an electronic spreadsheet designed by the first author. Different types of data were extracted from each study including: (a) country in which the data were collected, (b) participants' characteristics (including diagnosis, age and gender), (c) number of subjects, (d) type of intervention (including modality, setting and duration of treatment) (e) type of outcome measure, (f) main results, and (g) study limitations.

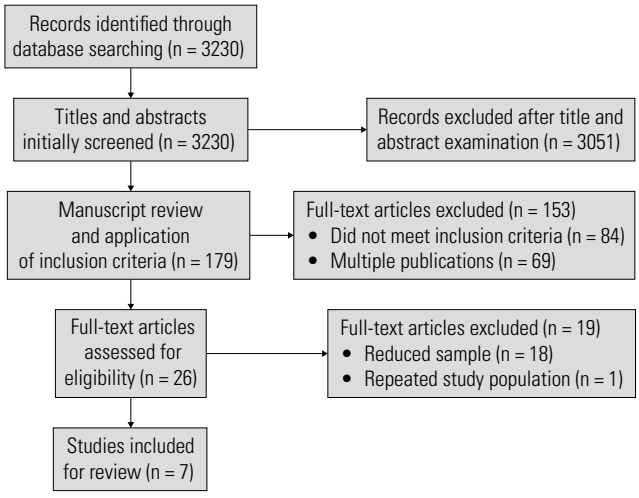

Figure 1. PRISMA flow diagram of the study selection process.

ROBINS-I and Cochrane Collaboration's tool for assessing risk of bias were adopted to evaluate the risk of bias in individual studies[15,16]. The following risk of biases were analysed: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of reported results. The assessments were completed by the first and third authors independently.

Results

Seven articles investigating the outcomes of psychotherapeutic interventions in adults with primary diagnosis of mixed features PDs were included in this review. One of them specifically focused on this diagnostic group, which corresponds to the study's whole sample[8]. Two other studies analysed the effectiveness of psychotherapeutic interventions in mixed features PDs, among other PDs types, yet drawing concrete conclusions for this specific patient subgroup[17,18]. The remaining four studies[19-22] were concerned with intervention outcomes in samples of patients with different PDs types, mixed features personality disorders included, where specific findings about this patient group were not described. Despite that, they included a representative number of subjects with the diagnosis of interest (at least one-third of the total sample studied) and, henceforth, its results were of interest to this review.

Four studies were from The Netherlands, two were from Norway, and one from Poland. Reviewed studies included 399 participants with a primary diagnosis of mixed features PD. Considering that six of the studies include varied samples and not only the mentioned diagnosis, known data related to gender distribution and average age are relative to whole samples and not only to this subgroup.

A summary of results is presented in Table 1 and risk of bias in individual studies based on ROBINS-I and Cochrane Collaboration's tool for assessing risk of bias is presented in Table 2. As shown in this table, deviations from intended interventions was the most frequent bias, with six of seven studies assessed having moderate risk for this type of bias. No bias due to confounding and in selection of reported result were found, although the risk of bias was not always clear.

Table 1. Effectiveness of psychotherapeutic interventions in adults with primary diagnosis of mixed features personality disorders

Study	Country; Study design	Subjects	Type of intervention	Type of outcome measure; Main findings	Study limitations
Horn *et al.*, 2015[8]	The Netherlands; Multicenter quasi-experimental	PDNOS N = 205 (100% of the sample): – PD mixed only (65%); – Appendix PD only (17%); – PD mixed and appendix PD (18%) Mean age 35.1 (SD = 10.3) years 72% female.	Short-term (≤ 6 months) and long-term (> 6 months) outpatient, day hospital and inpatient psychotherapy Psychodynamic (27%), cognitive-behavioural (21%) or integrative orientation (52%) 60 months follow-up.	Symptom severity; Psychosocial functioning; Quality of life Patients in all treatment modalities showed positive outcomes at short-term and long-term follow-ups, especially in terms of improvements of symptom severity and social role functioning. Short-term outpatient psychotherapy and short-term inpatient psychotherapy seem to be superior at 12-month follow-up. At 60-month after baseline, effectiveness remained but observed differences between modalities mostly diminished.	Not a randomized controlled trial. Difference of loss to follow-up. Did not take into acount other treatment attributes – potential impact of theoretical orientation and medication use, or patient attributes – axis I comorbidity. Effectiveness is determined by self-report, without information if whether patients still meet criteria for a PD diagnosis after 5 years. Sites overlapped only partially in terms of the (equal) availability of the six modalities.

Study	Country; Study design	Subjects	Type of intervention	Type of outcome measure; Main findings	Study limitations
Horn *et al.*, 2015[17]	The Netherlands; Matched-control study	PDNOS N = 61 (42% of the STIP-TA patients and 49% of the OP patients) Mean age 39.4 (SD 9.8) years in STIP-TA patients, and 39.3 (SD 10.2) in OP patients 70% female.	Short-term (3-month) inpatient Psychotherapy based on transactional analysis (STIP-TA) and other psychotherapies (OP) varying widely in terms of setting, duration, and theoretical orientation 36 months follow-up.	General psychiatric symptomatology; Psychosocial functioning; Quality of life At 36 months, 68% of STIP-TA patients were symptomatically recovered compared to 48% of OP patients. STIP-TA outperformed OP in terms of improvements in general psychiatric symptomatology and quality of life. Superiority of STIP-TA was most pronounced at 12-month follow-up, but remained intact over the course of the 3-year follow-up. A very promising and effective treatment option in mainly PDNOS patients.	Not a randomized controlled trial. Only self-report instruments used as outcome measures. Information about the treatment fidelity and adherence was not collected. The interpretation of the results is limited by the variation of treatment modalities in the OP condition.
Kvarstein *et al.*, 2017[18]	Norway; Naturalistic study	PDNOS N = 18 (17.4% of the sample) Mean age 38.5 (SD 10) years 60% female.	Outpatient Psychodynamic groups, mean treatment duration 1.5 (SD 0.9) years 3-year follow-up.	Symptom distress; Interpersonal problems; Occupational functioning; Psychiatric health service use. PDNOS benefits across all outcomes. The most favourable outcomes were found for patients with PDNOS. PDNOS patients may be well managed within outpatient group therapy.	Naturalistic designs limits inferences on outcome as an effect of the treatment. Dual roles of clinicians and researches may also limit validity of patient reported ratings. Diagnostic procedures held a high standard, but reliability was not investigated.
Chakhssi *et al.*, 2015[19]	The Netherlands; Nonrandomized exploratory study	PDNOS N = 38 (48.3% of the ACT patients and 42.9% of the CBT-TAU patients) Mean age 32.88 (SD 10.13) years in ACT patients, and 33.26 (SD 9.63) in CBT-TAU patients 82.7% female.	Specialized day hospital setting for patients with personality disorders that did not respond to previous treatments 26-week group-based acceptance and commitment therapy (ACT). Same duration group-based treatment-as-usual based on cognitive behaviour therapy (CBT-TAU) Both supplemented by arts therapy, including creative and drama therapy, and rehabilitation counselling.	Change in personality pathology; General psychological functioning; Experimental avoidance; Coping skills; Positive outcomes; Quality of life Group-based interventions for treatment-resistant patients with personality disorders led to significant improvements in personality pathology, general psychological functioning, coping skills and quality of life, regardless of whether participants received ACT or CBT-TAU. In group analysis, no main effect of therapy condition was observed on the outcome measures. Assessment of change on an individual level showed that a significantly higher percentage of participants receiving ACT improved on personality pathology.	Patients were not randomized. Treatment fidelity was not assessed. The unequal sample size across groups may have affect the results. The patients were not only provided with ACT or CBT-TAU but also with other treatments, and the effect of these treatments on the outcomes remains unknown. Medication use during the study was not measured. No independent data was available on the type and quality of previous outpatient treatment interventions. Do not report results for the PDNOS group separately.
Schaap *et al.*, 2016[20]	The Netherlands; Naturalistic prospective study	PDNOS N = 24 (42.9% of treatment completers and 26.1% of dropouts) Mean age 26.94 (SD 6.45) years 72.3% female.	12 months group schema therapy (ST) inpatient for patients with PDs who did not respond to previous psychotherapy Specific ST techniques, psychodrama, art, movement and music therapies, social services, pharmacotherapy, education about medication 6 months follow-up.	Maladaptive schemas; Schema modes; Maladaptive coping styles; Mental well-being; Psychological distress after treatment Over participants improved significantly on all outcome measures from pretreatment to posttreatment, and these improvements were maintained at follow-up. Experienced parenting styles was the one area that showed no improvement. These findings are comparable with treatment results for patients without such a nonresponsive treatment history.	Lack of a control-group. Treatment fidelity was not assessed. The patients were not only provided with ST, but also with additional therapies. Diagnosis were based on the clinical judgement and not by structured interviews. The relationship between the YSQ (Young schema questionnaire) and SMI (Short schema mode inventory) was large. Do not report results for the PDNOS group separately.

Study	Country; Study design	Subjects	Type of intervention	Type of outcome measure; Main findings	Study limitations
Cyranka *et al.*, 2016[21]	Poland; Naturalistic study	Mixed features PDs N = 34: – Other PDs (24% of the sample); – Mixed and other PDs (15% of the sample); – PDs unspecified (2% of the sample) Mean age 31.5 (SD 6.9) years 74% female	10-14 weeks intensive short-term group psychotherapy in a day ward with elements of individual therapy Integrated the elements of psychodynamic, cognitive and behavioural theories	Personality functioning using MMPI-2 clinical scales. Having undergone the psychotherapy treatment, the majority of the examined were observed to demonstrate positive changes in personality functioning which were classified as severe or moderate pathology.	Lack of a control-group. Not carrying out a follow-up study. Not extending the analysis with other questionnaire scales. Do not report results for the mixed features PDs group separately.
Hoglend *et al.*, 2011[22]	Norway; Randomized controlled clinical trial	PDNOS N = 19 (35% of transference group and 49% of comparison group) Mean age 34.9 (SD 8.7) years in transference patients, and 32.7 (SD 9.5) in comparison patients 63% female.	1 year of dynamic psychotherapy with low to moderate use of transference interpretations (transference group). Dynamic psychotherapy without this component (comparison group). Both with other treatments components such as clarifications, confrontations and extra-transference interpretations.	Remission from personality disorder; Improvement in interpersonal functioning; Use of mental health resources in the 3-year period after treatment termination. After therapy with transference interpretation, PD-patients improved significantly more in core psychopathology and interpersonal functioning, the drop-out rate was reduced to zero, and use of health services was reduced to 50%, compared to therapy without this ingredient. Three years after treatment termination, 73% no longer met diagnostic criteria for any PD in the transference group, compared to 44% in the comparison group.	Only clinician-rated outcome measures were used. No longer meeting full criteria for any PD may be seen as a problematic measure of recovery, since it also may include patients who just drop one criterion below the cut-off scores for a definite diagnosis. Primary outcome (recovery from PD) was based on non-blind ratings. Do not report results for the PDNOS group separately.

Table 2. Assessment of risk of bias in individual studies

Study	Bias due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias due to Deviations from Intended Interventions	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result
Horn *et al.*[8]	Low	Moderate	Moderate	Moderate	Moderate	Low	Low
Horn *et al.*[17]	Low	Moderate	Moderate	Moderate	Moderate	Low	Low
Kvarstein *et al.*[18]	Low	Low	Low	Moderate	Low	Moderate	Low
Chakhssi *et al.*[19]	Low	Moderate	Low	Moderate	Low	Low	Low
Schaap *et al.*[20]	Low	Low	Low	Moderate	Low	Moderate	Low
Cyranka *et al.*[21]	Low	Moderate	Low	Moderate	Moderate	Moderate	Low
Hoglend *et al.*[22]	Low	Moderate	Low	Low	Low	Low	Low

Discussion

Being psychotherapy the treatment of choice for personality disorders, and with so few treatment studies on mixed features PDs, despite their high prevalence and high burden, the authors addressed and reviewed empirical evidence for different formats, settings, modalities and dosages that are available for psychotherapy delivery in adults with this primary diagnosis. Psychotherapy treatment studies typically focus on specific PDs types, with borderline PD being more extensively studied than any other PD; results for mixed features PDs are unfrequently reported in separate, even when they are included in trials.

We chose to include: (1) studies that analysed psychotherapeutic intervention outcomes in these patients, even among samples with other types of PDs, drawing concrete conclusions for the group, and (2) studies where specific findings in this group of patients are not reported as long as they included a representative number of subjects with this diagnosis (at least one-third of the total sample studied), so the results could be somehow applicable to this subgroup. Eighteen full-text articles assessed for eligibility were excluded due to small (up to 21% participants) sample size, making its results extrapolation inadequate.

Horn *et al.*[8] specifically focuses on PDNOS patients, a group that corresponded to the total studied sample. It was the first large-scale treatment study in patients with PDNOS, having investigated the effectiveness of different psychotherapy modalities in patients with PDNOS, i.e., short-term and long-term outpatient, day hospital and inpatient psychotherapy. The treatments offered included varied theoretical orientations, such as psychodynamic orientation (27% of all given treatments), a cognitive-behavioural orientation (21% of all given treatments) or an integrative orientation (combining different theoretical frameworks, 52% of all given treatments). Patients in all treatment modalities showed positive outcomes at short-term and long-term follow-ups, especially in terms of improvements of symptom severity and social role functioning. Short-term outpatient

psychotherapy and short-term inpatient psychotherapy seem to be superior at 12-month follow-up, and at 60-month after baseline, effectiveness remained but observed differences between modalities mostly diminished.

In fact, cognitive-behavioural and psychodynamic approaches have been the object of the most extensive research in patients with PDs.

Cognitive behavioural therapy (CBT) is well suited to address the varied and often long-standing problems of patients with PDs for several reasons. From a cognitive behavioural perspective, PDs are maintained by a combination of maladaptive beliefs about self and others; contextual/environmental factors that reinforce problematic behaviour and/or undermine effective behaviour; and skill deficits that preclude adaptive responding. CBT incorporates a wide range of techniques to modify these factors, including cognitive restructuring, behaviour modification, exposure, psychoeducation, and skills training. In addition, CBT for PDs emphasizes the importance of a supportive, collaborative, and well-defined therapeutic relationship, which enhances the patient's willingness to make changes and serves as a potent source of contingency. In sum, several aspects of CBT's conceptual framework and its technical flexibility make it appropriate to address the pervasive and diffuse impairment commonly observed among patients with PDs[23,24].

Psychoanalytic psychotherapy, also referred to as psychodynamic psychotherapy, is a type of therapy that incorporates concepts such as the unconscious, the use of defense mechanisms, and the role of an individual's past via their social processes such as attachment and early childhood experience. The approach provides useful tools for expanding, consolidating, and enriching one's own life and one's relationships with others. Contemporary psychodynamic therapy involves many Freudian concepts, such as the existence of the unconscious, yet it has also moved away from a purely Freudian focus on drive, ego, and conflict. Contemporary psychodynamic theory includes a rich body of theory, and now incorporates various aspects of many 20th century psychoanalytic theories including object relations, self-psychology, interpersonal/relational theory, attachment theory, trauma theory, and intersubjective theory[25].

In another study, Horn *et al.*[17] compared 3-month short-term inpatient psychotherapy based on transactional analysis (STIP-TA) with other psychotherapies (OP) up to 36-month follow-up. At 36 months, 68% of STIP-TA patients were symptomatically recovered compared to 48% of OP patients. This therapy outperformed OP in terms of improvements in general psychiatric symptomatology and quality of life. That superiority was most pronounced at 12-month follow-up but remained intact over the course of the 3-year follow-up. The authors concluded that it could be a very promising and effective treatment option in mainly PDNOS patients, which corresponded to 42% of the STIP-TA patients and 49% of the OP patients. Kvarstein *et al.*[18] also conclude that PDNOS patients may be well managed within outpatient group therapy, in a trial involving outpatient psychodynamic groups with mean treatment duration 1.5 years and 3-year follow-up evaluating symptom distress, interpersonal problems, occupational functioning, and psychiatric health service use. The most favourable outcomes were found exactly for patients with PDNOS.

The remaining four studies included for review[19-22] do not report results for the mixed features PDs patients group separately. Both Chakhssi *et al.*[19] and Schaap *et al.*[20] studied PDNOS patients, among others, that did not respond to previous treatments. The first compared day hospital group-based acceptance and commitment therapy (ACT) and group-based treatment-as-usual based on cognitive behaviour therapy (CBT-TAU), led to significant improvements in personality pathology, general psychological functioning, coping skills and quality of life in both groups. The second author and colleagues evaluated the outcomes of an impatient group schema therapy (ST) in maladaptive schemas, schema modes, maladaptive coping styles, mental well-being, and psychological distress after treatment. Overall, participants improved significantly on all outcome measures from pretreatment to posttreatment, and these improvements were maintained at 6-month follow-up. Experienced parenting styles was the one area that had no improvement.

Cyranka *et al.*[21] evaluated intensive short-term group psychotherapy in a day ward with elements of individual therapy, integrating the elements of psychodynamic, cognitive and behavioural theories, in mixed features PDs patients, which demonstrated positive changes in personality functioning which were classified as severe or moderate pathology. Hoglend *et al.*[22] carried out the only randomized controlled trial included in this review, comparing 1 year of dynamic psychotherapy with low to moderate use of transference interpretations and dynamic psychotherapy without this component in a sample including PDNOS patients. After therapy with transference interpretation, patients improved significantly more in core psychopathology and interpersonal functioning, the drop-out rate was reduced to zero, and use of health services was reduced to 50%, compared to therapy without this ingredient. Three years after treatment termination, 73% no longer met diagnostic criteria for any PD in the transference group, compared to 44% in the comparison group.

Researchers have highlighted the diversity of treatments as an obstacle to identifying efficacious treatments[26]. In addition, some authors emphasize that instead of conducting further comparisons of different treatments, research should be concentrated on the active ingredients of treatments[17, 27].

Various independent psychotherapies demonstrated efficacy for these patients. However, several factors limit our ability to draw strong conclusions from available research. Overall, the limited number of studies included, with only one randomized controlled trial, is insubstantial. Although certainly lacking the rigor of RCTs, uncontrolled studies can provide clinically important information about mechanisms of change and moderators of treatment outcome. In addition to their use for driving theory and hypotheses for testing in future RCTs, uncontrolled studies can be useful for uncovering essential qualities of effective interventions and the effectiveness of psychotherapy as it is delivered in the field. Furthermore, co-occurring of other disorders, particularly within Axis I conditions, the possibility that maturational processes or life events may be responsible for part of the changes measured, and the use of medications along with the psychotherapy, further hampers existing research. An additional concern is substantial heterogeneity among studies included in the review. Besides, differences with respect to therapy format, the length, patient samples, gender distribution, and length of follow-up periods are very variable.

Subgroup analysis directed at "what works for whom" could give more valuable information for clinical practice about which treatments work best for which category of patients instead for which category of diagnosis. This is even more important in this patient group since various definitions of PDNOS are used in clinical practice and across studies, limiting the comparability and generalizability of study findings[5,7,8,28].

Despite previously mentioned limitations, findings from recent studies make an important contribution to our understanding of the role of psychotherapy in mixed features PDs.

Conclusions

Despite the toll of mixed features PDs on healthcare systems, there are vast gaps in the treatment literature on these disorders, a frequently overlooked mental health problem, for which there are no established psychosocial treatments.

Overall, there are some psychotherapeutic approaches with different modalities and durations offered to these individuals, and the research findings we reviewed suggest that there is hope for significant and meaningful changes after psychotherapy in individuals with PDNOS.

The most important conclusion is that mixed features personality pathology *per se* does not seem to be an impediment to benefit from psychotherapy, and improvement in different areas of life is possible for the patients who undergo psychotherapeutic treatment. It would be important to make psychotherapy more accessible for this patient group in order to reach health gains for this vulnerable group of psychiatric patients.

Although promising in many ways, the extant literature is marked by multiple challenges and inconsistencies across studies. Further research on the effectiveness of psychotherapy for mixed features PD patients is undoubtedly needed.

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A fatal case of bipolar disorder and comorbid hepatitis C

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Dear Editor,

Bipolar disorder is associated with an increased risk of substance use disorders and hepatitis C virus (HCV) infection[1]. The prevalence of HCV in bipolar patients is 5 to 13-fold higher than in the general population, presenting a major clinical and therapeutic challenge[2]. We report a case of a patient with bipolar disorder, a history of heroin addiction, and HCV related cirrhosis with fatal outcome.

Case

Mr. A was a 44-year-old married white male, an artist, who was diagnosed with bipolar disorder in his late adolescence. He had recurrent manic or mixed psychotic episodes, effectively treated with antipsychotics and mood stabilizers. During a ten-year period of intravenous heroin misuse and dependency, he contracted HCV and subsequently developed liver cirrhosis. Induction of psychotic exacerbation hindered specific HCV infection treatment, which continued with hepatoprotectors and diuretics with poor adherence. The patient's timeline is presented in Figure 1.

The last psychiatric admission of Mr. A was at the age of 44. He presented with insomnia, elevated mood, megalomania, delusions, dysphoria, and lack of insight. Anaemia, thrombocytopenia, hypoalbuminemia, ascites and elevated transaminases were present. Zuclopenthixol resolved the psychiatric symptoms and the patient was referred to the hepatology department. A follow-up after one year was scheduled. The patient's wife reported that he had died. He had been in stable mood following discharge and discontinued the psychiatric treatment. The improvement in the mental state improved the compliance with the somatic treatment and regimen, which led to temporary stabilization of the somatic state. However, his somatic condition deteriorated and he died from liver failure 3 months prior to the scheduled follow-up at the age of 45.

Discussion

Individuals with severe mental illness are estimated to die approximately 25 years earlier than the general population and up to 60% of the premature deaths are due to general medical conditions[3]. Chronic HCV infection is a major concern, with an estimated infection rate up to 10–23.3% in bipolar patients as compared to 1.8% in the general population[4]. The risk of liver cirrhosis is between 15 and 30% within 20 years[5] but risky social environment, high-risk behaviors, and non-compliance can aggravate the condition in bipolar patients[2].

New and highly effective therapies for chronic HCV infection are present, however access to treatment remains limited and psychiatric patients still suffer stigmatization[6,7]. Mental disorders were previously seen as contraindications against the use of interferon alfa and ribavirin in patients with chronic hepatitis C, as cases of mania and psychosis induced after initiation of treatment or upon withdrawal have been reported[8,9]. Current guidelines state that all HCV-infected patients should receive treatment, with patients with life-threatening conditions not expected to survive beyond 1 year being the only exclusion[7].

The case highlights the importance of an integrated model for clinical management of patients with comorbid HCV infection and bipolar disorder. An interdisciplinary approach and education of the patient are required in order to ensure the adequate treatment and compliance and prevent fatal outcomes[10].

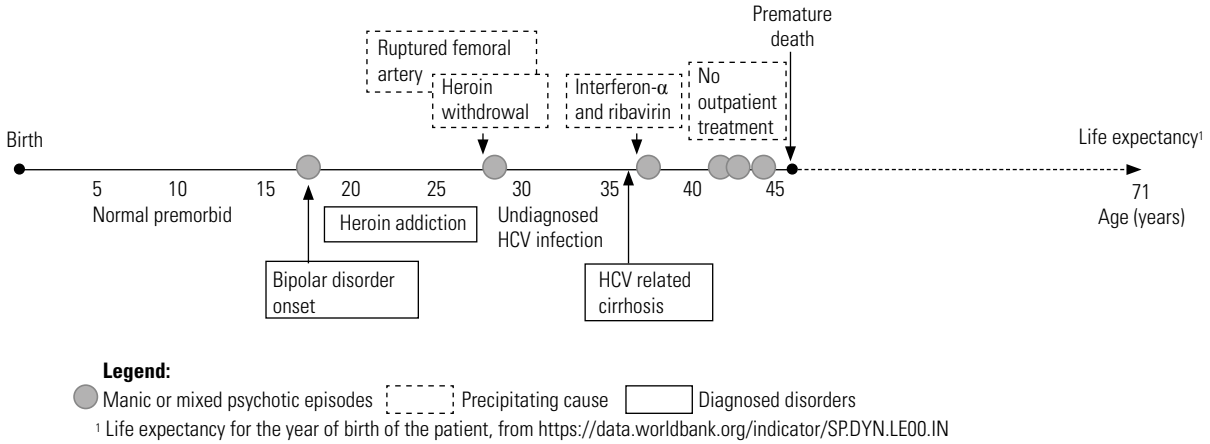

Figure 1. History of the patient.

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