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Letters to the editor

Thought and language disorders in very early onset schizophrenia, schizoaffective disorder and bipolar disorder

Telma Pantano[1], Lee Fu I[1], Eliana Curatolo[1], Camila Bertini Martins[1,2], Helio Elkis[1]

[1] *Department and Institute of Psychiatry, University of São Paulo Medical School (FMUSP), São Paulo, SP, Brazil.*
[2] *Federal University of São Paulo (Unifesp), São José dos Campos, SP, Brazil.*

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Abstract

Background: Thought and language disorders are main features of adults with schizophrenia and bipolar disorders however studies on such abnormalities are scant in young patients with very early onset psychosis (VEOS). The aim of the present study is to assess the relationship between language and thought disorders in patients with very early onset schizophrenia (SCZ), schizoaffective disorders (SCA) and bipolar disorders (BD). **Method:** Forty-one patients (18 SCZ, 16 BD, and 7 SCA) with mean age less than 15 years old were assessed through a series of neurocognitive and psycholinguistic tests, including the Thought, Language and Communication Scale (TLC). **Results:** SCZ group performed worse in all tests as well as the TLC, followed by SCA and BD groups respectively. Thought disorders were related to deficits in executive functioning and semantic processing, and the metaphors' test was the best predictor of TLC functioning. **Discussion:** TD in SCZ, SCA and BD are one of the most important features in patients with VEOS and that the evaluation of metaphor comprehension can be an important instrument in the early detection of this disorder.

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Keywords: Thought disorders, language, schizophrenia, bipolar disorder, schizoaffective disorder.

Introduction

Schizophrenia is a psychotic disorder which affects 1% of adult population and usually begins in late adolescence or early adulthood. When the disorder begins in early adolescence (under 18 years old) it is termed early onset schizophrenia (EOS), with some cases beginning even earlier (under 14 years old) and called child onset schizophrenia (COS) or very early onset schizophrenia (VEOS)[1-3].

EOS is a rare condition and it is estimated to account for less than 4% of the cases of schizophrenia[4]. Delusions, hallucinations and thought disorders are considered prominent psychopathological features of EOS[1,4] similar to adult onset schizophrenia.

Particularly formal thought disorders are also considered one main characteristic of psychotic manifestations in children or adolescents[1]. However such abnormalities are rarely studied in pediatric psychosis, especially in patients with early onset schizophrenia (VEOS)[1].

All these thought impairments are also present in patients with bipolar disorders[5-7] and to date there is only a few descriptions of such abnormalities in patients with early or very early onset of these disorders.

In fact thought disorders can be regarded as a failure to maintain a speech plan and thus encompassing a great number of abnormalities of logical sequencing of ideas however the connection between language and these disorders is not clearly established. Our hypothesis is that thought disorders are present in patients with VEOS and BD in different degrees of severity and are related to neuropsychological and language impairments.

The aim of the present study is to compare the performance of patients with schizophrenia (SCZ) or schizoaffective disorders (SCA) with patients with bipolar disorders (BD) in terms of thought disorders. Secondary objectives include investigating the relationship between thought disorders and neuropsychological performance, especially language disorders, using a battery of tests adapted to Brazilian Portuguese language.

Methods

Sample

Forty-one patients with psychotic symptoms (18 with diagnosis of the schizophrenia, 16 with bipolar disorders and 7 with schizoaffective disorder) were recruited for treatment at outpatient clinic of the Child and Adolescent Psychiatric Clinic of the Institute of Psychiatry of the University of São Paulo General Hospital (IPq) in São Paulo, Brazil. The study had the approval of the local Institutional Review Board of University of São Paulo General Hospital CAPPESQ nº 0088/07 and families signed an informed consent for the participation in the study. To take part in the study patients had to be clinically stable after the medical treatment but which not received the language or cognition rehabilitation.

All the patients had between 10 and 17 years old at baseline and at the time of language and cognition evaluation. Patients were excluded if they had a previous or current history substance abuse, organic brain disease or marked intellectual impairment. For the control of the intellectual performance prior the illness all the patients had to be able to write and read and perform the four basic mathematical operations according to the school level and should not have any previous history of school performance impairment before the onset of the disorder. Additional information was obtained from chart reviews, parents' reports, school information and clinical interview.

Clinical assessment

Patients were interviewed by experienced child psychiatrists and met DSM-IV criteria for schizophrenia, schizoaffective disorder or bipolar disorder based on an interview using the Schedule for Affective Disorders and Schizophrenia for school age Children present and Lifetime version K-SADS[8] adapted into Portuguese. The K-Sads was applied by well-trained researchers with expertise in this instrument.

Address for correspondence: Telma Pantano. Department and Institute of Psychiatry – University of São Paulo Medical School. Rua Dr. Ovídio Pires de Campos, 785, Cerqueira César – 05403-010 – São Paulo, SP, Brazil. Telephone: +55 (11) 99751-8209. E-mail: telmapantano@terra.com.br

Neuropsychological and linguistic assessment

All patients were evaluated through a battery comprising semantic and syntactic psycholinguistic tests, measures of executive functions and tests of general neurocognition. Such tests were usually performed within a week to the clinical interview for the DSM-IV and K-SADS diagnosis and administered by the same professional blind to the diagnosis. The battery was standardized to ensure the appropriate use of time, avoid tiredness of the patient and the application took approximately two sessions of 45 minutes.

Semantic tests

MT-86b modified[9]

The protocol consists of different linguistics verbal, reading and writing tests to evaluate linguistic levels with or without visual images:

- Written comprehension: comprehension by the visual way – word and phrases and the subsequent visual identification of this objects and situations;
- Reading: the patient must decode the words and talk them out loud.

Peabody Picture Vocabulary test[10]

Oral comprehension: The subject is required to indicate which one of four pictures best describes a word spoken by an examiner. It is a thus of the comprehension of single words that refer to things or actions.

Boston Naming Test[11]

Is a test of visual confrontation naming in which the subject must retrieve (name).

Semantic fluency[12]

The patient must produce as many examples as possible of animals (90 seconds). A score of "semantic efficiency" is related with the organization of semantic storage in the brain and the working memory tasks.

Lexical decision[13]

The patient distinguishes orally real words from nonexistent words with the oral and writes presentation.

Metaphor's comprehension[14]

Tests of oral comprehension of phrases with high symbolic significance.

Syntactic tests

Syntactic Awareness[15]

The protocol consist of the differences abilities for evaluated syntactic awareness.

- Grammatical judgment: the patients should tell if there was something wrong in the phrases presented.
- Grammatical correction: the patients should to correct the phrases with wrong syntactic.
- Grammatical correction than phrases with grammatical and semantics inaccuracies: in this test the patients should to correct just the grammatical phrases but originally the phrases were with semantics inaccuracies which shouldn't be correct.
- Word's categorization: The patients should categorize the words in: substantive, adjective or verb.

Executive function tests

Stroop test[16]

In the word task, the response is shown a card with the words BLUE, ROSE, GREEN and BROWN (printed in contrasting colors) arranged in four columns and six lines, to be read as quickly as possible ignoring their color. In the color task, a similar set of words is shown to the respondent who must how identify the color in which each word is printed. The Stroop effect is the difference (in seconds) between the time to complete the two tasks.

Phonological fluency[17]

In this test the respondent should produce as many words as possible beginning with the letters T (90 seconds). This test is thought to depend on the integrity of the left frontal lobe. The score is the total number of words generated excluding repetitions.

More general cognitive function

Forward and reverse digit span[18]

Forward digit span assess short-term memory. Respondents must repeat progressively longer sequences of digits read aloud to them at a rate of one digit per second. Span is defined as the longest string of digits correctly recalled at least once. Reverse span is administered in similar fashion but respondents must now reproduce the sequence in the reverse of the presentation order. This task involves manipulation of information as well as simple reiteration of it, and is often cited as a measure of working memory[19].

Speed processing

The time for realization of each linguistic test (semantic and syntactic) was measured and added.

Thought, Language and Communication Scale (TLC[20]*)*

The Thought, Language, and Communication Scale (TLC) was used for language and thought evaluation. All the patients completed a detailed clinical interview lasting approximately 1 hour.

Data analysis

The descriptive statistics for continuous variables were mean and standard deviation; and for categorical variables, proportions. The relationship between the groups and categorical variables were analyzed by Chi Square Tests. For the continuous variables, the groups were compared using a series of ANOVA and Post Hoc Tests (Tukey), with normality tested using the Kolmogorov-Smirnov and Levene tests. The relationship between TLC and the others tests was explored by linear regression. The relationship among the tests was analyzed by Pearson coefficient. The significance was set to 0.05.

Results

Demographic and Clinical characteristics between the groups SCZ, BD, SCA

There were no significant differences between groups in respect of age, gender, years of education and number of previous hospitalization. However in terms of duration of illness there was a significant difference between groups ($F = 3.77$, $p = 0.03$), with bipolar patients showing an earlier age of onset (Table 1).

Table 1. Demographic and clinical characteristics of the three diagnostic groups

	SCZ (N = 19)	BD (N = 16)	SCA (N = 7)	Test, *p*
Age – Mean (SD)	15,9 (1,63)	14,7 (2,47)	15,8 (1,87)	F = 1.67, 0.20
Gender	11(M)	10 (M)	5 (M)	X^2 = 0.401, 0.818
Male (M), female (F)	8 (F)	6 (F)	2 (F)	
Years of education	7,47 (2,04)	7 (1,83)	7,29 (1,7)	F = 0.27, 0.77
Age of onset	11,37 (3,34)	8,37 (4,65)	12,43 (3,04)	F = 3.77, **0.032**
Duration of illness	4,58 (2,89)	6,37 (3,94)	3,40 (1,99)	F = 2.44, 0.10
Antipsychotic 1 (Main)				
First-generation	0	0	1 (14.3%)	**X^2 = 21.18, p = 0.048**
Second-generation	19 (100%)	16 (100%)	6 (85.7%)	
Antipsychotic 2 (add-on)				
First-generation	1 (5.3%)	0	0	X^2 = 17.48, p = 0.064
Second-generation	1 (5.3%)	3 (18.8%)	3 (42.8%)	
Antipsychotic monotherapy	17 (89.5%)	13 (81.3%)	3 (42.8%)	
Mean dose (in Chlorpromazine equivalents)	647 mg (sd 530)	322 mg (sd314)	454 mg (sd 199)	F = 2.52, p = 0.094
Mood stabilizer 1				
Lithium	1 (5.3%)	5 (31.3%)	1 (14.3%)	**X^2 = 10.13, p = 0.04**
Anticonvulsant	4 (21%)	6 (37.5%)	0	
Mood stabilizer 2 (add-on)				
Lithium	0	0	0	X^2 = 2.43, p = 0.3
Anticonvulsant	0	1 (6.3%)	1 (14.3%)	
Mood stabilizer monotherapy	5 (26.3%)	10 (62.5%)	0	
Antidepressant monotherapy				
SSPA	3 (15.8%)	2 (12.5%)	3 (42.8%)	X^2 = 5.96, p = 0.20
Dual agent	1 (5.3%)	0	1 (14.3%)	

SCZ: schizophrenia; BD: bipolar disorder; SCA: schizoaffective disorder.

The medications in use by the subjects were classified according to the following psychopharmacological characteristics: antipsychotics (first and second generation) with their respective total mean dose expressed in chlorpromazine equivalents, types of mood stabilizer (lithium or anticonvulsants) and antidepressant prescribed (selective serotonin receptor agonist or dual agent). All the patients of the sample were receiving antipsychotics regardless of the diagnosis. The majority of the subjects were treated with antipsychotic monotherapy, with a second generation antipsychotic as the main or secondary treatment. The mean dose of antipsychotics (expressed in Chlorpromazine equivalents) was not significantly different between the groups (F = 2.52, p = 0.094), but mood stabilizers were predominantly used by patients with BD than patients with SCZ or SCA (X^2 = 12.74, p = 0.047). The three groups showed no difference in terms of use of antidepressants (X^2 = 5.96, 0 = 0.20) (Table 1).

We found no significant differences between groups in respect of the frequency of symptoms such as affective blunting, delusions, olfactory hallucinations, tactile hallucinations, disorganized speech and disorganized behavior. Patients with SCZ showed significantly higher frequencies of visual and auditory hallucinations when compared with SCA or BD (Table 2).

Language and thoughts outcomes

Table 3 displays the multiple comparisons of semantic and syntactic tests between diagnostic groups showed that, when compared with patients with BD, patients with SCZ showed a significantly poorer performance in terms of written comprehension (p = 0.006), oral comprehension (p = 0. 041), naming (p = 0.001), semantic fluency (p = 0.006), lexical decision (p = 0.003), metaphor (p = 0.000), grammatical judgment (p = 0.030), grammatical correction with semantics inaccuracies (0.005) and word's categorization (p = 0.000). In terms of reading abilities and grammatical corrections both groups showed no significant differences. Patients with diagnostic of SCA had no substantial differences in terms of the tests previously described when compared with patients with BD or SCZ.

Neurocognitive, executive function and psycholinguistic tests

As can be observed by Table 4 the performance between the groups SCZ, BD and SCA showed no statistical significant differences in terms of the Stroop factor, phonological fluency, digit spam – forward and speed processing. However significant statistical differences between groups were found in terms of the of the TLC scale (F = 18.73, p = 0.000) and digit spam – reverse (F = 5.46, p = 0.008). The multiple comparisons between the three groups showed that the SCZ had a poorer performance as compared with patients with BD in terms of the TLC (p = 0.000), phonological fluency (p = 0.056) and digit-spam reverse (p = 0.019). No significant differences between the performance of the comparison between BD and SCA group as BD and SCA group.

Predictors of TLC

The relationship between total thought disorder, as measured by the TLC scale, and semantic, syntactic, neurocognitive, executive and psycholinguistic functions and was further examined using multiple regression. Separate stepwise analyses were performed with total TLC as the dependent variable and each of the above tests as predictor variables. As can be seen in Table 5 no relationship was found between TLC and any of linguistic or neurocognitive test except for the metaphor which showed to be the strongest predictor of thought disorder impairment in this population.

Table 2. Frequency of K-SADS Psychopathology by diagnostic groups

	SCZ	BD	SCA	Chi Square, *p*
Affective blunting	1	0	1	2.21, 0.33
Delusions	9	3	3	3.28, 0.19
Auditory hallucinations	17	7	6	9.74, **0.008**
Visual hallucinations	14	4	5	9.25, 0.01
Olfactory hallucinations	1	0	0	1.24, 0.54
Tactile hallucinations	1	0	0	1.24, 0.54
Disorganized speech	6	3	3	1.54, 0.46
Disorganized behavior	1	1	0	0.44, 0.80

SCZ: schizophrenia; BD: bipolar disorder; SCA: schizoaffective disorder.

Table 3. Comparison of semantic and syntactic tests between diagnostic groups (post-hoc analysis)

		Mean (SD)	F, p	Group Diagnostic	Mean Difference	Sig.
Writing Comprehension	SCZ	9,26 (3,16)		SCZ X BD	-2,61	**0,006**
	BD	11,88 (1,31)	5.98, **p = 0.005**	BD X SCA	0,45	0,906
	SCA	11,43 (0,98)		SCA X SCZ	2,17	0,102
Reading	SCZ	13,53 (4,79)		SCZ X BD	-2,54	0,101
	BD	16,06 (2,11)	2.71, p = 0.079	BD X SCA	-0,08	0,999
	SCA	16,14 (1,35)		SCA X SCZ	2,62	0,230
Oral Comprehension	SCZ	17,05 (4,06)		SCZ X BD	-2,64	**0,041**
	BD	19,69 (2,06)	3.21, **p = 0.051**	BD X SCA	1,12	0,706
	SCA	18,57 (1,27)		SCA X SCZ	1,52	0,511
Naming	SCZ	11,37 (2,19)		SCZ X BD	-2,51	**0,001**
	BD	13,88 (1,25)	7.34, **p = 0.002**	BD X SCA	1,73	0,134
	SCA	12,14 (2,48)		SCA X SCZ	0,77	0,642
Semantic Fluency	SCZ	11,63 (4,65)		SCZ X BD	-5,81*	**0,006**
	BD	17,44 (5,55)	5.87, **p = 0.006**	BD X SCA	1,01	0,905
	SCA	16,43 (5,91)		SCA X SCZ	4,80	0,107
Lexical Decision	SCZ	13,05 (2,46)		SCZ X BD	-2,20	**0,003**
	BD	15,25 (1,07)	8.319, **p = 0.001**	BD X SCA	-0,32	0,920
	SCA	15,57 (0,79)		SCA X SCZ	2,52*	0,009
Metaphor	SCZ	3,21 (3,63)		SCZ X BD	-6,04*	**0,000**
	BD	9,25 (4,30)	9.60, **p = 0.000**	BD X SCA	2,25	0,454
	SCA	7,00 (4,87)		SCA X SCZ	3,80	0,105
Grammatical Judgment	SCZ	16,83 (3,68)		SCZ X BD	-2,42	**0,030**
	BD	19,25 (1,18)	3.64, **p = 0.036**	BD X SCA	0,75	0,825
	SCA	18,50 (1,23)		SCA X SCZ	1,67	0,385
Grammatical Correction	SCZ	6,94 (3,12)		SCZ X BD	-1,49	0,279
	BD	8,44 (2,48)	1.22, **p = 0.030**	BD X SCA	0,60	0,894
	SCA	7,83 (2,56)		SCA X SCZ	0,89	0,780
Grammatical correction with semantics inaccuracies	SCZ	6,39 (2,85)		SCZ X BD	-2,49*	**0,005**
	BD	8,88 (1,41)	5.99, **p = 0.006**	BD X SCA	0,54	0,859
	SCA	8,33 (0,82)		SCA X SCZ	1,94	0,148
Word's categorization	SCZ	6,61 (4,41)		SCZ X BD	-6,20	**0,000**
	BD	12,81 (3,31)	11.611, **p = 0.000**	BD X SCA	0,65	0,938
	SCA	12,17 (4,02)		SCA X SCZ	5,56	0,013

SCZ: schizophrenia; BD: bipolar disorder; SCA: schizoaffective disorder.

Table 4. Comparison of selected neurocognitive, executive and psycholinguistic tests between diagnostic groups (*post-hoc* analysis)

		Mean (SD)	F, p	Group Diagnostic	Mean Difference	Sig.
TLC	SCZ	32,47 (12,37)	18.73. p = **0.000**	SCZ X BD	20,54*	**0,000**
	BD	11,94 (7,73)		BD X SCA	-14,06*	**0,009**
	SCA	26,00 (5,97)		SCA X SCZ	-6,47	0,316
Stroop Factor	SCZ	16,11 (13,98)	1.72, p = 0.193	SCZ X BD	2,61	0,770
	BD	13,50 (8,54)		BD X SCA	6,50	0,409
	SCA	7,00 (5,80)		SCA X SCZ	-9,11	0,166
Phonological Fluency	SCZ	6,89 (4,83)	3.13, p = 0.055	SCZ X BD	-3,86	0,056
	BD	10,75 (4,73)		BD X SCA	0,61	0,957
	SCA	10,14 (4,67)		SCA X SCZ	3,25	0,283
Digit Spam – forward	SCZ	5,00 (1,03)	1.78, p = 0.183	SCZ X BD	-0,69	0,157
	BD	5,69 (1,08)		BD X SCA	0,41	0,684
	SCA	5,29 (1,11)		SCA X SCZ	0,29	0,819
Digit Spam – reverse	SCZ	2,39 (1,38)	5.46, p = **0.008**	SCZ X BD	-1,24*	**0,019**
	BD	3,63 (1,31)		BD X SCA	-0,23	0,914
	SCA	3,86 (0,69)		SCA X SCZ	1,47*	**0,034**
Time Processing	SCZ	404,84 (173,37)	2.45, p = **0.100**	SCZ X BD	123,28	0,085
	BD	281,56 (155,06)		BD X SCA	-86,44	0,488
	SCA	368,00 (166,99)		SCA X SCZ	-36,84	0,870

SCZ: schizophrenia; BD: bipolar disorder; SCA: schizoaffective disorder.

Table 5. Regression Analysis: Thought Language and Communication Scale (TLC) vs. tests (predictors)

Tests	Beta	t	p
Writing Comprehension	-0.008	-.051	0.960
Reading	0.055	0.375	0.710
Oral Comprehension	-0.064	-0.448	0.657
Naming	-0.181	-1.185	0.244
Semantic Fluency	-0.252	-1.715	0.095
Lexical Decision	0.123	0.802	0.428
Grammatical Judgment	-0.208	-1.449	0.156
Grammatical Correction	0.107	0.634	0.530
Grammatical correction with semantics inaccuracies	-0.221	-1.354	0.184
Word's categorization	0.116	0.592	0.558
Stroop Factor	-0.182	-1.449	0.156
Phonological Fluency	0.045	-0.275	0.785
Digit Spam – forward	-0.252	-1.941	0.060
Digit Spam – reverse	0.085	0.596	0.555
Time processing	0.040	0.252	0.802
Metaphor	-0.626	-4.951	**0.000**

Model = F = 24.514, p = 0.000.

Discussion

To our knowledge this is the first study which compared patients with very early onset schizophrenia, bipolar disorder and schizoaffective disorder in terms of language disorders and its relationship with cognitive impairment. We found that patients with schizophrenia showed the highest degree of severity of thought disorders when compared with patients with other diagnostic categories.

Our data provide evidence that in terms of neurocognitive functions patients with schizophrenia have shown the worst performance when compared with patients with bipolar disorders or schizoaffective disorders even if we consider that the population studied the onset of symptoms of each disease was higher for patients with BD than patients with SCZ or SCA. These results are in agreement with several studies which related schizophrenia and bipolar disorders[21] and show a distribution as observed what is called the "continuum of the psychosis" hypothesis[22] with patients with schizophrenia showing the worst performance, patients with bipolar disorder with the best performance and schizoaffective disorder patients in an intermediate position.

Although patients with schizophrenia performed significantly poorly in terms of the most of the linguistic and cognitive tests as thought disorders the differences were not significant in tests of reading abilities, grammatical correction, attention, phonological fluency and digit spam probably because these abilities were learned before the onset of the illness. When considered the alteration with thought disorders the regression analyses identified the metaphor comprehension as the best predictor for this alteration.

It was observed that the metaphor comprehension is possibly associated with frontal and temporal lobe functioning and in the

left hemisphere involving activation of the prefrontal and basal frontal cortex, the middle and inferior temporal gyri, the temporal pole, the parietal cortex and the precuneus. In the language comprehension, activation is also observed in the right hemisphere: prefrontal cortex, middle temporal gyrus, precuneus and posterior cingulated gyrus[23].

Our findings are thus broadly congruent with a small but growing body of evidence linking thought disorder to a combination of executive dysfunction and circumscribed semantic impairment[24-26] related to, but possibly not restricted to, access and adds the right hemisphere functioning as injured in the thought disorders.

It is important to observe that the metaphor's test (figurative language) has largely been ignored in the cognitive science investigation field in favor of the investigation of literal language[27]. The present finding that metaphor comprehension is the best indicator of the thought disorder's performance must be replicated in larger studies. A limitation of the present study is the small number of subjects due to the low prevalence of the disorders in pediatric populations. Our findings show that language disorder are directly related with thought disorders[19,24,25,28-34] with the relationship semantic and inter hemispheric frontal lobe.

This is important since cognitive features of these disorders, such as language and thought abnormalities, should become an important guide to new classifications about the cognitive dysfunction to understand the relation between functional capacities of these illnesses[35]. However, little is known about the behavior of these alterations in early-onset psychotic disorders and this study intends to bring new data on this subject.

The present paper also provides evidence that in terms of severity of thought and language disorders that the distribution of the impairments favors the idea of the so called continuum of psychosis[36-38].

Caution is needed when interpreting the findings due to methodological limitations. First, the possibility of a recruitment bias stemming from the fairly demanding nature of some of the tests in our neuropsychological battery, with some patients possibly being judged as "not competent to complete" them. Secondly, the premorbid neurocognitive status could not be estimated since tests like the National Adult Reading Test (Nelson, 1991[18]), which estimates the premorbid IQ, are not available in Portuguese and the actual IQ was not investigated. However based on the clinical judgment patients with intelligence deficits were not included. Additionally neuropsychological functions were assessed using specific tests in Portuguese but not through a standard neuropsychological battery.

In conclusion, our data provide evidence that thought disorder in schizophrenia, schizoaffective disorder and bipolar disorder are one of the most important features in patients with VEOS and that the evaluation of metaphor comprehension can be an important instrument in the early detection of this disorder. In the present study though disorders showed to be associated with impairment in tests such as metaphor are related to frontal lobe function as well as semantic tests which are related to dysfunction of right and left hemispheres. Further investigations of relationship between executive and semantic impairments with thought disorder in schizophrenia accompanied by neuroimaging findings in patients with very early onset psychosis are warranted.

Declaration of interest

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Original article

Relationships of anxiety and depressive symptoms with pain perception in post-mastectomy women. An intragroup analysis

Rita Hansdorfer-Korzon[1], Gabriela Chojnacka-Szawłowska[2], Jerzy Landowski[3], Mikołaj Majkowicz[4,5], Krzysztof Basiński[4], Agata Zdun-Ryżewska[4], Iwona Wasilewko[6]

[1] *Medical University of Gdańsk, Department of Physical Therapy, Gdańsk, Poland.*
[2] *University of Finance and Management, Department of Psychology, Warsaw, Poland.*
[3] *Medical University of Gdańsk, Clinic of Adult Psychiatry, Gdańsk, Poland.*
[4] *Medical University of Gdańsk, Department of Quality of Life Research, Gdańsk, Poland.*
[5] *Pomeranian University in Słupsk, Department of Public Health, Słupsk, Poland.*
[6] *Medical University of Gdańsk, Post-graduate studies, Clinical Psychooncology, Gdańsk, Poland.*

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Abstract

Background: Breast cancer confronts women with a threat to life and is classified among the most traumatic life experiences. The disease is often accompanied by strong negative emotions, often in the form of anxiety and depressive symptoms. Studies also point to the presence of chronic pain breast-cancer survivors. **Objective:** To determine the relationships of: (1) anxiety and depressive symptoms with the experienced severity and interference of pain in post-mastectomy women; (2) anxiety and depressive symptoms with beliefs about pain. **Method:** The studied group consisted of 53 women after radical mastectomy, experiencing chronic pain, despite positive results of cancer treatment. IPQ-R (Illness Perception Questionnaire – Revised) and HADS (The Hospital Anxiety and Depression Scale) were applied. **Results:** Correlation and regression analyses confirmed relationships of anxiety and depressive symptoms with pain in the group of post-mastectomy women. Cluster analysis separated three groups of patients, differing in the severity of depressive symptoms and anxiety. For each group, a different pattern of beliefs about pain was characteristic. **Discussion:** The study has shown that psychological determinants play a significant role in the perception of pain severity and interference, which are related to anxiety, depressive symptoms and a system of beliefs about pain duration.

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Keywords: Chronic pain, anxiety, mastectomy, depression, illness perception.

Introduction

Diagnosis and treatment of breast cancer are traumatic experiences involving agitation, insomnia, loss of appetite, anxiety about death, worry, and regret. All the symptoms gradually subside, but in about 20%-40% of women anxiety and depression persist for many years after treatment[1-3]. Remote chronic pain affects 20%-60% women treated in the early stage of breast cancer[4,5]. According to International Association for the Study of Pain, pain as a psychosomatic sensation is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Chronic pain is defined as serving no purposes of adaptation, devoid of biological value, persisting beyond the expected period of healing, not responding to typical treatment, and lasting more than 6 months. By distress and suffering, chronic pain contributes interactively towards deteriorating patient's quality of life in biological, psychological, social and spiritual dimensions. Recurrence is a specific feature of chronic pain, and anxiety and depression play an important role in its perception[6-8].

Intrusive thinking and catastrophizing related to breast cancer are among factors supporting the presence of pain. Intrusive thoughts are unwanted and recurrent reflections of stressful experiences. If those thoughts linger after the stressor ends, they may be a risk factor for poor adjustment. This kind of cognition and pain recurrence have been associated with anxiety about cancer metastases. Intrusive thinking may be related to somatic symptoms by sleep disorders, chronic fatigue and increased susceptibility to physical sensations; its presence is indicative of an adaptation failure[9-11].

Intrusiveness of a disease is understood as a variable mediating in relationships between characteristics and treatment of the disease and patient's subjectively perceived well-being. It results in limitations or abandonment of patient's previous lifestyle, physical activity and interests. Relationships between intrusiveness and wellbeing are related not only to the variables associated with disease (*e.g.* pain, disability) and treatment (medication and treatment side effects), but to the psychosocial context as well. Intrusiveness is considered to be a fundamental determinant in the quality of life in patients with chronic conditions[12,13].

As the data in literature show, symptoms of pain, depression and anxiety (referred to as *post-mastectomy pain syndrome*, PMPS) are recorded in a relatively large group of women, many years after successful breast-cancer treatment[14]. Research on factors responsible for the persistence of anxiety and depressive symptoms *and* chronic pain has not yet arrived at conclusions about their psychosomatic determinants.

Research within this study was aimed at understanding how anxiety and depressive symptoms are related to pain and was based on the concept of cognitive representation of pain perception by Leventhal *et al.* (Common Sense Model of Illness Perceptions)[15]. The assumption of Leventhal's model is that the effectiveness of treatment in chronic disease is strongly dependent on cognitive and emotional processes associated with perception of health risk (or disease) symptoms.

The following research questions were formulated:

1. Is there a relationship between anxiety level and depressive symptoms severity and: (a) severity of pain, (b) pain interference, experienced by post-mastectomy women?
2. Is there a relationship between anxiety and depressive symptoms severity and a quality of beliefs about pain?

Materials and methods

The study was conducted in a rehabilitation clinic in 2014 (the clinic is visited by about 120 patients monthly). From all of the patients

Address for correspondence: Krzysztof Basiński. Department of Quality of Life Research – Medical University of Gdańsk. Ul. Tuwima 15 – 80-210 – Gdańsk, Poland. Phone/Fax: +48 58 349-1555. E-mail: k.basinski@gumed.edu.pl

Study conducted at: Department of Quality of Life Research – Medical University of Gdańsk. Ul. Tuwima 15 – 80-210 – Gdańsk, Poland.

53 women were recruited for the study. The inclusion criteria were: radical mastectomy, pain-related ailments lasting for more than 3 months, physiotherapeutic treatment. All subjects were under oncological care and patients with active cancer were excluded, based upon clinical, laboratory and radiological diagnosis.

Participants age was between 38-80 years (mean 62.73 ± 9.31). Fifteen subjects (28.3%) had higher education, 34 (64.2%) – secondary education, 2 (3.8%) – primary, and 2 failed to answer. Twelve women were economically active (22.6%), 34 were not (64.2%), and 7 subjects (13.2%) failed to answer. The total sample size varies in the range of N = 51 to N = 53 due to the missing responses in certain positions of research tools.

All of the subjects had undergone a radical mastectomy as a result of breast cancer. The mean time from mastectomy was 8.24 ± 4.8 with the minimum and maximum period of 3 and 24 years respectively. Participation in the research was anonymous and voluntary. Informed consents of the association president and all subjects were obtained. Illness Perception Questionnaire-Revised (IPQ-R), Hospital Anxiety and Depression Scale (HADS) and Brief Pain Inventory (BPI) were used for the assessment of pain causes and pain perception.

Illness Perception Questionnaire–Revised

IPQ-R is based on the theoretical background of a self-regulatory model (SRM) by Leventhal *et al.*, in which patient's behavior is modified by a cognitive representation of an illness[15,16]. Leventhal's model is used to describe the processes by which an individual responds (reacts) to the perception of health risk symptoms. As the model assumes, the symptoms generate a cognitive and emotional representation of a disease or health risk. In the study the IPQ-R version for chronic pain assessment was applied. The questionnaire allows for the assessment of a cognitive representation of pain in 7 dimensions:

1. Timeline (acute/chronic),
2. Consequences,
3. Personal control,
4. Treatment control,
5. Illness coherence,
6. Timeline cyclical,
7. Emotional representations (negative)[17].

The Hospital Anxiety and Depression Scale

Authors of the Hospital Anxiety and Depression Scale (HADS)[18] aimed to create a reliable tool for measuring anxiety (statements of tension, nervousness, dread) and depressive symptoms (statements of loss of joy, lowered mood, sadness, loss of interests) in patients population. The scale can also serve as a screening test for early diagnosis of psychological disorders in the group of patients with somatic illnesses[19].

Brief Pain Inventory

The Brief Pain Inventory tool (BPI) allows for measuring pain severity (sensory dimension) and pain interference (dimension showing the degree to which pain affects patient's life)[20]. The Inventory also comprises items to identify: the kind of pain, subjectively perceived causes of pain, and actions to relieve pain. BPI is a tool with proven validity and reliability, applied in many countries[21].

Statistical procedures

To evaluate the results of the study, correlation, regression and cluster analyses were conducted. As an assumption that tested variables were drawn from a normally distributed population was impossible, Spearman's rank correlation coefficient (Spearman's rho) was applied to the correlation analysis. All the calculations were performed with Statistica software, version 10 (StatSoft Inc., 1984-2011).

Results

Table 1 shows the mean, minimum, maximum values and standard deviations (SD) for variables of the BPI, HADS and IPQ-R scales. Additionally, the possible value ranges of the variables are presented. As indicators of the IPQ-R are dimensions, the midpoints corresponding to *It's hard to say* answer in all positions were also marked.

Table 1. Mean, minimum, maximum values, standard deviations, and possible value ranges of the analyzed variables

Scale	Mean	Min	Max	SD	Possible range
BPI					
Pain severity	4.29	1	8.75	1.74	0-10
Pain interference	4.39	0	9.14	2.31	0-10
HADS					
Depressive symptoms	5.73	0	14	3.52	0-21
Anxiety	9.54	0	20	4.11	0-21
IPQ-R					
Timeline	18.54	10	27	3.70	6-(18)-30
Timeline cyclical	13.77	7	18	2.32	4-(12)-20
Consequences	19.84	12	27	3.75	6-(18)-30
Personal control	18.22	13	26	2.55	6-(18)-30
Treatment control	17.44	7	23	2.48	5-(15)-25
Emotional representation	20.66	10	30	3.89	6-(18)-30
Illness coherence	16.06	5	24	3.66	5-(15)-25

Moderate pain severity and interference was characteristic of all subjects. The results for BPI revealed mean pain severity at 4.29 ± 1.74 in a ten-point scale. Mean pain interference ranged between 4.39 ± 2.31.

For the HADS, results of < 8, 8-10, and > 10 are considered low, medium or high respectively[19]. The depressive symptoms were of moderate severity, with the mean value of the variable at 5.72 ± 3.52. The highest obtained score was 14, and 38 subjects (71.7%) had low scores. Anxiety results were relatively high, with the mean value of 9.53 ± 4.10. For this variable, 35 people (66.1%) reached medium or high scores.

In the cognitive representation of disease (IPQ-R) the mean values of the dimensions were: 18.54 ± 3.70 for timeline; 13.77 ± 2.32 for timeline cyclical; 19.84 ± 3.75 for consequences; 18.22 ± 2 55 for personal control; 17.44 ± 2.48 for treatment control; 20.66 ± 3.89 for emotional representation; and 6.06 ± 3.66 for illness coherence. Although all of the mean values are higher than the center points of dimensions, the difference in any case does not exceed one standard deviation. Results of the analysis of correlations between the psychological variables and the indicators of pain severity and pain interference are presented in Table 2.

Table 2. Correlations between pain severity and interference with analyzed psychological indicators

Scale	Pain severity	Pain interference
HADS		
Depression	0.17	**0.39****
Anxiety	0.23	**0.33***
IPQ-R		
Timeline	0.21	0.25
Timeline cyclical	0.02	0.08
Consequences	0.14	0.26
Personal control	–0.09	–0.07
Treatment control	**–0.29***	–0.18
Emotional representations	0.13	**0.32***
Illness coherence	0.06	0.09

Statistically significant correlations are in bold; *$p < 0.05$; **$p < 0.01$.

Pain severity was significantly negatively correlated with treatment control (rho = –0.29, $p < 0.05$). Pain interference was significantly correlated with depressive symptoms (rho = 0.39; $p < 0.01$), anxiety symptoms (rho = 0.33; $p < 0.05$), and with the emotional representations dimension (rho = 0.32; $p < 0.05$). Other variables were not significantly correlated with the indicators of pain severity and interference.

In order to determine the impact of the measured psychological variables on pain intensity and interference, regression analysis was conducted. A model assuming the impact of aggregated indicators of anxiety and depressive symptoms on the severity of pain proved to fit the data well (F (1.49) = 4.60; $p < 0.05$) and allowed to explain 9% of the variance ($R^2 = 0.09$). The analysis confirmed the existence of positive relationships between the aggregated indicators of anxiety and depressive symptoms and pain severity (β = 0.29; t(49) = 2.14, $p < 0.05$). Pain interference was also assessed in the course of regression analysis. A model assuming an impact of the aggregated indicators of anxiety and depressive symptoms on this variable proved to fit the data well [F(1.49) = 6.64; $p < 0.05$] and allowed to explain 10% of the variance ($R^2 = 0.10$). The analysis confirmed a correlation between the aggregated indicator of anxiety and depressive symptoms and pain interference (β = 0.34; t(49) = 2.58; $p < 0.05$).

To answer the second question formulated in the study, *k*-means clustering was performed on the basis of anxiety and depressive symptoms, with the assumption of 3 clusters. Table 3 presents the mean values of depressiveness and anxiety in the separated clusters.

Table 3. Characteristics of the separated clusters in terms of size and levels of depressive symptoms and anxiety

Cluster	N	Indicators (mean)	
		Depressive symptoms	Anxiety
#1	32 (60.4%)	3.68 ± 2.00	7.09 ± 2.38
#2	10 (18.9%)	7.70 ± 2.54	15.30 ± 2.54
#3	9 (17%)	10.77 ± 2.33	11.77 ± 2.68

Norms of depressive symptoms and anxiety: low < 8; moderate 8-10; high > 10.

Cluster #1 comprised 32 subjects and was characterized by low levels of both depressive symptoms (mean 3.68 ± 2.00) and anxiety (mean 7.09 ± 2.38). Cluster #2 comprised 10 subjects with low levels of depressive symptoms (mean 3.68 ± 2.00) and high levels of anxiety (mean 7.09 ± 2.38). In Cluster #3, 9 subjects had outcomes close to high in the range of depressive symptoms (mean 10.77 ± 2.33) and close to high in the range of anxiety symptoms (mean 11.77 ± 2.68).

Table 4 presents pain severity correlation coefficients for negative emotions and beliefs about pain in the three separated clusters.

Table 4. Correlations of pain severity with negative emotions and beliefs about pain in 3 separated clusters

Dimension	Pain severity		
	Cluster #1	Cluster #2	Cluster #3
HADS			
Depression	0.14	–0.23	0.07
Anxiety	**0.37***	–0.08	0.16
IPQ-R			
Timeline	0.02	**0.79****	–0.06
Timeline cyclical	–0.03	0.34	–0.39
Consequences	0.22	0.18	–0.25
Personal control	–0.04	–0.20	0.25
Treatment control	–0.28	–0.14	–0.59
Emotional representation	0.28	0.22	–0.58
Illness coherence	–0.21	0.08	**0.68***

Statistically significant correlations are in bold: *p < 0.05; **p < 0.01.

Pain severity positively correlated with symptoms of anxiety in subjects from Cluster #1 (rho = 0.37; $p < 0.05$), with the timeline dimension in subjects from Cluster #2 (rho = 0.79, $p < 0.01$) and with the illness coherence dimension in subjects from Cluster #3 (rho = 0.68; $p < 0.05$). Tables 3 and 4 show that in women with low anxiety and depressive symptoms, assessing pain as more severe was associated with an increase in the experienced anxiety level. Beliefs that pain was going to persist remained closely connected with assessing anxiety as severe. Women with high levels of anxiety and depressive symptoms assessed pain as more severe when they were certain of its relation to the disease. Other correlations proved to be statistically insignificant. Table 5 presents the values of pain interference correlation coefficients with anxiety and depressive symptoms as well as with beliefs about pain, in the three separated clusters.

Table 5. Correlations of pain interference with negative emotions and beliefs about pain in 3 separated clusters

Dimension	Pain interference		
	Cluster #1	Cluster #2	Cluster #3
HADS			
Depression	0.18	–0.11	–0.08
Anxiety	**0.38***	–0.21	–0.03
IPQ-R			
Timeline	0.07	**0.80****	0.02
Timeline cyclical	0.12	0.36	–0.21
Consequences	0.23	0.35	0.03
Personal control	0.10	–0.33	0.31
Treatment control	–0.11	–0.11	–0.57
Emotional representation	**0.51****	0.29	–0.53
Illness coherence	–0.18	–0.02	0.62

Statistically significant correlations are in bold: *$p < 0.05$; **$p < 0.01$.

Pain interference positively correlated with anxiety (rho = 0.38; $p < 0.05$) and with the dimension of cognitive representation of negative emotions (rho = 0.51; $p < 0.01$) in subjects from Cluster #1. The correlation between pain intrusiveness and timeline (rho = 0.80; $p < 0.01$) proved to be significant in Cluster #2. In women with low anxiety and depressive symptoms, cognitive representation of negative emotions was associated with high pain interference. In contrast, high anxiety level was associated with an interfering role of pain, if the pain was linked to the beliefs of its chronic nature. In Cluster #3 no statistically significant correlations were found.

Discussion

Results obtained in this study point to significant relationships of anxiety and depressive symptoms with pain in women after mastectomy. In the research on chronic pain, understanding the role of psychosocial factors is now well recognized, as combining it with a biomedical perspective allows a more sophisticated perspective on the complex and multifactor nature of pain. An answer is therefore actively sought to the question of how emotions, beliefs, social support, socioeconomic status and behavior make it possible to identify factors involved in initiating, changing severity, and maintaining the presence of chronic pain symptoms. The presence of anxiety and depressive symptoms in breast cancer survivors has been noted in other authors' studies[1-3,8,11,22-24].

It was also observed that the severer were depressive symptoms and anxiety, the more destructively pain interfered in the respondents' daily functioning (intrusiveness). Pain interference was associated with higher anxiety levels: the more severe the anxiety, the higher the assessment of pain interference. Results from other studies indicate an analogous tendency[12,13,25].

We have also demonstrated that the coexistence of depressive symptoms and anxiety increased the assessment of chronic pain severity and interference. With reference to Leventhal's model, the results of this study indicate that pain experienced by post-mastectomy women is significantly determined by an emotional component – a belief that the pain exists. These results are corroborative of the conception that experiencing symptoms generate a cognitive and an emotional representation of a disease or emergency. The parallel presence of both representations is particularly important as the symptoms has been proven to manifest in all three stages of coping with disease (health risk): from creation of an own representation of the disease, through behaviors related to coping, to the stage of evaluating the effectiveness of adapted behavior[17]. Other studies have shown that the assessment of experienced pain severity depends on the meaning attributed to pain[26], on the existing cognitive schemata, and on expectations about symptoms associated with the disease[27].

According to the severity of depressive symptoms and anxiety, 3 clusters were separated. Among women with characteristic relatively low levels of anxiety and depressive symptoms (Cluster #1), it has been demonstrated that anxiety significantly correlates with perception of pain severity and with pain interference. Among women with characteristic relatively low depressive symptoms and high anxiety (Cluster #2), the assessment of pain as more severe and more intrusive was associated with a belief of its chronic nature. In patients with high anxiety and severe depressive symptoms (Cluster #3), the perception of lower pain severity referred to women who did not link the pain presence to cancer. The obtained results indicate a need for further research on illness coherence in the perception of chronic pain.

The results of this study suggest that the perception of pain severity is related to the intensity of anxiety and depressive symptoms and to the beliefs about pain duration. In conclusion, the completion of cancer treatment didn't eliminate neither the anxiety about a life threat nor the negative affect. Regardless of the biological determinants of chronic pain in post-mastectomy women[28-31], the results of this study indicate a vital importance of psychological determinants in the severity and intrusiveness of pain associated with anxiety and depressive symptoms and with a system of beliefs relating to pain duration. Consistent with these results are studies showing correlations of anxiety and depressive symptoms with severity of pain[32] and with quality of life, or particularly its physical dimension[33], in post-mastectomy women.

The obtained results are in agreement with the observation that intrusive thinking is related to negative psychological and somatic sequelae[34]. The connection between illness intrusiveness and exacerbation of depressive symptoms, regardless of age, physical disability, severity of the disease, current condition or contextual variables, is emphasized in many studies[12,13,25] and appears important in psychoeducational approach to this group of patients.

Summary

According to the findings of this study, the presence of chronic pain in post-mastectomy women is associated with anxiety and depressive symptoms. The connections between anxiety and depressive symptoms in the 3 subgroups of subjects were of varied intensity and were differently linked to pain severity, pain interference, and to the beliefs about pain.

This study has also revealed significant relationships of anxiety and depressive symptoms with beliefs about pain persistence in the future and with beliefs about a destructive role of pain in everyday life. Chronic pain appeared more intrusive in women who associated it with an ineffective treatment (duration) and disease.

In this group of patients, it should be vital to build the belief that breast cancer is a chronic disease, more and more often treated successfully. Convictions about the impossibility to cure cancer alleviate anxiety and depressive symptoms and become a cause of delaying the proper diagnostic tests, which perpetuates the vicious circle and the negative picture of the disease[35].

Limitations

Results of this study refer to a relatively small group of women selected according to predetermined clinical criteria (in the course of physiotherapy, after radical mastectomy, the presence of chronic pain). The results make a preliminary report of a broader research on psychosocial contexts of chronic pain, comprising various clinical groups with different etiopathogeneses of pain.

Conclusions

In post-mastectomy patients, pain severity was associated with anxiety and depressive symptoms severity and with beliefs about pain duration.

Symptoms of anxiety and depression as well as the system of beliefs about pain duration were associated with pain interference (everyday functioning distortion).

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Patterns of chronic benzodiazepine use in the elderly

Vanessa Sgnaolin[1], Paula Engroff[2], Camila Pereira Andrade[3], Fernanda Loureiro[1], Eduardo Lopes Nogueira[1,4], Alfredo Cataldo Neto[1,4], Irenio Gomes[1,5]

[1] *Post-Graduate Program in Biomedical Gerontology of Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil.*
[2] *Institute of Geriatrics and Gerontology of PUCRS, Porto Alegre, RS, Brazil.*
[3] *Pharmacy College of PUCRS, Porto Alegre, RS, Brazil.*
[4] *Department of Psychiatry Hospital São Lucas of PUCRS, Porto Alegre, RS, Brazil.*
[5] *Department of Neurology Hospital São Lucas of PUCRS, Porto Alegre, RS, Brazil.*

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Abstract

Background: In several countries, prevalence studies demonstrate that chronic use of BZD in the elderly population is very high. This scenario has reached pandemic proportions for decades and is an important public health problem. **Objectives:** To examine the independent association between chronic benzodiazepine use in depression, anxiety and bipolar disorder, as well as other clinical and sociodemographic factors. **Methods:** This cross-sectional study was developed from a population-based survey and conducted from March, 2011 to December, 2012 using a random sample of 550 elderly people who were enrolled in the Family Health Strategy in Porto Alegre, Brazil. Data was collected from identifying epidemiological and health data (sociodemographic, self-perception health, self-reported diseases, smoking, alcohol and pharmacotherapeutic evaluation) and from the diagnoses of mood and anxiety disorders. **Results:** Elderly patients diagnosed with depression, anxiety, concomitant depression/anxiety and bipolar disorders, and those who were using antidepressants have a higher risk of benzodiazepine use. Individuals who self-reported drinking alcohol had a lower risk of benzodiazepine use. **Discussion:** Benzodiazepines are often used by the elderly for long periods, which has a direct impact on the treatment of mood and anxiety disorders and on vulnerable groups such as the elderly, who may be unnecessarily taking these drugs.

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Keywords: Elderly, anxiety, benzodiazepines, depression, public health.

Introduction

Benzodiazepines (BZD) comprise a subgroup of psychotropic drugs that act selectively to allosterically modulate gamma-aminobutyric acid subtype A ($GABA_A$) receptor and mediate inhibitory synaptic transmission throughout the central nervous system[1]. They are commonly recommended for a variety of conditions such as anxiety, depression, somatic complaints, insomnia, alcohol withdrawal, delirium and violence and aggressive behavior in psychoses and disorders induced by neuroleptics[2,3]. The therapeutic indication for this group of drugs should be short term and for specific conditions such as those mentioned above.

Elderly people are more likely to use BZD[4], but they feel less secure and have questionable clinical indications for taking BZD such as nonspecific emotional suffering[5] or a chronic insomnia complaint. In several countries, prevalence studies demonstrate that chronic use of BZD in the elderly population is high, ranging from 3.9% to 35.9%[6-8]. This scenario has reached pandemic proportions for decades and is an important public health problem, because chronic use of this drug results in an increase in morbidity factors related to the risk of falls, intoxication and worsening of depressive symptoms and cognition[9,10].

Depressive[11,12] and anxiety disorders are frequent in the elderly, constituting an important source of emotional suffering and consequently the increased use of this pharmacological class[8,13]. Newer treatment consensus recommendations for depressive and anxiety disorders do not suggest BZDs as a first-line therapeutic[14,15]. The risk/benefit ratio increases when treating these disorders in the elderly, making the indication for BZD even more unfavorable. This is because of pharmacokinetic and pharmacodynamic changes that occur with aging, which may lead to an increased sensitivity of these individuals to the effects of BZD.

Thus, this study aims to examine the independent association between chronic BZD use in depression, anxiety and bipolar disorders, as well as other clinical and sociodemographic factors in a sample of elderly people who are enrolled in the Family Health Strategy (FHS).

Methods

Study design

This cross-sectional study was developed from the population-based survey entitled "The multidimensional study of the elderly in the family health strategy in Porto Alegre, Brazil (EMI-SUS)"[16]. The EMI-SUS was conducted from March, 2011 to December, 2012 and enrolled a random sample of elderly people who were participating in the FHS in Porto Alegre (RS/Brazil). Inclusion criteria were age ≥ 60 years and records registered in the FHS.

Data collection

The data collection procedure included identifying epidemiological and health data (sociodemographic, self-perception health, self-reported diseases, smoking, alcohol and pharmacotherapeutic evaluation) that were collected by community health agents at the homes of the elderly and during specialized psychiatric evaluation, which was carried out by professionals trained at the Hospital São Lucas of Pontifícia Universidade Católica do Rio Grande do Sul.

The mood disorder (major depression/dysthymia, bipolar) and anxiety diagnosis was made by psychiatrists using the DSM-IV criteria, and following the mental health evaluation protocol of the study[17]. The validated Brazilian version of the Mini-International Neuropsychiatric Interview (MINI) was used for evaluating psychiatric diagnoses[18], and the psychometric properties of the instrument were considered satisfactory to excellent, with a good accuracy for anxiety and mood disorders in primary health care in Brazil[19].

For pharmacotherapeutic evaluation, the participants were asked to specify all drugs used. In the interview conducted by the

Address for correspondence: Vanessa Sgnaolin. Laboratório de Bioquímica, Genética Molecular e Parasitologia. Av. Ipiranga, 6690, prédio 60, 3º andar – 90610-000 – Porto Alegre, RS, Brazil. Phone/Fax: (51) 3320-3000 (extension line: 2660). E-mail: vanessasgnaolin@yahoo.com.br

community health agent, this information was confirmed from prescriptions, drug packaging and medical records at the FHS. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the World Health Organization[20]. In this study, psychotropic medications included were BZD (N05BA, N03AE01), antidepressants (N06A, N06CA01), antiepileptic (N03A), antipsychotics (N05A) and other psychotropic drugs (N04AA02, N04BA01, N05BB01, N06BA07, N06BC01).

Sample size

The sample size of the study was calculated using a 0.05 significance level. Considering a target population of 22,000 elderly people enrolled by ESF in Porto Alegre, a minimum sample size of 491 elderly people was chosen, considering a 3.5% acceptable error for an expected prevalence of 20.0%.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (IBM SPSS Inc. Chicago, Illinois, version 17). The variables were described by the frequency, mean and standard deviation. Associations between categorical variables were tested using Pearson's chi-square test. In specific cases, the chi-square test for linear tendency (ordinal variables with few categories) was used. To control for confounding variables and independence of variables, multivariate analysis was performed through Poisson regression.

Ethical considerations

This study was approved by the Ethical Research Committee of the Pontifícia Universidade Católica do Rio Grande do Sul (number 10/04967) and Porto Alegre Municipal Department of Health (registration 499/process 001.021434.10.7). All participants were informed of the objectives and research methods and they signed an informed consent form, according to the Guidelines and Norms Regulating Research of Resolution 196/96 of the National Health Council of the Ministry of Health.

Results

The 550 individuals included in the study were between 60 and 103 years of age (mean age, 68.6 ± 7.2 years), and comprised mostly females (63.1%). Most of these elderly people were married (37.8%), had incomplete primary education (69.1%), a little more than half of the individuals (55.0%) received less than one minimum wage (250 US dollars) and little more than half of the families (55.5%) received less than three minimum wages.

The prevalence of BZD use was 7.3%. This prevalence is compared with sociodemographic variables in Table 1. Those who had been widowed were found to use more BZD (10.8%) while single people used less BZD (1.1%; $P = 0.044$). There were no statistically significant differences in the other sociodemographic variables.

Elders diagnosed with mood disorders represented 38.2% of the total population studied, with depression responsible for 28.8% and anxiety 20.2%. Elderly people without a diagnosis of mood disorder used less BZD (2.2%); however, those with depression (15.5%; $P < 0.001$) and anxiety (10.5%) used BZD more often. Those who self-identified and classified their health as poor/very poor used more BZD (21.2%; $P = 0.003$). Those who drank alcohol had a lower prevalence of use of BZD than those who did not drink alcohol (1.3%, $P = 0.001$; Table 2).

The average number of drugs used was 4.0 ± 2.9 (range, 0-13 drugs). Individuals who used 5 or more drugs showed a high prevalence of BZD use (11.7%, $P < 0.001$). Antidepressants (32.5%; $P < 0.001$), antipsychotics (33.3%; $P < 0.001$) and the antiepileptic (25.0%; $P = 0.017$) were the psychotropic classes that were most frequently used concomitantly with BZD (Table 2).

The final model of multivariate analysis was used to determine which variables were independently associated with the BZD use, and the results are presented in Table 3. Elderly people diagnosed with depression, anxiety, depression and anxiety concomitantly and bipolar disorder, and those who were using antidepressants had a higher risk of using BZD. Individuals who self-reported that they drank alcohol had a lower risk of BZD use.

Discussion

Large-scale BZD use has been widely accepted worldwide, because these drugs have been considered to be effective as anxiolytics and they are safer than the drugs that were previously available, such as barbiturates. The benefit of a lower toxicity and less potential to develop a chemical dependency contributed to the widespread BZD use over the past decades; this transformed a "benefit" into an important public health problem, especially in the elderly who are typically the main consumers this type of drug.

The prevalence of BZD use (7.3%) is considered high. Brunoni *et al.* presented data from six universities located in different Brazilian regions (São Paulo, Rio de Janeiro, Salvador, Porto Alegre, Belo Horizonte and Vitória), where they detected a BZD use prevalence of 3.9% (in those 35 to 75 years of age), and older people were the most likely to use BZD (OR 3.48)[8]. The prevalence was even higher (21.7%) in an elderly community sample of residents of the city of Bambuí, Minas Gerais, Brazil[21]. Prevalence rates in other countries ranged from 16% in Australia[22] to 31% in Finland[7] and 36% in Canada[6]. These results are particularly important because there are guidelines that classify the BZD use as inappropriate, particularly because of side effects in the elderly[23].

Table 1. Benzodiazepine (BZD) use compared with sociodemographic variables

Sociodemographic variables	BZD use		*P*
	No n (%)	Yes n (%)	
Gender			
Female	317 (91.4)	30 (8.6)	0.105†
Male	193 (95.1)	10 (4.9)	
Age (years)			
60-69	315 (92.6)	25 (7.4)	0.875‡
70-79	152 (92.7)	12 (7.3)	
80 or more	43 (93.5)	3 (6.5)	
Race			
White	320 (91.2)	31 (8.8)	0.270†
Black	96 (97.0)	3 (3.0)	
Brown	71 (93.4)	5 (6.6)	
Other	15 (93.8)	1 (6.3)	
Marital status			
Married	190 (92.7)	15 (7.3)	0.044†
Widowed	141 (89.2)	17 (10.8)^{2,1}	
Divorced	83 (93.3)	6 (6.7)	
Single	90 (98.9)	1 (1.1)$^{-2,5}$	
Education (years)			
0	79 (95.2)	4 (4.8)	0.299‡
1-7	341 (91.4)	32 (8.6)	
8 or more	80 (95.2)	4 (4.8)	
Individual income (minimum wage)			
< 1	302 (91.8)	27 (8.2)	0.215‡
1 or more	179 (94.7)	10 (5.3)	
Total	510 (92.7)	40 (7.3)	

† Pearson chi-square test; superscript numbers show results of residual analyses.
‡ Chi-square test for linear tendency.

Table 2. Benzodiazepines(BZD) use compared with clinical and health variables

Clinical and health variables	BZD		*P*
	No n (%)	Yes n (%)	
Mood or Anxiety disorder			
No	307 (97.8)	7 (2.2)$^{-5,3}$	< 0.001†
Depression	87 (84.5)	16 (15.5)^{3,6}	
Anxiety	34 (89.5)	4 (10.5)	
Depression and Anxiety	45 (86.5)	7 (13.5)	
Bipolarity	27 (84.4)	5 (15.6)	
Self-perceived health			
Great/Good	183 (94.8)	10 (5.2)	0.003‡
Regular	279 (93.6)	19 (6.4)	
Poor/Very poor	41 (78.8)	11 (21.2)^{4,0}	
Smoker			
No	214 (93.4)	15 (6.6)	0.161†
Yes	183 (93.8)	12 (6.2)	
Ex-smoker	98 (88.3)	13 (11.7)	
Alcohol use			
No	327 (90.8)	33 (9.2)	0.001†
Yes	150 (98.7)	2 (1.3)	
Drug use			
0	74 (100.0)	0 (0.0)$^{-2,6}$	< 0.001‡
1-2	111 (95.7)	5 (4.3)	
3-4	127 (93.4)	9 (6.6)	
5 or more	196 (88.3)	26 (11.7)^{3,3}	
Pharmacological classes			
Antidepressants			
No	458 (96.8)	15 (3.2)	< 0.001†
Yes	52 (67.5)	25 (32.5)	
Antipsychotics			
No	498 (93.6)	34 (6.4)	< 0.001†
Yes	12 (66.7)	6 (33.3)	
Antiepileptics			
No	501 (93.1)	37 (6.9)	0.017†
Yes	9 (75.0)	3 (25.0)	
Others psychotropics			
No	494 (92.9)	38 (7.1)	0.524†
Yes	16 (88.9)	2 (11.1)	

† Pearson chi-square test; superscript numbers show results of residual analyses.
‡ Chi-square test for linear tendency.

Table 3. Final model of multivariate analysis using Poisson regression

Variable	PR	CI 95%	*P*
Mood or Anxiety disorder			
No	1		
Depression	2.92	1.08-7.85	0.034
Anxiety	7.06	2.44-20.44	< 0.001
Depression and Anxiety	3.51	1.32-9.37	0.012
Bipolarity	3.54	1.04-12.11	0.044
Antidepressants			
No	1		
Yes	8.60	4.14-17.89	< 0.001
Alcohol use			
No	1		
Yes	0.23	0.06-0.94	0.040

PR: prevalence ratio; CI: confidence interval.

The main socio-demographic characteristics related to chronic BZD use were female (8.6%), white (8.6%), widowed (10.8%) and income less than the one minimum wage (8.2%). Only the marital status showed a significant difference, with those who had been widowed using more BZDs. In this group, the majority were women who had depression and used antidepressants, which are factors that are strongly related to BZD use[24]. Previous studies that examined the role of living alone or marital status obtained similar results[13,25]. This finding was not an independent factor that was associated with outcome in a multivariate analysis.

The highest frequency of BZD use is associated with a diagnosis of mood or anxiety disorders, poor self-perceived health, the use of five or more drugs and concomitant use of other psychotropic drugs, particularly antidepressants, antipsychotics and antiepileptics. In a multivariate analysis, the factors that remained were diagnosed with depression (RP: 2.92), anxiety (RP: 7.06), depression and anxiety (RP: 3.51) and bipolar disorder (RP: 3.54). When considering these diagnoses, the elderly person with these psychiatric disorders can be considered very likely to receive BZD. These drugs are indicated for use in various syndromes that present as nonspecific emotional suffering. However, in almost all situations, the BZD use is contraindicated in elderly people[23], as well as in the general population. BZDs are not indicated for moderate to severe depression, and there is also no evidence to support their use in minor depression[26]. Toxic effects, cognitive dysfunction, risk of worsening depression and fall hazards, among others, will probably outweigh any positive effect of the BZD in the elderly.

According to some authors, the concomitant BZD and antidepressant use can be considered a strategy to increase treatment effectiveness[27]. Short-term use is the most widely accepted use of BZD to treat depression and anxiety, mainly to achieve rapid relief of symptoms at the start of therapy. There is subsequent reduction of the antidepressant dose when it starts to show its effect, thus improving the adherence to antidepressant therapy[28]. The rationale for combination treatment is multidimensional, including neurological bases and clinical factors, because of different pharmacokinetic mechanisms and clinical effects. However, this must be balanced because there is the potential for BZD dependency, and there are antidepressants with anxiolytic/sedative effects that can be used instead of BZDs. This association also raises the issue of polypharmacy, which should be an exception in treating elderly people. In multivariate analysis, antidepressants were most often associated with BZD, showing a high chance of co-prescription (RP: 8.60). Data from a Dutch cohort study of people with depression and anxiety found a milder association between BZD and antidepressants (OR: 3.5)[13], while another Brazilian study showed a strong association (OR: 7.95)[8].

BZDs have been reported to be associated with alcohol consumption[24]. This combination is important because of the possibility of mood disorders, excessive sedation, increased risk of falls, memory problems and traffic accidents, especially in the elderly. In contrast, our results showed that older people who used BZD consumed less alcohol. These elderly people potentially should have been instructed not to consume alcohol during treatment.

This study is subject to some limitations, as follows: 1) the cross-sectional design is limited to establishing cause and consequence; 2) while the diagnostic examination is important, overestimation of the diagnosis is recognized in structured interviews based on current diagnostic systems[29]; and 3) the results of the multivariate analysis should be interpreted with caution because of the small absolute number of individuals with diagnoses who were investigated.

In conclusion, BZDs are often used by elderly people over long periods of time. Elderly people who make take multiple drugs, especially antidepressants, are more likely to use BZDs, as are those with a clinical diagnosis of depression, anxiety, depression/anxiety and bipolar disorders. These questions have a direct impact on an increase in morbidity that results from negative effects of psychotropic drug over-prescription and mistreatment of mood and anxiety disorders.

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Conflicts of interest and financial disclosure

None was declared.

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Heritability of social anxiety disorder: a systematic review of methodological designs

André Luiz Moreno[1], Flávia de Lima Osório[1], Rocio Martín-Santos[2], José Alexandre S. Crippa[1]

[1] *Graduate Program in Mental Health, Ribeirão Preto Medical School, University of São Paulo (USP), São Paulo, SP, Brazil.*
[2] *Service of Psychiatry and Psychology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (Idibaps), Centro de Investigación en Red de Salud Mental (Cibersam), and Department of Psychiatry and Clinical Psychobiology, University of Barcelona.*

Study developed in Graduate Program in Mental Health, Ribeirão Preto Medical School, University of São Paulo.

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Abstract

Background: The investigation of heritability stands out as an important means to establish the weight of genetic and environmental factors in the development of social anxiety disorder. **Objective:** This study aims to make a critical review of methodological designs used in the investigation of the social anxiety disorder (SAD) heritability. **Methods:** We reviewed 31 research articles published until October 2015 and found through the electronic search bases PubMed, Web of Science, and Scopus and manual searches in the reference lists of the selected references. Most of the investigations involved adult samples and twins to assess heritability. **Results:** There was great variability in the screening and diagnostic instruments used in the studies, leading to different outcomes. Structural equation models proved to be the most adequate to assess SAD heritability, allowing better estimates of this aspect of the disorder. SAD heritability rates varied between 13% and 76% in the articles reviewed. **Discussion:** We discuss methodological aspects that may affect the quality and the development of improved studies to investigate SAD heritability such as sample size, quality of screening instruments, and use of diagnostic interviews. More homogeneous investigations involving larger samples and standardized instruments and methods are desirable and opportune.

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Keywords: Social anxiety disorder, heritability, genetics, methodological design, social phobia.

Introduction

Social anxiety disorder (SAD) or social phobia is an anxiety disorder characterized by the presence of fear and anxiety in social situations, associated with the avoidance of such situations or significant personal distress that affect daily life. The prevalence of SAD has been estimated between 7%-12%[1,2], causing impairment in the life of diagnosed individuals[3] and direct and indirect costs to health systems[4].

The current model of the development and maintenance of SAD holds that multiple factors interact at specific moments and circumstances for the disorder to occur[5]. This interaction model combines both genetic factors, such as polymorphisms[6] and temperament[7], and environmental factors including the perception of family environment[8] and parental conflicts[9]. However, despite the existence of studies in this field, it is not yet possible to determine the specific contribution of each factor for the development of SAD. Therefore, the investigation of heritability stands out as an important means to establish the weight of genetic and environmental factors in the development of disorders, and different methodological designs can be used for this purpose.

In one methodological approach, heritability can be assessed by the chance that one relative will have the disorder, given the diagnosis of a patient, compared to a volunteer without the disorder (odds ratio). In this case, the participation of several relatives is required for each participant, divided according to the degree of genetic similarity (*e.g.*: 50% genetic similarity for first-degree relatives, 25% for second-degree relatives, 12.5 for third-degree relatives, and zero for spouses and adopted siblings). In this study design, the comparison of odds ratios (relative risk) for each degree of genetic similarity indicates the importance of genetic factors, whereas the analysis of relatives with no genetic similarity allows the observation of environmental factors. However, this design makes it difficult to determine the specific weight of genetic and environmental factors, since it is impossible to establish which environmental factors are social/shared or individual, as well as whether any genetic factors associated with the disorder are related to additive effects or dominant alleles.

Another method to assess heritability involves the participation of twins. In these studies, the genetic similarity between monozygotic (MZ) and dizygotic (DZ) twins is used to determine shared elements, since MZ twins virtually share 100% of their genes, while DZ twins share around half of their genes. It is also possible to explore gender differences in this type of investigation given the different gender-related experiences of the twins. Studies involving twins allow a more accurate determination of the factors that influence a given disorder, which are observed according to four possible outcomes: additive genetic effects, genetic effects resulting from dominant or non-additive alleles, familial or shared environmental effects (*e.g.*: parental conflict), and environmental effects that are not shared by individuals (*e.g.*: perception of family environment).

In research with twins, heritability can be assessed through types of analyses. The first involves the correlations of a given disorder indicator (diagnosis, interview, instrument) between MZ and DZ twins. In this approach, differences indicate additive genetic effects (A), which can be considered dominant (D) if the correlation in MZ twins is at least twice as that of DZ twins. In another type of analysis, the factors are explored in structural equation models that indicate the model that best fits the sample data (*e.g.*: a model considering only additive genetic effects and environmental factors that are not shared; or another model that will also contemplate shared environmental factors) and the estimated explained percentage for each factor.

In respect to SAD, a meta-analysis[10] estimated the heritability of the disorder as ranging between 20%-40%. This result, however, refers to a group comprising individuals with SAD, specific phobia, and agoraphobia, and does not specify the heritability of each disorder. A more recent review estimated the heritability of SAD between 27%-56%[11], but it included only studies with twins and which described precise estimates of variance explained by genetic factors.

Despite these efforts and as far as we know, no study to date made a comprehensive assessment of investigations on the heritability

Address for correspondence: José Alexandre S. Crippa. Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo – Campus Universitário, s/n, Monte Alegre – 14048-900 – Ribeirão Preto, SP, Brazil. E-mail: moreno.andreluiz@gmail.com

of SAD that used different methodological designs. Therefore, the objective of our study was to review articles dealing with the heritability of SAD with an emphasis on their methodological design and to provide directions for future research.

Method

Systematic searches were performed using the online databases PubMed, Web of Science, and Scopus for articles published until October 2015 using the following search terms: "social phobia AND genetics", "social phobia AND heritability", "social anxiety AND genetics", and "social anxiety AND heritability". The reference lists of articles found through the electronic databases and other review articles were hand-searched for additional references.

We included articles that described any measure or SAD heritability as an outcome. Animal studies, studies on genetic polymorphisms related to SAD, articles with no specific SAD heritability data, letters to the editor, editorials, book chapters, and review articles were not included in this review.

From each selected article, the following data were extracted whenever possible: (I) origin of the study sample; (II) country; (III) sample size; (IV) instruments used for the screening or diagnosis of SAD; (V) method of data analysis; (VI) primary outcome; (VII) correlation values between MZ and DZ twins; (VIII) genetic model; and (IX) values of additive genetic effects (A), shared environmental effects (C), and environmental effects (E). The data of the different articles were than assessed conjointly based on these categories. In addition, the studies were assessed according to the criteria of the STROBE initiative[12], which consist of a list of 22 items that assess the methodological quality of scientific articles.

Results

A total of 888 articles were found through the electronic searches. After a selection based on the inclusion and exclusion criteria, 28 articles were included in the review. Three other articles were found through the reference lists of selected articles and were also included in the review. Therefore, this review comprises the data of 31 articles. Details of the search and selection procedures are presented in Figure 1.

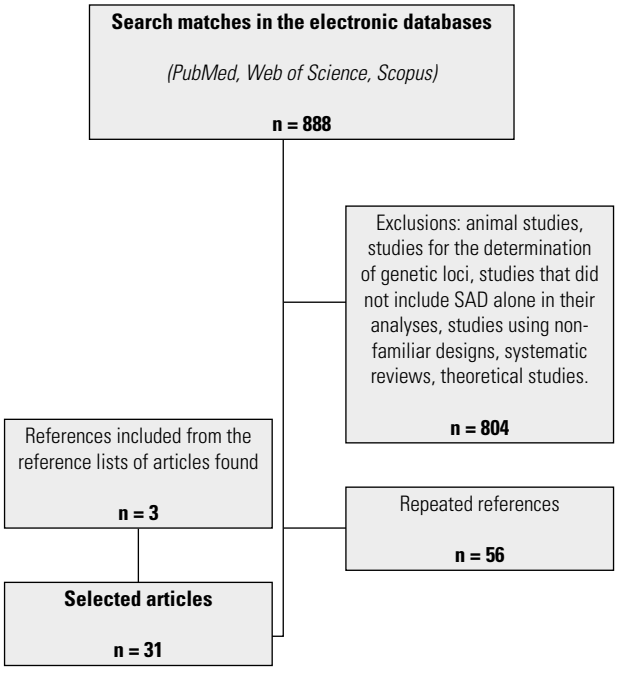

Figure 1. Flowchart showing the steps of the search and selection of articles for the review.

Table 1 presents the data of each article included in the review. From the studies selected, 21 (67.75%) recruited twins, and only one of these included volunteers recruited through community ads. Thus, 20 (95.23%) of the studies involving twins used public or private medical records, where data on the twin pairs were available since their birth until the data collection. In respect to the origin of articles included in this review, 19 (61.3%) were from Europe, 9 (29.03%) were from North America, and 2 (6.4%) came from Oceania. One study involved samples from two continents (Europe and Oceania).

Concerning the age range of participants, 17 studies (54.83%) involved adult samples and 12 studies (38.7%) involved children and adolescents. Two longitudinal studies collected data from participants at different age ranges, including periods of childhood, adolescence, and adult life. In general, the instruments used to measure symptoms or diagnose SAD varied widely across the studies. Despite this variation, self-report instruments were used as the only measure of SAD symptoms in 13 studies (41.93%). Thus, whereas some of the studies reviewed used well-established measures for the assessment of SAD (*e.g.*, Social Phobia Inventory[13]), others used sets of items taken from assessment instruments (*e.g.*[14]). Interviews were used as the only diagnostic instrument in 11 studies (35.48%) and structured interviews as the Structured Clinical Interview for DSM-IV (SCID)[15] and the Composite International Diagnostic Interview (CIDI)[16] were the most common among these. Two investigations (6.4%) used only medical records to establish diagnosis, with no procedures included to confirm the criteria applied or the accuracy of diagnosis during the period of the study. Other studies used more than one type of instrument to assess symptoms or diagnosis due to different profiles of their participants. In these studies, cases and controls were assessed with diagnostic interviews (three studies) or self-report instruments (two studies), whereas relatives (parents, siblings, uncles and grandparents) were assessed through previous diagnostic records or assessments by their health networks.

The studies included in this review also differed significantly in respect to methods of data analysis and the outcomes derived from these analyses. Among all the articles selected, 14 (45.16%) analyzed correlations between the twins in their samples, using the correlations between monozygotic and dizygotic siblings as outcomes, and also provided models and heritability estimates as outcomes based on structural equations. Two studies assessed only correlation differences between twins, while five others reported only heritability estimates based on structural equation models. Five of the articles reviewed analyzed the odds ratios for SAD in relatives of participants diagnosed with the disorder and presented as outcomes the differences between the degrees of relatedness, including that of twins, considering cases and controls. In addition, two studies reported heritability estimates obtained from structural equation models together with odds ratios for relatives of affected patients, and only one study provided heritability estimates based on the difference of correlations between siblings and half-siblings together with odds ratios. The investigation by Stein *et al.*[17] used factorial analysis to assess the extent to which the degree of consanguinity of SAD patients explained SAD symptoms in relatives, presenting as their outcome the variance explained by consanguinity relative to other factors. Finally, the study by Li *et al.*[18] assessed the incidence of SAD in siblings of patients diagnosed with anxiety disorders, presenting the standardized index ratio as outcome.

All the articles included in this review had satisfactory methodological quality, fulfilling at least 15 (68%) of the STROBE assessment items[12]. Additionally, 17 articles (55%) fulfilled more than 80% of the methodological recommendations of that initiative. Conversely, none of the studies included followed all the guidelines of the STROBE. The mains items that were not fulfilled by the studies reviewed here refer to the absence of information on sample size calculations and efforts to reduce possible biases.

Table 1. Population, number of participants, age of participants, instruments used to assess SAD, data analysis method, outcome and items fulfilled of STROBE of each study included

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Coelho *et al.*, 2007[21]	UK/Outpatients	37 SAD 22 GAD 15 SAD + GAD 60 HC 403 Relatives	Cases: 32.1 (3.77) Relatives: 47.4 (14.98)	SCID. Diagnosis of relatives based on information provided by cases/ controls	OR Case X Relative	OR SAD X SAD = 3.38 (1.25-9.16); SAD X Comorbidity OR (SAD-GAD) = 3.50 (0.98-12.55); Comorbidity OR (SAD-GAD) X TAS = 7.01 (0.82-60.23); Comorbidity OR X Comorbidity = 17.34 (1.96-153.62)	19 (86%)
Czajkowski *et al.*, 2011[22]	Norway/Twins (medical record services)	446 P Mz F; 264 P Dz F; 10 I	28.1	CIDI	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Eley *et al.*, 2003[23]	UK/Twins (medical record services)	723 P Mz M; 769 P Dz M; 818 P Mz F; 760 P Dz F; 1494 P Dz O	4	16-item questionnaire on anxiety-related behaviors	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	18 (82%)
Eley *et al.*, 2008[24]	UK/Twins (medical record services)	T0: 754 P Mz M; 783 P Dz M; 845 P Mz F; 768 P Dz F; 1512 P Dz O; T1: 120 P Mz M; 133 P Mz F; 138 P Dz M; 136 P Dz F; 327 P Dz O	T0: 4 T1: 6	T0 Anxiety Related Behaviors Questionnaire. T1 Anxiety Disorders Interview Schedule for Children and Parents	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	18 (82%)
Hallett *et al.*, 2009[14]	UK/Twins (medical record services)	T0 1205 P Mz M; 1118 P Dz M; 1370 P Mz F; 1219 P Dz F; 2255 P Dz O; T1: 538 P Mz M; 674 P Dz M; 503 P Mz F; 557 P Dz F; 1004 P Dz O	T0: 7 T1: 9	25 items taken from other instruments	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Hallett *et al.*, 2012[25]	UK/Twins (medical record services)	T0: 1232 P Mz M; 1164 P Dz M; 1375 P Mz F; 1230 P Dz F; 2310 P DzO; T1: 1069P Mz M; 1044 P Dz M; 1195 P Mz F; 1054 P Dz F; 2064 P Dz O	T0: 7 T1: 9	22 items taken from other instruments	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	18 (82%)
Hettema *et al.*, 2005[26]	USA/Community sample	2156 P F; 2939 P M	_	Diagnostic interviews based on DSM = III-R criteria	Structural Equation Models	Heritability estimates	17 (77%)

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Hettema *et al.*, 2006[27]	USA/Twins (medical record services)	679 P Mz F; 467 P Dz F; 869 P Mz M; 653 P Dz M; 1429 P Dz O; 125 I Mz F; 56 I Dz F; 230 I Mz M; 275 I Dz M; 462 I Dz O	–	Diagnostic interviews based on DSM = III-R criteria	Structural Equation Models	Heritability estimates	18 (82%)
Hudson *et al.*, 2003[28]	Austria/Outpatient services	64 MDD 58 HC 152 relatives	Cases: 39.5 (15) Relatives (cases): 39.6 (13.7) Controls: 40.9 (14.1). Relatives (controls): 37.4 (13.1)	SCID	OR Case X Relative	OR without depression = 4.6 (1.2-18); OR with comorbid depression = 2.7 (0.59-12)	17 (77%)
Isomura *et al.*, 2015[29]	Sweden/Population records with mental disorder diagnoses	18399 SAD 2673 APD 210.720 HC 2.959.278 Relatives	–	Previous diagnoses in medical records	OR Case X Relative Correlations between siblings and half-siblings	OR First-degree = 4.74 (4.28-5.25). OR Second-degree = 2.3 (2.01-2.63). OR Third-degree = 1.72 (1.52-1.94). OR Non-biological parents = 4.01 (3.26-4.95). Correlation for siblings = 0.27; half-siblings (mother's side) = 0.13. Heritability estimated by the correlation = 0.56	17 (77%)
Kendler *et al.*, 2001[30]	USA/Twins (medical record services)	707 P Mz M; 290 P Dz M; 254 I Mz M; 290 I Dz M	36.8 (9.1)	Diagnostic Interview Scale (DIS). Version III-A	OR Case X Sibling Structural Equation Models	Differences in OR. MZ = 2.3 (0.92-5.77); DZ = 1.73 (0.50-6.07)	14 (64%)
Kendler *et al.*, 2008[31]	Sweden/Twins (medical record services)	242 P Mz F; 182 P Dz F; 240 P Mz M; 168 P Dz M; 390 P Dz O	T0: 13-14 T1: 16-17 T2 19-20	Items dealing with fear of specific situations and objects	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	17 (77%)
Knappe *et al.*, 2009[32]	Germany/Cohort population for the study of psychopathology	T0: 1395 I T1: 1228 I T2: 1169 I T3 1,022 I	T0: 14-17 T1: 16-19 T2: 18-21 T3: 24-27	CIDI	OR Case X Relative	Symptomatic: OR = 1.3 (0.76-2.23); Subthreshold: OR = 1.44 (0.75-2.78); Diagnosis: OR = 3.21 (1.21-8.49)	18 (82%)
Lahey *et al.*, 2011[33]	USA/Twins (medical record services)	1571 PMz/Dz	6-17	Child and Adolescent Psychopathology Scale	Structural Equation Models	Heritability estimates	17 (77%)
Li *et al.*, 2011[18]	Sweden/Population records with mental disorder diagnoses	42602 AD; 2093 relatives		Previous diagnoses in medical records	Standardized incidence ratios	Men: 4.49 (1.88-10.07); Women: 2.51 (0.7-7.35); Total: 3.68 (1.68-7.69)	17 (77%)
López-Solà *et al.*, 2014[34]	Australia/Twins (medical record services)	204 P Mz M; 299 P Mz F; 111 P Dz M; 194 P Dz F; 125 I Mz M; 150 I Mz F; 132 I Dz M; 192 I Dz F;	MZ: 34.5 (7.8) DZ: 33.9 (8)	SPIN	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Low *et al.*, 2008[35]	USA/Patients recruited from outpatient services and the community. Relatives contacted.	26 I SAD + PD 40 I PD 46 I SAD 32 I AD 81 I HC. 1053 relatives	SAD + PD: 39 (5.9) PD: 39.5 (5.2) SP: 40.8 (6.3) AD: 40.4 (6.2) Controls: 41 (6.3)	Schedule for Affective Disorders and Schizophrenia. Family History-Research Diagnostic Criteria	OR Case X Relatives	OR SP-SP = 1.8 (1.1-2.9)	17 (77%)
Low *et al.*, 2008[36]	USA/Patients recruited from outpatient services and the community. Relatives contacted.	76 I SAD 60 I HC 620 relatives	Cases: 39.9 (5.3) Controls: 40.9 (6.28)	SCID for cases and controls. Best estimate Diagnoses for relatives	OR Case X Relatives	Clinical OR = 2.74 (1.1-6.84); Community OR = 2.38 (0.91-6.22)	16 (73%)
Michelini *et al.*, 2015[37]	UK/Twins (medical record services)	88 P Mz M; 134 P Mz F; 64 P Dz M; 130 P Dz F; 214 P Dz O; 30 P S M; 51 P S F; 71 P S O	17 (1.66)	Spence Children's Anxiety Scale	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	21 (95%)
Middedorp *et al.*, 2005[38]	The Netherlands and Australia/ Twins (medical record services)	1334 I M; 2088 I F	Men: 35.15 Women: 35.15	CIDI	Correlations between Mz and Dz	Correlation differences Brothers: 0.20 (0.09-0.31) Sisters: 0.20 (0.09-0.31) Different gender: 0.20 (0.09-0.31)	20 (91%)
Mosing *et al.*, 2009[39]	Australia/Twins (medical record services)	1337 P Mz 1384 P Dz	Mz: 44.07 (12.4); Dz: 29.9 (2.5)	Computer algorithms based on responses in the Semi-Structured Assessment for the Genetics of Alcoholism (SSA-GA)	OR Case X Sibling Structural Equation Models	Differences in OR. MZ = 11.9 (3.7-38.8); DZ = 1.5 (0.2-11.0). Heritability estimates	17 (77%)
Nelson *et al.*, 2000[40]	USA/Twins (medical record services)	672 P F Mz/Dz	18.2	Telephone interview with questions adapted from the Diagnostic Interview for Children and Adolescents	Correlations between Mz and Dz	Heritability estimates	18 (82%)
Ogliari *et al.*, 2006[41]	Italy/Twins (medical record services)	70 P Mz M; 65 P Mz F; 50 P Dz M; 78 P Dz F; 115 P Dz O	13.03 (2.6)	SCARED	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Ogliari *et al.*, 2010[42]	Italy/Twins (medical record services)	70 P Mz M; 65 P Mz F; 50 P Dz M; 78 P Dz F; 115 P Dz O	8-17	SCARED	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Reichborn-Kjennerud *et al.*, 2007[43]	Norway/Twins (medical record services)	898 P Mz F; 529 P Dz F	–	CIDI	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Skre *et al.*, 2000[44]	Norway/Twins (medical record services)	17 P Mz F; 6 I Mz M; 21 I Dz F; 17I Dz M	41 (9)	Items dealing with fear of specific situations and objects	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Stein *et al.*, 2001[17]	Canada/Patients recruited from outpatient services and the community. Relatives contacted	31 I SAD 24 I HC 65 relatives	Cases: 42.5 (16.8) Controls: 40.7 (15.6)	SCID (cases); Fear of Negative Evaluation Scale; Social Phobia Scale; Social Interactional Anxiety Scale (subjects) Scale, Social Interactional Anxiety Scale	Factorial analysis	Being a first-degree relative explains 84% of the variance	15 (68%)
Stein *et al.*, 2002[45]	Canada/Twins (community advertisement)	55 P Mz M; 154 P Mz F; 30 P Dz M; 115P Dz F; 35 P Dz O	MzM: 36.66 (16.86) MzF: 34.82 (14.1) DzM: 31.53 (13.37) DzF: 32.38 (13.13) DzO: 29.88 (12.82)	Brief Fear of Negative Evaluation	Correlations between Mz and Dz Structural Equation Models	Correlation between twins Heritability estimates	17 (77%)
Trzaskowski *et al.*, 2012[46]	UK/Twins (medical record services)	T0: 7834 I T1: 3644 I	T0: 7 T1: 9	Anxiety-Related Behaviors Questionnaire	Correlations between Mz and Dz Structural Equation Models Correlations between factors at ages 7 and 9	Phenotypical correlation of 0.54 (0.54-0.56) between ages 7 and 9 Correlation differences between MZ and DZ in the two ages	17 (77%)
Van Hulle *et al.*, 2012[47]	USA/Twins (medical record services)	175 P Mz; 150 P Dz; 160 P Dz O	7.7 (0.7)	Diagnostic Interview Schedule for Children	Correlations between Mz and Dz	Correlation differences	17 (77%)
Waszczuk *et al.*, 2014[20]	UK/Twins (medical record services)	T0: 100 P Mz; 82 P Dz; 117 P Dz O; T1: 83 P Mz; 69 P Dz; 98 P Dz O; T2 350 P Mz; 313 P Dz; 334 P Dz O; 330 P S; T3: 243 P Mz; 207 P Dz; 232 P Dz O; 182 S; T4: 230 P Mz; 214 P Dz; 232 P Dz O; 201 P S	T0: 8 years and 6 months T1: 10 years and 1 month T2: 15 years T3: 17 years T4: 20 years	SCARED for children; SCAS for adolescents; Revised Symptoms of Anxiety Scale for adults	Structural Equation Models	Heritability estimates	19 (86%)

P: Pairs; I: Single Individuals; Mz: monozygotic twins; Dz: dizygotic twins; S: siblings; M: Male; F: Female; O: Opposite Sex; SAD: Social Anxiety Disorder Case; GAD: Generalized Anxiety Disorder Case; PD: Panic Disorder Case; AD: Anxiety Disorder Case; MDD: Major Depression Disorder Case; APD: Avoidant Personality Disorder Case; HC: Health Control; OR: Odds ratio.

The analysis of correlational differences between monozygotic and dizygotic twins and heritability models that best explain the genetic and environmental contributions to SAD, in addition to estimates of each factor, are core elements for the assessment of heritability[19]. Therefore, we extracted the data from studies describing these variables, detailed in Table 2. Among these articles, the model that best fit the sample in most studies (66.7%) was the one that considers only additive genetic factors (A) and non-shared environmental factors (E). However, a significant share of the articles (28.6%) proposed that shared environmental factors (C) were an important component of the best explicative model. The study by Waszczuk *et al.*[20], that assessed pairs of twins as they aged, was the only one that suggested two models as most adequate because of the sample characteristics. Specifically, the authors considered the ACE model to be the most adequate for children, whereas the AE model was regarded as the most adequate for adults. There was great variability in the estimated heritability rates across studies, with heritability measured according to additive genetic factors ranging between 13% and 76%.

Table 2. Correlation between Monozygotic and Dizygotic twins, model that best fits the sample, additive genetic effects, shared environmental effects and non-shared environmental effects of each study included

Reference	RMz (CI)	RDz (CI)	Model	A (CI)	C (CI)	E (CI)
Czajkowski *et al.*, 2011[22]	0.56 (0.32-0.73)	0.14 (0.23-0.48)	AE	0.55	_	0.45
Eley *et al.*, 2003[23]	Males = 0.57 Females = 0.56	Males = 0.02 Females = 0.13	AE	Males 0.76 (0.71-0.79) Females 0.66 (0.59-0.71)	_	Males 0.24 (0.21-0.29) Females 0.34 (0.29-0.41)
Eley *et al.*, 2008[24]	0.27 (-0.04-0.54)	0.14 (–.07-0.35)	ACE	0.14 (0.00-0.45)	0.10 (0.00-0.30)	0.76 (0.52-0.93)
Hallett *et al.*, 2009[14]	Mz7 = 0.7 (0.68-0.72) Mz9 = 0.77 (0.75-0.79)	Dz7 = 0.31 (0.28-0.35) Dz9 = 0.48 (0.45-0.51)	ACE	7 years 0.61 (0.57-0.63) 9 years 0.56 (0.48-0.63)	7 Years 0.07 (0.05-0.1) 9 Years 0.2 (0.13-0.26)	7 years 0.32 (0.3-0.33) 9 years 0.25 (0.23-0.27)
Hallett *et al.*, 2012[25]	MzM = 0.7 (0.67-0.72) MzF = 0.69 (0.66-0.73)	DzM = 0.30 (0.29-0.33) DzF = 0.34 (0.32-0.36)	ACE	Males 0.6 (0.54-0.66) Females 0.59 (0.53-0.65)	Males 0.09 (0.04-0.14) Females 0.10 (0.03-0.17)	Males 0.31 (0.27-0.35) Females 0.31 (0.27-0.35)
Hettema *et al.*, 2005[10]	_	_	ACE	0.1	0.11	0.79
Hettema *et al.*, 2001[26]	_	_	ACE	0.13	0.09	0.78
Isomura *et al.*, 2015[29]	_	_	_	0.56	_	_
Kendler *et al.*, 2001[30]	_	_	AE	0.2 (0-0.41)	_	0.8 (0.59-1)
Kendler *et al.*, 2008[31]	MzF 13-14 = 0.51 MzF 16-17 = 0.52 MzF 19-20 = 0.44 MzM 13-14 = 0.45 MzM 16-17 = 0.41 MzM 19-20 = 0.17	DzF 13-14 = 0.17 DzF 16-17 = 0.14 DzF 19-20 = 0.08 DzM 13-14 = 0.31 DzM 16-17 = 0.14 DzM 19-20 = 0.49	AE	13-14 = 0.49 16-17 = 0.44 19-20 = 0.34	_	13-14 = 0.50 16-17 = 0.55 19-20 = 0.65
Lahey *et al.*, 2011[33]	_	_	AE	0.45	_	0.55
López-Solà *et al.*, 2014[34]	Mz Total = 0.46 (0.39-0.52); MzM = 0.38 (0.25-0.49); MzF = 0.49 (0.40-0.56)	Dz TOTAL 0.18 (0.09-0.27) DzM 0.07 (0.11-0.25) DzF 0.24 (0.11-0.36) DzO 0.16 (0.01-0.32	AE	Males 0.34 (0.23-0.45) Females 0.47 (0.39-0.55)	_	Males 0.66 (0.55-0.77) Females 0.53 (0.45-0.61)
Michelini *et al.*, 2015[37]	MzM = 0.43 (0.24-0.59) MzF = 0.34 (0.17-0.48)	DzM/SM = 0.37 (0.18-0.54); DzF/SF = 0.24 (0.09-0.38); DzO/SO = 0.09 (-0.04-0.21)	AE	0.35 (0.26-0.44)	_	0.65 (0.56-0.74)
Mosing *et al.*, 2009[39]	_	_	AE	0.39 (0.16-0.65)	_	_
Nelson *et al.*, 2000[40]	_	_	AE	0.28 (Common factor)	_	0.72 (Specific factor)
Ogliari *et al.*, 2006[41]	0.58 (8-11 years) 0.561 (12-17 years)	0.26 (8-11 years) 0.303 (8-11 years)	AE	0.56 (0.46-0.66)	_	0.44 (0.34-0.54)
Ogliari *et al.*, 2010[42]	0.57 (0.45-0.66)	0.31 (0.19-0.42)	AE	0.56 (0.46-0.65)	_	0.44 (0.35-0.54)
Reichborn-Kjennerud *et al.*, 2007[43]	0.57 (0.29-0.78)	0.06 (-0.41-0.50)	AE	0.39	_	0.61
Skre *et al.*, 2000[44]	0.53	-0.02	AE	0.47	_	0.53
Stein *et al.*, 2002[45]	MzM = 0.462 MzF = 0.503	DzM = 0.253 DzF = 0.124 DzO = 0.143	AE	0.42 (0.32-0.51)	_	0.58 (0.49-0.69)
Trzaskowski *et al.*, 2012[46]	7 years = 0.70 (0.68-0.72) 9 years = 0.77 (0.75-0.79)	7 years = 0.31 (0.28-0.35) 9 years = 0.48 (0.45-0.51)	ACE	7 to 9 years 0.66 (0.59-0.66)	7 to 9 years 0.55 (0.35-0.75)	7 to 9 years 0.42 (0.37-0.42)
Van Hulle *et al.*, 2012[47]	0.39	0.09	_	_	_	_

Reference	RMz (CI)	RDz (CI)	Model	A (CI)	C (CI)	E (CI)
Waszczuk *et al.*, 2014[20]	_	_	ACE (Children) AE (Adults)	8 years Common factor 0.12 (0-0.24) + Specific factor 0 (0-0.07) 10 years Common factor = 0.38 (0-0.53) + Specific factor = 0 (0-0.42) Adults All variables factor = 0.4 (0.3-0.49) Fear model factor = 0.07 (0.01-0.12)	8 years Common factor = 0.0 (0-0.08) + Specific factor = 0 (0-0.04) 10 years Common factor = 0.1 (0-0.27) + Specific factor = 0 (0-0.25)	8 years Common factor = 0.28 (0.17-0.46) + Specific factor = 0.59 (0.49-0.68) 10 years Common factor = 0.21 (0.09-0.40) + Specific factor = 0.40 (0.27-0.54) Adults Common factor = 0.26 (0.18-0.34) Specific factor = 0.27 (0.22-0.33)

MzM: monozygotic males; MzF: monozygotic females; DzM: dizygotic males; DzF: dizygotic females; DzO: dizygotic different sex; SM: sibling males; SF: sibling females; SO: siblings different sex; RMz: correlations between monozygotic twins; RDz: correlations between dizygotic twins; CI: confidence interval; A: additive genetic effects; C: shared environmental effects; E: non-shared environmental effects.

Discussion

The objective of this study was to systematically review articles assessing heritability to SAD, with no limits regarding publication date and including different methodological designs. A total of 31 articles were included in the review, most of which involved pairs of twins as their sample. The studies were conducted mainly in Europe and used mostly self-reporting instruments to assess SAD symptoms. SAD heritability was estimated through correlation differences between twins and based structural equation models. We found that additive genetic factors and non-shared environmental factors formed the most adequate model to explain SAD heritability, with genetic transmission rates estimated between 13% and 76%.

The vast majority of studies that recruited twins for their samples used birth and medical follow-up records, which allowed the enrollment of a large number of twins and provided a significant amount of information on the heritability of SAD. Conversely, only one study involving twins recruited participants by means of community advertisement. This study included fewer participants than the mean in twin studies, probably as a result of the difficulty of recruiting participants through this method.

Generally speaking, genetic studies for heritability estimates require large samples[48,49] in order to ensure the statistical power of their analyses. It is thus important to encourage the creation and maintenance of records about twins, especially in low- and middle-income countries. This fact becomes evident in the present review, as no articles from developing countries were included due to not using methodological designs compatible with the investigation of SAD heritability.

Clinical interviews are regarded as the gold standard for the diagnosis of SAD and are widely used both as validation parameters for instruments that assess SAD symptoms (*e.g.*: [50,51]) and as a criterion for the selection of participants in clinical trials (*e.g.*: [52,53]) and genetic investigations (*e.g.*: [21,28]). Nevertheless, in order to be effective as diagnostic instruments, clinical interviews must be performed within a short interval from enrollment in studies because of the longitudinal instability of psychiatric diagnoses. Some of the articles reviewed here (*e.g.*: [29]) mentioned the limitation of using previous medical records without later diagnostic confirmation, which affects the reliability of the data presented.

An important feature of clinical interviews is that their outcome is a dichotomous variable, that is, a positive or negative diagnosis. On the other hand, a number of initiatives have been made for the adoption of dimensional criteria in the assessment of mental disorders ([54,55]), aiming at greater adequacy of the diagnostic process. These measures tend to bring the clinical setting closer to basic research, providing a more global comprehension of psychopathology, especially in the case of SAD, since social inhibition is an innate aspect of humans and thus of little accuracy for the establishment of psychiatric diagnosis. Particularly in genetic research, such initiatives may allow a closer association between the factors that influence a disorder and the symptoms of this disorder[56]. In this direction, the use of instruments that assess symptoms within a disorder continuum and that offer dimensional criteria for disorder assessment is of great importance[57].

Most of the studies included in this review used this type of instrument, enabling the assessment of different possibilities of symptom manifestations. However, in order to provide reliable data, the instruments must present minimally adequate psychometric qualities and be compatible with the research interests. An important issue in some of the articles reviewed here was the use of instruments that were not subject to validation studies (*e.g.*: [31]) or versions derived from other instruments without the conduction of new psychometric evaluations[14].

The concept of heritability is broad and generally refers to the proportion of the variance that can be explained by genetic factors[58]. As a result of the broadness of the concept, different methods can be employed to observe its occurrence in a given condition. The diversity in the methods used by the studies reviewed may have been a consequence of this variability. A high amount of variance explained by the fact of being related to a patient diagnosed with SAD in factorial analyses, the increased risk of being diagnosed with the disorder when a relative has received the same diagnosis (and the decrease in risk as genetic distance increases), and differences in the incidence of SAD between relatives with anxiety disorders suggest that heritability is an important variable in SAD[17,18,29]. Nonetheless, although evidence points to the participation of genetic factors in SAD, it is not yet possible to determine the degree to which these conditions contribute for the effective determination of SAD diagnosis.

According to this issue, the enrollment of pairs of twins in the studies fosters relevant progress in the study of SAD heritability. Some of the studies included in this review, for instance, estimated heritability based on correlational differences between monozygotic and dizygotic twins. This method provides a clearer assessment of the contribution of genetic factors, to the extent that it allows a certain control over common external environmental variables. However, even with this outcome, it is not yet possible to determine the precise influence of genetics in the manifestation of SAD.

The use of structural equation models associated with the inclusion of samples of twins is, therefore, an advance in this direction. With this design, it is possible to develop models that explain better how genetic and environmental factors interact within a given sample to cause SAD, including also estimates of how much of the variance can be explained by each factor. However, although

the articles reviewed did use these methods, we still observed a large amplitude in the variance explained by genetic factors in this review, which hinders precise estimates of these factors. Likewise, the diversity of results does not allow for a common interpretation of gender-related differences, nor of aspects such as the variability between age ranges regarding the establishment of diagnoses. We thus suggest the performance of studies involving carefully selected samples and instruments with adequate psychometric qualities.

One limitation of our review is the exclusion of studies that may have described results related to the heritability of SAD as secondary outcomes. Another possible limitation is the large variability in the instruments, methods, and outcomes in the studies reviewed, which hinders the homogenization in the presentation of results. This same limitation, however, ends up as an important part of this study as it describes the several ways that can used to assess heritability in SAD. Likewise, the conclusions of this review might contribute for the development of further research in this specific field.

In general terms, we conclude that heritability has been investigated in SAD through different methodological approaches, providing important evidence for a better comprehension of the factors that participate in the development of the condition. Future studies involving homogeneous samples and standardized instruments that allow a better diagnostic assessment of SAD would contribute for the estimation of more accurate heritability rates and for a better comprehension of the genetic factors associated with SAD.

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Quality of life in euthymic bipolar I patients: a prospective study

Sidnei Barbosa Lira[1], Mônica Andrade-Nascimento[2], Mychelle Morais-de-Jesus[1], Lucas C. Quarantini[1], Fabiana Nery Fernandes[1], Diogo Esmeraldo Cavalcanti[3], Amanda Galvão-de-Almeida[1], Gisela Guedes[1], Ângela Miranda-Scippa[1]

[1] *Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil.*
[2] *Universidade Estadual de Feira de Santana (UEFS), Feira de Santana, BA, Brazil.*
[3] *Universidade do Estado da Bahia (UNEB), Salvador, BA, Brazil.*

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Dear Editor,

According to the World Health Organization (WHO), Bipolar Disorder (BD) type I has a prevalence of between 1.0% and 1.6% in the general population and is one of the twenty major causes on the worldwide list of diseases that compromise an individual's total functioning[1-3]. Most of the quality of life (QOL) studies on BD emphasize the negative impact in the different QOL domains at all disease stages, but mainly the depressive episodes. Few studies have investigated QOL of bipolar patients during euthymia.

Thus, the present study aims to compare QOL scores in BD type I euthymic patients at two different times, with an interval of 2.5 years (only 38 from 84 could be compared due to absence of euthymia, refusal to participate, unknown location and death).

The Hamilton Rating Scale for Depression (HAM-D-17 ≤ 7)[4] as well as from the Young Mania Rating Scale (YMRS ≤ 7)[5] were used to evaluate if patients were euthymic. They answered a questionnaire to gather clinical and socio-demographic data. Afterwards, they were evaluated through the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, axis I (SCID-I)[6]. Once confirmed the BD type I diagnosis and the state of euthymia, the patient answered the World Health Organization Quality of Life-BRIEF (WHOQOL-BRIEF) instrument[7].

Observations regarding the analyzed patients are as follows: female (78.9%); average age 39.39 years (standard deviation, SD = 11.24); with no permanent partner (84.2%); with paid occupation (60.5%); having predominantly manic/hypomanic first episode (57.9%); no rapid cycling (97.4%); without suicide attempt (73.7%); without psychiatric comorbidities (78.4%); average age at first episode 24.5 years (SD = 11.31), without presence of psychosis during life (55.3%); and time of disease evolution of 14.91 years (SD = 9.9). In relation to the socio-demographic and clinical characteristics of the 38 subjects analyzed at both times, there were also no significant long-lasting differences ($p > 0.05$).

The physical, social and psychological health domains presented reductions, but these reductions were only significant in the psychological health domain ($p = 0.02$) (Table 1).

The psychological health domain refers to individuals' subjective experience regarding their state of psychic well-being related to their personal experience. Therefore, one assumes that BD, by inflicting intense psychic suffering, may cause unfavorable self-analysis in these subjects, regardless of the presence of mood symptoms, resulting in the low scores found in this work. On the other hand, our results confirm the idea that bipolar patients, even when they achieve full clinical remission, show difficulties in returning to their previous level of functioning[8-10]. These findings point to the need of greater care to these individuals, even when euthymic, since unfavorable self-analysis can contribute to more social isolation behaviors, more hopelessness and greater chances of new episodes of the disease.

The main limitation of this study was the small sample size. Additionally, other limitations should be highlighted: first, the retrospective data gathered, which increased the chance of memory bias; second, the selected sample of patients from a specific medical service prevented us from generalizing the results.

Table 1. Quality of life in two different moments (n = 38)

WHOQOL domains	Baseline	Follow-up	Test Z*; *p* value
Physical Health Md (Min-Max)	64.28 (35.71-89.29)	60.71 (32.14-78.57)	- 1.69**; 0.091
Psychological Health Md (Min-Max)	66.67 (33.33-100)	60.42 (29.17-79.17)	- 2.29**; 0.022
Social Relations Md (Min-Max)	66.67 (16.67-100)	58.33 (25-100)	- 0.045**; 0.964
Environment Md (Min-Max)	51.56 (31.25-90.63)	59.37 (18.75-87.50)	- .788***; 0.431

Md: median; Min: minimum; Max: maximum.* Wilcoxon Test. ** Based on positive ranks. *** Based on negative ranks.

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Address for correspondence: Diogo Esmeraldo Cavalcanti. Universidade do Estado da Bahia – Departamento de Educação. Rua Silveira Martins, 2555, Cabula – 41150-000 – Salvador Bahia, Brazil. Phone: +55 (71) 9246-3838. E-mail: desmeraldo.cavalcanti@gmail.com

Letter to the editor

Study 329 and the use of paroxetine in child and adolescent unipolar depression

Juan Carlos Martínez-Aguayo[1], Marcelo Arancibia[2], Sebastián Concha[3], Eva Madrid[4]

[1] Department of Pediatrics, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.
[2] Department of Psychiatry, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.
[3] School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.
[4] Department of Public Health, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile. Biomedical Research Centre, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.

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Dear Editor,

We have recently published the article "Ten years after the FDA black box warning for antidepressant drugs: a critical narrative review" regarding the warning issued in 2003 by the United States Food and Drug Administration (FDA) about the use of serotonin reuptake inhibitors and venlafaxine for the treatment of child and adolescent depression, and its association to an increased suicidality risk[1]. However, considering the new evidence emerged on the topic, we would like to update our article using new available information regarding paroxetine use, a serotonin reuptake inhibitor involved in FDA's warning as well.

In 2001, Keller *et al.* published the study "Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial"[2] (Study 329), sponsored and conducted by SmithKline Beecham (which later became Glaxo SmithKline), concluding that paroxetine is generally well tolerated and effective for unipolar major depression in adolescents when compared with placebo. The "ghostwritten" published results of Study 329 were used for a marketing campaign characterizing paroxetine as remarkably effective and safe. After the campaign, over 2 million off-label prescriptions were written. In 2012, Glaxo SmithKline was fined a record $3 billion for dishonest encouragement of paroxetine use[3]. Additionally, the manuscript was made by a medical writer hired by the laboratory, and all the 22 authors in the manuscript denied having participated in writing the draft[3].

Recently, the British Medical Journal has published the reanalysis of Study 329, carried out by independent researchers[4], using Clinical Data Records, in the context of the RIAT initiative "Restoring Invisible and Abandoned Trials," and in order to check whether access to and reanalysis of a full dataset from a randomized controlled trial would have clinically relevant implications for evidence based medicine. The authors demonstrated that the antidepressant is neither safe nor effective in adolescent depression. Indeed, the effect of paroxetine was not significantly different from placebo for primary or secondary outcome measure. There were significant increases in harms, suicidal ideation and behavior in paroxetine group, while imipramine group displayed cardiovascular problems. The authors highlighted the need of making primary trial data and protocols available to increase the thoroughness of the evidence. In our study, Study 329 was not included, and neither was its reanalysis[1].

We consider of utmost relevance to take this case into account, especially when considering that the outcome of a clinical intervention is directly related to suicide spectrum. Although in our article we showed some criticism about the ambiguity of the FDA warning, we do not support, in whatever way, these type of practices, which discredit the medical community and science in general.

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Address for correspondence: Eva Madrid. Department of Public Health, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile. Angamos 655, Viña del Mar – Chile. Phone: +56 (32) 260-3099. E-mail: eva.madrid@uv.cl