ARCHIVES OF
Clinical Psychiatry
Revista de Psiquiatria Clínica

ISSN 0101-6083
Online version: www.hcnet.usp.br/ipq/revista
iPad edition: APPSTORE/categoria MEDICINA/Psiquiatria Clinica

VOLUME 45 • NUMBER 2 • 2018

Information 45 YEARS in Psychiatry

Editors

Editorial Board

INSTRUCTIONS FOR AUTHORS
Available on the journal's website (www.archivespsy.com) and published in the last issue every year (number 6).

We would like to thank the artist Laila Gattaz, who gently allowed, for exclusive use on the covers of the Archives of Clinical Psychiatry, the series of art works named "Imagens de São Paulo".

This journal is printed on acid-free paper.

CATALOGUING IN PUBLICATION (CIP) DATA

Archives of Clinical Psychiatry / University of São Paulo Medical School. Institute of Psychiatry - vol. 45, n. 2 (2018). – São Paulo: / IPq-USP, 2011-

From volume 29 (2001), the articles of this journal are available in electronic form in the SciELO (Scientific Electronic Library Online) database.

1.1. Clinical Psychiatry. University of São Paulo Medical School. Institute of Psychiatry.

ISSN : 0101-6083 printed version

ISSN : 1806-938X online version

CDD 616.89

Indexing Sources

- ISI (Institute for Scientific Information)
  - Science Citation Index Expanded (SciSearch®)
  - Journal Citation Reports/Science Edition
- EMBASE - Excerpta Medica Database
- LILACS - Literatura Latino-Americana e do Caribe de Informação em Ciências da Saúde
- PERIODICA - Índice de Revistas Latino-Americanas em Ciências
- SciELO - Scientific Eletronic Library Online
- SIIC - Sociedad Iberamericana de Información Científica
- Scopus (www.scopus.com)
- Gale Cengage Learning
- DOAJ - Directory of Open Access Journals
- HINARI - World Health Organization

Segmento Farma editores

Rua Anseriz, 27, Campo Belo – 04618-050 – São Paulo, SP. Fone: 11 3093-3300 • www.segmentofarma.com.br • segmentofarma@segmentofarma.com.br

Cód. da publicação: 22888.4.18

Todos os anúncios devem respeitar rigorosamente o disposto na RDC nº96/08

Financial Support

CEIP Centro de Estudos do Instituto de Psiquiatria

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

INDEX

VOLUME 45 • NUMBER 2 • 2018

Original articles

Review articles

Letters to the editor

Psychometric properties of a Brazilian Portuguese version of the Children's Revised Impact of Event Scale (CRIES-8)

Sabrina de Sousa Magalhães[1], Diana Kraiser Miranda[1], Jonas Jardim de Paula[1,2], Débora Marques de Miranda[1,3], Marco Aurélio Romano-Silva[1,4], Leandro Fernandes Malloy-Diniz[1,4]

[1] *Laboratory of Molecular Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.*
[2] *Department of Psychology, Faculty of Medical Sciences of Minas Gerais, Belo Horizonte, MG, Brazil.*
[3] *Department of Pediatrics, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.*
[4] *Department of Mental Health, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.*

Institution where the study was conducted: Faculty of Medicine, Federal University of Minas Gerais (UFMG). Av. Prof. Alfredo Balena, 190, sala 114, Centro – 30130-100 – Belo Horizonte, MG, Brazil.

Received: 08/18/17 – **Accepted:** 04/13/18
DOI: 10.1590/0101-60830000000151

Magalhães SS et al. / Arch Clin Psychiatry. 2018;45(2):27-32

Abstract

Background: Children and adolescents are considered a population at risk for developing posttraumatic stress disorder (PTSD) after a traumatic event. The Children's Revised Impact Scale (CRIES-8) is a self-report scale with 8 items that investigates avoidance and intrusion behaviors related to posttraumatic stress symptoms. **Objective:** The study consisted of translation and transcultural adaptation of CRIES-8 to Brazilian Portuguese and evaluation of its psychometric properties. **Methods:** A sample of 235 Brazilian children and adolescents exposed to natural hazards (drought or flood) and non-exposed children participated in the study. The methodological procedure for translation and cultural adaptation were in accordance with the principles described by ISPOR Task Force for Translation and Cultural Adaptation. We also evaluated test reliability and validity based on test content, the relations to other variables, and internal structure. **Results:** The procedures lead to a final Portuguese version proofread and cultural-adapted. Empirical evidence supports CRIES-8's division in two latent constructs (Intrusion and Avoidance), as well convergence correlations with other measures of child mental health and high reliability. **Discussion:** A Brazilian-Portuguese version of CRIES-8 is an important tool for a better screening of PTSD among youth who face traumatic events, being a potential informative instrument to identify children at risk.

Keywords: Post-traumatic stress disorders, child, psychological trauma, natural disasters, CRIES-8.

Introduction

From natural to human-made/technological events, disasters are potentially traumatic events. Virtually all people affected by a traumatic event exhibit posttraumatic stress (PTS) symptoms in some level, even though the full diagnostic criteria for posttraumatic stress disorder (PTSD) may not be fully reached[1]. The acute traumatic stress is the more common response after a disaster and it is associated with symptoms that show a tendency to disappear after safety conditions are restored[2-5].

Children and adolescents are usually more affected than adults after a traumatic event. Along with other vulnerable population, they are at a higher risk of developing PTSD after a stressful event, especially the youngest ones[6]. Circumstances of life-threatening, a probability of being apart from family, less efficient coping strategies, and disturbances in social support all account for the anxiety-like response after disasters[6,7].

PTSD can be defined as an anxiety disorder triggered by severe traumatic life stress. It was not until 1987 that childhood PTSD has been recognized as different from adult trauma. Rather than responding to a traumatic situation with helplessness or fear, children may exhibit an agitated or disorganized behavior, as well as physical symptoms, such as headaches. Therefore, when assessing children's PTSD it is crucial to be prepared to deal with their peculiarities related to the developmental level[8].

For children older than 6 years, the DSM-5 diagnostic criteria for PTSD are: the need of exposure to an actual or threatened death, serious injury, or sexual violence through directly experiencing the traumatic event, witnessing it, having awareness that it happened to a family member or friend or by re-experiencing the traumatic event. PTSD symptoms can be divided into four main clusters. The first one comprises reliving the traumatic event through intrusive memories and nightmares or physiological and psychological suffering when the trauma is recollected. The second cluster is related to persistent avoidance behavior and include the following symptoms: attempts to avoid feelings and thoughts associated with the event, and to avoid external reminders (people or activities) that are related to re-experiencing the trauma. The third cluster consists of negative alteration in cognitions and mood following the traumatic event. The last cluster is related to arousal symptoms and is marked by irritability, aggressive behavior, hypervigilance, sleep disturbances and difficulty to concentrate. The symptoms should persist for at least one month after the traumatic event and result in impairment to one's functioning[8,9].

Screening tools are regarded as important instruments to evaluate effects following a distress, being considered reliable and cost-effective. Horowitz *et al.*[10] first developed the Impact of Event Scale (IES) to assess the effect of traumatic events experienced. This original version counted with 15 items, and two clusters of symptoms Intrusion and Avoidance, but it is applied solely in adults. The next step was to produce a shortened version of the scale to be used among children and adolescents. For this purpose, seven items were excluded, and the remaining eight were adapted to a younger population[11]. The new version, Children's Revised Impact of Event Scale (CRIES-8), consists of 4 items measuring Intrusion and 4 items measuring Avoidance, becoming one of the most widely used screening tools for evaluating PTSD among children and adolescents[5]. Studies investigating the reliability and consistency of the scale have shown that PTSD is not culture bound and its factor structure has been proven to be stable across gender, age and different types of trauma[12-14].

Address for correspondence: Sabrina de Sousa Magalhães. Av. Prof. Alfredo Balena, 190, sala 114, Centro – 30130-100 – Belo Horizonte, MG, Brazil. Telephone: + 55 (31) 3409-9650.
E-mail: magalhaesabrina@gmail.com

The main aim of this study is to describe the process of translation and cultural adaptation of CRIES-8 to a Portuguese version. Secondly, we aim to investigate the psychometric properties of the Brazilian version of CRIES-8, which includes validity and reliability, in a sample of children affected by flood or drought. Among the numerous events that could result in trauma, we selected a sample from those exposed to natural disaster. At present, the world is facing a substantial growth of these extreme events due to environmental changes related to global warming[15]. In Brazil, flood and drought are the most common natural adversities and the main cause of human damage and a similar pattern is also observed worldwide[16,17].

Methods

Participants

Different samples were used according to the specific methods of the study. For the psychometric properties analysis, the sample consists of Brazilian children exposed to an adverse climate condition, especially drought or flood (n = 146), and a control group not exposed to the specific climate stressor considered. Children from the drought subgroup lived at Rio Pardo de Minas or Francisco Sá, both cities at the semi-arid zone of Minas Gerais state, Brazil. For the flood subgroup, children from Rio Branco, state of Acre, were recruited. This city is located in the north of Brazil and in 2015 it faced the worst flood incident of its history. The survey in Rio Branco was conducted up to 40 days after the peak of the disaster. The mean age for the exposed group was 11.17 (±3.30) and 77 were female. For the non-exposed group, students from two public schools at Belo Horizonte, capital state of Minas Gerais, were recruited (n = 89). The mean age was 11.06 (±2,74) and 56 were female.

Assessment

CRIES

CRIES-8 is a screening tool for PTS symptoms in children, aged 8 and above and which reading abilities are sufficiently developed to understand and interpret the items. The scale is self-administrated and consists of 8 items, 4 measuring Intrusion (items 1, 3, 6, and 7) and 4 measuring Avoidance (items 2, 4, 5, 8). The items are scored on a four-point scale: "not at all" receives 0 scores, "rarely" sums 1 point, "sometimes" adds 3 points, and "often" computes 5 points. The Intrusion and Avoidance subscales are obtained counting the respective point for the appropriate subscale item. CRIES has more than 25 translations in different languages. All of it is available free of charge on the website of Children and War Foundation (http://www.childrenandwar.org).

CBCL

The Child Behavior Checklist (CBCL) consists of a questionnaire, answered by a caregiver, to identify behavior problem in school-aged children from 6 to 18 years old[18]. In this study, we used the Internalizing Problems category, which is composed by the sum of the anxious/depressed, withdrawn-depressed, somatic complaints, social problems, thought problems, and attention problems raw scores; the Externalizing Problems category that resides on rule-breaking behavior and aggressive behavior raw scores; and the Total Problems raw score. Higher scores indicate greater problems.

Study design

The translation and cultural adaptation of CRIES-8 are part of a broader project to study the impact of extreme natural events on children mental health conducted by our research group, which was approved by the local Ethics Committee. The procedure of transcultural adaptation was conducted following the practices described by Wild *et al.*[19] which comprises ten steps described in Figure 1.

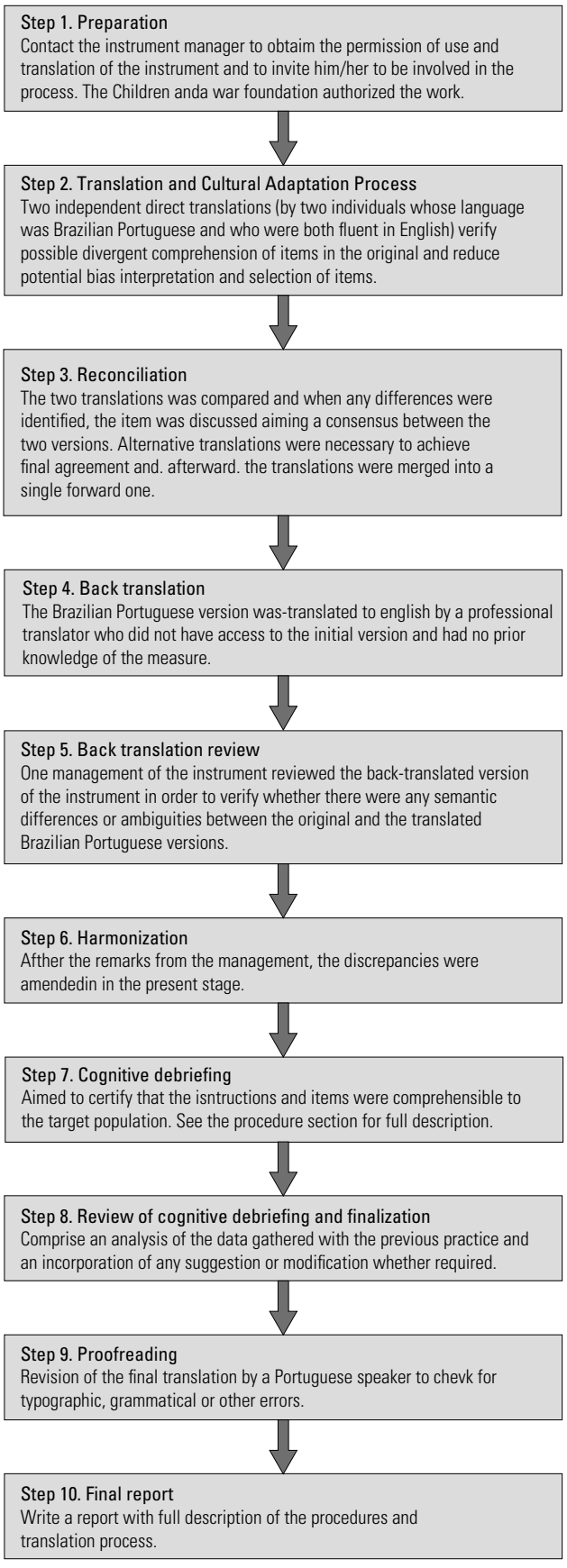

Figure 1. Flow chart with methodological steps to Translation and Cultural Adaptation process, according to ISPOR Translation and Cultural Adaptation Task Force[19].

The seventh step for Translation and Cultural Adaptation process, namely the Cognitive Debriefing, was performed by five young boys from Rio Pardo de Minas, and by four young children from Sabará, a city at the center of Minas Gerais state that faced flood consequences. Their age ranged from 6 to 13 years old (mean age 8,67 ± 2,45 years) and they were all primary students of public schools. A five-point verbal numerical scale[20] was used to assess the comprehensibility of the CRIES. The guide question was: "Do you understand what has been asked?". The participant should choose between the minimum value 0 ("I don't understand anything") to the maximum value 5 ("I understand perfectly, and I do not have any doubts about it"). The correspondent meaning of the extreme values was displaced above the numbers. The question must reach at least three points to be considered with satisfactory comprehension. For all the items, the participants had the option to suggest any modifications to improve understanding.

After transcultural adaption procedures, we investigated CRIES-8 psychometric properties. We evaluated the reliability by computing internal consistency using Cronbach's alpha and Split-Half methods. Validity was investigates focusing on test content (assessment by different judges during transcultural adaptation), its association with other variables (correlations with CBCL scores and comparison of youths exposed and non-exposed to natural disasters) and by assessment of internal structure (exploratory and confirmatory factor analysis). The latter procedure involved a principal component analysis with oblique rotation and confirmatory factor analysis using a diagonally weighted least squares method, commonly adopted to analyze ordinal data. Fit indexes commonly adopted in psychometric studies were computed, including Comparative Fit Index (CFI); Tucker-Lewis Index (TLI); Root Mean Square Error of Approximation (RMSEA).

Results

The process of transcultural adaptation of CRIES-8 began with an initial translation which was back-translated to the original language, English (see Table 1), then members of the Children and War Foundation reviewed it. Any discrepancies, semantic differences or conceptual nonequivalence were investigated and highlighted. Five items received a critical observation (question 2, 3, 4, 6, and 7) because they did not adequately correspond to the concept depicted in the original version. Subtle lexical and grammar differences were identified between the meaning of original terms in English and the supposed equivalent words chosen in Portuguese. For question 2, was identified a different meaning between *remove* and *think in erasing*, one being more permanent than the other. Due to the failed first attempt to proper translate the expression *waves of strong feelings* depicted in question 3, the reviewers emphasized the importance of stressing that the moment when an emotion affects someone is in a suddenly and profoundly manner. Lastly, the question 7 received a syntactic critic because of its construction. If the auxiliary *do* was used, the intention was to only ask whether the action occurs; on the other hand, the verb *to be* implied an interest in what other things trigger memories of the traumatic event. Another harmonization process was conducted to overcome these discrepancies and to ensure the equivalence between the versions.

Only one item remained the same, despite the back-translation review. The original item, question 6, "Do pictures about it pop into your mind?" was back-translated to "Do images from the event suddenly pop up in your head?". The replacement of mind to head was a matter of cultural adaptation. In Brazil, we often assign to head instead of mind to refer to daily cognitive activity.

For cognitive debriefing process, nine children classified the instructions and all the eight items of CRIES, accordingly to their understanding. They did not present any suggestions to improve the comprehension of the items. Only for the first question, a participant claimed not to understand it at all, probably due to his initial difficulty to understand what had been proposed with the task, as his original tendency was to answer the CRIES questions themselves. The question 2 also received a critical minimum rate. Further investigations at the moment of the evaluation revealed that some children recognize two different meaning for a keyword of the question. In Portuguese, the word *lembrança* is equivalent to memory, as well it can mean a gift someone gives to another. Nonetheless, because the meaning of retaining and recalling something was also recognized we decided to keep the word. Thus, the scale obtained suitable rates and therefore gathered its first evidence of validity.

The final proofreading checked for grammatical errors, the plausibility of comprehension by children population due to the concrete thinking they exhibit, and for theoretical consistency, to ensure the validity of test content. Table 1 presents the original CRIES version, the back-translated Portuguese version and the final Portuguese version.

For investigation of other psychometric properties of CRIES and the internal structure of the Portuguese CRIES-8 version, we

Table 1. Versions of CRIES accordingly to the translations and adaptation process

Original CRIES version	Back-translated Brazilian Portuguese version	Final Brazilian Portuguese version
Below is a list of comments made by people after stressful life events. Please tick each item showing how frequently these comments were true for you during the past seven days. If they did not occur during that time please tick the "not at all" box.	Below there is a list of comments made by people after stressful events. Please, mark the item that corresponds to the frequency these comments were true for you during the last seven days. If they did not happen during this time choose the option "not at all".	Abaixo se encontra uma lista de comentários feitos por pessoas após eventos estressantes. Por favor, marque o item que apresenta com qual frequência esses comentários foram verdadeiros para você durante os últimos sete dias. Se eles não aconteceram durante esse período, marque a opção "Nenhum pouco".
1. Do you think about it even when you don't mean to?	1. Do you think about it even when you do not want to?	1. Você pensa nisso mesmo quando não quer?
2. Do you try to remove it from your memory?	2. Do you think in erasing it out of your memory?	2. Você tenta afastar isso da sua lembrança?
3. Do you have waves of strong feelings about it?	3. Do you have moments with strong feelings about what has happened?	3. Você tem momentos em que sentimentos fortes sobre o que aconteceu invadem seus pensamentos?
4. Do you stay away from reminders of it (e.g. places or situations)?	4. Do you stay away from stuff, places or situations that make you remember what has happened?	4. Você fica longe de lugares ou situações que lhe fazem lembrar o que aconteceu?
5. Do you try not talk about it?	5. Do you try not to talk about it?	5. Você tenta não falar sobre isso?
6. Do pictures about it pop into your mind?	6. Do images from the event suddenly pop up in your head?	6. Imagens do acontecimento surgem de repente na sua cabeça?
7. Do other things keep making you think about it?	7. Are there other things that make you keep on thinking about what has happened?	7. Outras coisas fazem você ficar pensando sobre o que aconteceu?
8. Do you try not to think about it?	8. Do you try not to think about it?	8. Você tenta não pensar sobre isso?
Not at all	Not at all	Nenhum pouco
Rarely	Rarely	Raramente
Sometimes	Sometimes	De vez em quando
Often	A lot	Muitas vezes

evaluated a sample of 146 children affected by flood or drought and 89 children for control group. All indices of CRIES significant correlated with each other (data not show). Reliability analysis accessed through Cronbach's alpha and Split Half methods achieved an index of 0.79 and 0.83, respectively, for total sample (N = 235). The scales achieve a Cronbach's alpha at 0.79 for Intrusion and 0.77 for Avoidance subscales, for total sample. Table 2 exhibits reliability analysis for the subgroups according to different methods.

A principal component analysis, with *promax* rotation, exhibited a solution with 2 factors and it explained 55.37% of the variance (Table 3). The Bartlett's Test of Sphericity was significant ($p < 0.001$) and the KMO was 0.82, which indicate the adequacy of the sample. A confirmatory factor analysis tested the original two-factor solution (Intrusion and Avoidance). The final model sustained the original two-factor solution, with adequate fit-indexes (χ^2 = 39.98, df = 10, χ^2/df = 2.05, CFI = 0.98, TLI = 0.98, RMSEA = 0.067).

Another question addressed was whether CRIES-8 could be related to a screening tool for children behavioral problems (validity based on association with other measures). We recruited another sample of 91 healthy children, non-exposed to any specific stressful event, as a comparison group. There were no significant differences between the groups concerning age, years of formal schooling and sex (p = 0.85, p = 0.79, and p = 0.18, respectively). All CRIES scores indicated that those who experienced an adverse condition reported more symptoms of intrusion and avoidance related to the event, compared to those non-exposed to stressful condition. However, if we considered the cut-off score of 17 reported by Perrin *et al.*[21] to positive screening for PTSD, both groups did not reach this threshold. The Cohen's *d* effects sizes were moderate. There were no significant differences between groups in any kind of behavior problems described by the parent and both groups did not show any significant clinical problem in average accessed by the CBCL (Table 4).

To further evaluate its validity by its association with other measures we correlated CRIES total score with CBCL. We found significant correlations with CBCL internalizing problems (r = 0,16, p = 0,05) and CBCL total problems score (r = 0,16, p = 0,05). The avoidance index of CRIES is associated with the CBCL total problems (r = 0,18, p = 0,05) and the intrusion index is not correlated with any CBCL measures.

Discussion

Our study resulted in a transcultural adaptation of CRIES-8 for Brazilian-Portuguese. This version succeeds in reaching meticulous methodological steps to establish language adequacy, cultural adjustment, and language standards. Besides the translation procedures, we found evidences of validity and reliability for the adapted version, including moderate to high internal consistency, a two-components latent structure, significant score differences by children exposed and non-exposed to natural disasters and weak but significant correlations with other measures of behavioral problems.

After a trauma, most children do not develop PTSD[22]. Nevertheless, subclinical levels of PTS symptoms can significant impair social and educational functioning, and could impact psychological and developmental process. Age and the stage of development can lead to a greater recognition and memories of the event, jeopardizing mental health[21]. CRIES-8 is highly regarded as an important tool for screening children at risk for PTSD. The instrument is widely used in a variety of cultures, since posttraumatic stress symptoms in children have more similarities than differences from one place to the other[21]. As these versions enhance the worldwide comparability of research of the effects of disasters on children, it will be important and useful to introduce CRIES-8 in Brazil. In fact, it promptly covers a lack of valid and adapted instruments for these purposes in Brazil. To our knowledge, this is the first free PTSD screening tool adapted for Brazilian children and adolescents.

Reliability indices were moderate; however, the two distinct methods provide convergent results. Moderate values are expected in

Table 2. Reliability analysis for children exposed and non-exposed to an adverse condition related to natural hazard, according to different methods (N = 235)

	Exposed (n = 146)			Non-exposed (n = 89)		
	CRIES	Intrusion subscale	Avoidance subscale	CRIES	Intrusion subscale	Avoidance subscale
Cronbach's alpha	0.80	0.73	0.73	0.89	0.86	0.80
Split Half	0.84	0.77	0.70	0.89	0.85	0.81

Table 3. Principal components analysis of Portuguese CRIES-8 version, with *promax* rotation

	Loading	
	Factor 1 Intrusion	Factor 2 Avoidance
6. Do pictures about it pop into your mind?	**0.76**	
7. Do other things keep making you think about it?	**0.73**	
1. Do you think about it even when you don't mean to?	**0.73**	
3. Do you have waves of strong feelings about it?	**0.70**	0.40
4. Do you stay away from reminders of it (e.g. places or situations)?	**0.52**	0.50
8. Do you try not to think about it?	0.41	**0.84**
5. Do you try not talk about it?		**0.83**
2. Do you try to remove it from your memory?		**0.72**

Table 4. Comparison between CRIES and CBCL indices for children exposed to adverse weather event (drought or flood) and non-exposed children

	Exposed[1]		Non-exposed[2]		Statistics	
	Mean	*SD*	*Mean*	*SD*	*F*	*d*
CRIES total score	15.90	10.25	9.26	10.65	22.74*	**0.63**
CRIES intrusion	7.44	5.73	4.09	5.70	18.95*	**0.59**
CRIES avoidance	8.49	6.06	5.17	5.86	17.09*	**0.56**
CBCL Total Problems	37.19	20.17	33.06	20.17	1.75	0.20
CBCL Internalizing Problems	12.55	7.76	11.58	8.02	0.63	0.12
CBCL Externalizing Problems	9.09	6.82	8.30	6.08	0.61	0.12

[1] n = 146 for CRIES scores, and n = 111 for CBCL scores; [2] n = 89 for CRIES scores; n = 67 for CBCL scores; * p < 0.001.

screening tests or scales, since the low number of items may influence the internal reliability. In this sense, lower internal consistency values are usually accepted for those measures[23]. The values obtained were coherent with international literature. Studies with distinguished disaster events usually report a Cronbach's alpha varying between 0.70 to 0.86 for the total score of CRIES-8[2,11,13,24]. For the intrusion items, the Cronbach's alpha was reported at 0.60 to 0.88[2,11,13,14,24,25]. Finally, for the avoidance subscale, Cronbach's alpha was 0.58 to 0.85[2,11,13,14,24,25].

In exploratory principal component analysis, the underlying latent structure was similar to other versions of CRIES-8[13,14,21,25], with exception for the Question 4 that was supposed to count for Factor 2, Avoidance, although in our study it loads slightly more on Factor 1, Intrusion. Due to specificities of the trauma studied, children from both conditions (drought or flood) not always have the actual power to avoid places or situations that remind them of the disaster. The analysis of another sample exposed to a different traumatic event will help to elucidate this finding. However, a confirmatory factor analysis still corroborated the original items structure. Three of the four fit indexes showed optimal parameters ($\chi^2/gl < 3$, CFI > 0.95, TLI > 0.95) and one showed marginal results (RMSEA<0.06). Our results corroborate the internal structure validity of CRIES-8.

We verified a significant difference in CRIES scores between the exposed and non-exposed group, with moderate effect sizes. Although no differences were found on CBCL between groups, CRIES-8 better discriminated between groups of exposed and non-exposed. Thus, it was sensible to disclose distress symptoms that children probably were experiencing in consequence to the disaster.

PTSD is mainly an internal phenomena since it is characterized by a phenomenology of recollections, therefore not always clearly evident to others. This highlights the importance of self-report, especially child self-report data. We found a significant difference, with moderate size effects, between CRIES and CBCL scores. The apparent divergence between CRIES scores and the CBCL scores may be under the assumption that parents in a context of adversities may not be able in providing a suitable care for their kids, and their report could not be the most reliable concerning the experience of their children after an adverse experience. Furthermore, children and adolescents could exhibit a tendency to hide stress feelings and thoughts from their parents in order to preserve them from another source of distress. Therefore, the study suggests that child self-reports are the preferred source of information in the evaluation of youth PTSD.

In general, the significant correlations between CRIES and CBCL were few and modest. One hypothesis to explain the data may due to differences in self-reports and parental reports, as previously discussed. A second one could be due to the time period that the investigation occurs. Accordingly to DSM-5, PTSD symptoms usually appear within the first 3 months after the event[9]. For flood affected children, the acme of the rainy period occurred about one month previously to the data collection. On the other hand, CBCL requires parents to report the pattern of child behavior during the last 6 months. So the time lapse was before the peak of the disaster for the flood group and it could also include a different season with no rain/flood incidents.

This study has two important limitations. First, the original CRIES version was designed for children aged 8 or older, but we included children with 6 and 7 years of age (n = 31, 13,2% of total sample). The original authors of CRIES argue that children young as 6 years old may not have the proper reading and comprehension skills to answer the scale and they do not recommend 6 years old children answering the scale. Regarding this, experimenters were instructed to help young children achieve a better comprehension of the items. The decision to maintain this young age group was due to our plan to follow-up this population for future symptoms.

The second limitation refers to the type of stressful event chosen to validate the scale. Children reactions to different types of disasters may be very specific to the event. Research with different traumatic contexts is highly desired to consolidate CRIES for a screening tool for PTSD in the Brazilian population. After all, some studies found a lower prevalence of PTSD after natural disasters than after human-made/technological events[26].

Areas in need of research include the factors that might modulate and mediate PTSD symptoms (e.g. disaster-related media exposure, prior trauma, social support), the assessment of the long-term impact of disasters, as well as how PTS symptoms relate to measures of daily functioning. Resilience should also be put in perspective, as it is often neglected by post-disaster studies. Future proceedings must include studies of validity evidence based on consequences of testing of CRIES-8 for the diagnoses of PTSD and to verify a suitable cut off of CRIES-8 for the Brazilian population.

Children and adolescents are a population deemed to be at risk following a disaster, especially because they are still in development and less prepared to deal with stress and drastic changes. Screening tools are especially useful in the context of experiencing stressful events, as they optimize the evaluation process, and objectively identifying potential impairments in one's life. The translation and cultural adaptation of CRIES-8 to a Brazilian Portuguese version were conducted following gold standard guidelines to ensure the quality of the process[19]. The extensive revisions lead to a version that is intended to be comprehensible for even young children, it is theoretical representative of the two major factors of the scale (intrusion and avoidance), it is semantic equivalent to the original version, and empirical evidence supports his validity evidence based on test content, relations to other variables, internal structure, and the reliability of its measures. A further strength of the current study was the work definition of PTSD as a heterogeneous construct, which includes Intrusion and Avoidance symptoms.

Acknowledgment

This study was supported by *Conselho Nacional de Desenvolvimento Científico e Tecnológico* – CNPq (404047/2013-0), and *Fundação de Amparo à Pesquisa do Estado de Minas Gerais* – Fapemig (PPM-00183-14).

The authors address special acknowledgment for the Children and War Foundation for the permission to adapt and translate CRIES-8 to Portuguese and also for collaborating in the review of the back-translated Portuguese version.

References

1. Hughes V. Stress: The roots of resilience. Nature. 2012;490(7419):165-7.
2. Chen Z, Zhang Y, Liu Z, Liu Y, Dyregrov A. Structure of the Children's Revised Impact of Event Scale (CRIES) with Children and Adolescents Exposed to Debris Flood. PLoS One. 2012;7(8):1-6.
3. Furr JM, Comer JS, Edmunds JM, Kendall PC. Disasters and youth: a meta-analytic examination of posttraumatic stress. J Consult Clin Psychol. 2010;78(6):765-80.
4. Green BL, Korol M, Grace MC, Vary MG, Leonard AC, Gleser GC, et al. Children and disaster: age, gender, and parental effects on PTSD symptoms. J Am Acad Child Adolesc Psychiatry. 1991;30(6):945-51.
5. Trickey D, Siddaway AP, Meiser-Stedman R, Serpell L, Field AP. A meta-analysis of risk factors for post-traumatic stress disorder in children and adolescents. Clin Psychol Rev. 2012;32(2):122-38.
6. Masten AS, Osofsky JD. Disasters and their impact on child development: introduction to the special section. Child Dev. 2010;81(4):1029-39.
7. McDermott BM, Cobham VE, Berry H, Stallman HM. Vulnerability factors for disaster-induced child post-traumatic stress disorder: the case for low family resilience and previous mental illness. Aust N Z J Psychiatry. 2010;44(4):384-9.
8. Salmon K, Bryant RA. Posttraumatic stress disorder in children. The influence of developmental factors. Clin Psychol Rev. 2002;22(2):163-88.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.
10. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med. 1979;41(3):209-18.

11. Verlinden E, van Meijel EP, Opmeer BC, Beer R, de Roos C, Bicanic IA, et al. Characteristics of the Children's Revised Impact of Event Scale in a clinically referred Dutch sample. J Trauma Stress. 2014;27(3):338-44.
12. Beck JG, Grant DM, Read JP, Clapp JD, Coffey SF, Miller LM, et al. The impact of event scale-revised: psychometric properties in a sample of motor vehicle accident survivors. J Anxiety Disord. 2008;22(2):187-98.
13. Deeba F, Rapee RM, Prvan T. Psychometric properties of the Children's Revised Impact of Events Scale (CRIES) with Bangladeshi children and adolescents. PeerJ. 2014;2:e536.
14. Giannopoulou I, Smith P, Ecker C, Strouthos M, Dikajakou A, Yule W. Factor structure of the Children's Revised Impact of Event Scale (CRIES) with children exposed to earthquake. Pers Indiv Differ. 2006;40(5):1027-37.
15. IPCC, 2014: Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Core Writing Team, Pachauri RK and Meyer LA (eds.)]. IPCC, Geneva, Switzerland, 151 p.
16. Anuário Brasileiro de Desastres Naturais: 2013/Ministério da Integração Nacional. Secretaria Nacional de Proteção e Defesa Civil. Centro Nacional de Gerenciamento de Riscos e Desastres. Brasília: CENAD; 2014.
17. Guha-Sapir D, Hoyois PH, Below R. Annual Disaster Statistical Review 2015: The Numbers and Trends. Brussels: CRED; 2016.
18. Bordin IAS, Mari JJ, Caeiro MF. Validação da versão brasileira do "Child Behavior Checklist" (CBCL) (Inventário de Comportamentos da Infância e Adolescência): dados preliminares. Rev ABPAPAL. 1995;2(17):55-66.
19. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al.; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005;8(2):94-104.
20. Grassi-Oliveira R, Stein LM, Pezzi JC. Tradução e validação de conteúdo da versão em português do Childhood Trauma Questionnaire. Rev Saúde Pública. 2006;40(2):249-55.
21. Perrin S, Meiser-Stedman R, Smith P. The Children's Revised Impact of Event Scale (CRIES): Validity as a Screening Instrument for PTSD. Behav Cogn Psychother. 2005;33:487-98.
22. Alisic E, Jongmans MJ, van Wesel F, Kleber RJ. Building child trauma theory from longitudinal studies: a meta-analysis. Clin Psychol Rev. 2011;31(5):736-47.
23. Mitrushina M, Boone KB, Razani J, Delia LF. Handbook of normative data for neuropsychological assessment. New York: Oxford University Press; 2005.
24. Lau JT, Yeung NC, Yu XN, Zhang J, Mak WW, Lui WW, et al. Validation of the Chinese version of the Children's Revised Impact of Event Scale (CRIES) among Chinese adolescents in the aftermath of the Sichuan Earthquake in 2008. Compr Psychiatry. 2013;54(1):83-90.
25. Oh EA, Park EJ, Lee SH, Bae SM. Validation of the Korean version of the Children's Revised Impact of Event Scale. Clin Psychopharmacol Neurosci. 2014;12(2):149-56.
26. Galea S, Nandi A, Vlahov D. The epidemiology of post-traumatic stress disorder after disasters. Epidemiol Rev. 2005;27:78-91.

Assessing knowledge: psychometric properties of the BAMS semantic memory battery

Laiss Bertola[1], Leandro Fernandes Malloy-Diniz[1]

[1] *Department of Mental Health, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.*

Received: 01/15/2018 – **Accepted:** 02/05/2018
DOI: 10.1590/0101-60830000000152

Bertola L, Malloy-Diniz LF / Arch Clin Psychiatry. 2018;45(2):33-7

Abstract

Background: Semantic memory is a cultural influenced cognitive domain that is responsible for our knowledge about words and the world. Semantic Memory Battery (BAMS) is a new battery that evaluate semantic memory based on a compendium of tasks, including verbal fluency, naming, conceptualization, categorization, general questions, and word definitions, and was designed to consider cultural aspects. **Objectives:** We aimed to evaluate the BAMS psychometrics structure comprising classical and modern analysis, and also evaluate a clinical subdivision of the battery. **Methods:** 114 Brazilian cognitively healthy older adults BAMS performance provided data for psychometric analysis using validity tests, item response theory analysis and confirmatory factor analysis for goodness-of-fit measures. **Results:** BAMS results revealed good validity and good-fit measures in each subtest, total score ($X^2 = 20.684$, $p = 0.110$) and a hierarchical structure with clinical subdivision of the battery ($X^2 = 20.089$, $p = 0.093$). **Discussion:** BAMS is a new compendium of tasks that evaluate distinct aspects of semantic memory and can clinically consider the impact of executive function. This battery evaluates verbal fluency, naming, conceptualization, categorization, general knowledge and word definitions. The BAMS has clinical importance once semantic memory is mostly influenced by culture and language, and there is an absence of broadly semantic memory tests in our scenario, especially with older adults that can have a pathological aging condition that affects primarily or secondarily this domain.
Keywords: Semantic memory, older adults, psychometrics, neuropsychological test.

Introduction

Semantic memory is a subcomponent of long-term declarative memory responsible for general information about the world, words, definitions, categories, and concepts, operating like a knowledge store. Semantic memory allow us to give meaning to the unstoppable sensory information and gives us foundation for behavioral acts[1].

The semantic knowledge distributes across the brain[1]. This cognitive system has a semantic control network and a hub-and-spoke representational network, that interact providing a generalization of concepts across contexts and retrieving conceptual properties of stimuli, respectively[1]. These two semantic networks interact with neural basis that includes distributed temporoparietal areas related to conceptual properties, and convergence zones (anterior temporal lobe and angular gyrus) and prefrontal cortex related to semantic control. The semantic control network with neural basis at the prefrontal cortex and parts of the middle temporal gyrus suggests that these regions are also importantly active during executively demanding tasks[1].

Semantic memory can be divided into subcomponents to facilitate its assessment, comprehension, and also take into account the effects and use of the two described networks. Neuropsychological tests of categorical verbal fluency, naming, conceptualization, categorization, general knowledge questions, and definitions of words are considered tasks that assess the semantic memory system[2,3]. Semantic memory batteries often include a combination of tasks, allowing a more complex assessment of this cognitive domain than isolated tasks can offer.[2,3].

Impairments in semantic memory are core characteristics in some clinical conditions. For example, in the semantic variant of primary progressive aphasia (svPPA), semantic memory is the most prominent cognitive deficit[4]. Patients with this form of pre-senile dementia have a notable anomia and loss of knowledge about things, more than an episodic memory deficit. Usually, during this dementia, patients lose acquired general information, knowledge about things and words, and the words themselves[4].

Other degenerative conditions may have semantic memory deficits, such as some types of mild cognitive impairment (MCI)[5] and Alzheimer's disease (AD)[6]. Some patients with MCI have inconsistent findings in semantic memory evaluation[7-10]. Traditional tasks as naming have evidences of more preserved performance, otherwise, verbal fluency evidence some degree of impairment[11]. AD patients otherwise frequently presents semantic deficits in tasks such as verbal fluency, naming, categorization and general knowledge information[12,13].

Among these clinical conditions the semantic system may reveal a pattern of dissociations or profiles related to the use of abstract and concrete words, and also living and non-living items. svPPA patients may show deficits for concrete words but not for abstract concepts[14], although we also have controversial evidence suggesting that this dissociation does not occur[15].

Category-specific impairments may indicate that knowledge about living and non-living are independent semantic information. svPPA patients, considering the lost of general knowledge related to degeneration of a convergence zone do not normally present category specific deficits[16].

Considering that we do not have a Brazilian semantic battery, we propose the present instrument. Even though we have some individual tasks in our neuropsychological scenario, as the Boston Naming Test[17] and semantic verbal fluency[18], we lack of a culturally developed and broadly semantic evaluation. This absence results in some clinical difficulties with conditions that require a more precise semantic examination and also considers the cultural influence upon this cognitive domain.

Aiming to perform a better semantic memory assessment in the older adults, we developed a battery that would consider the actual theoretical literature about semantic memory as a cognitive construct and a clinical marker for healthy and pathological aging. This new battery was design to take into account distinct tasks that evaluate specific aspects of the semantic memory, and also the patterns of abstract/concrete and living/non-living items.

Methods

BAMS

The Semantic Memory Battery (Bateria de Avaliação da Memória Semântica – BAMS) is composed of seven tasks that assess different

Address for correspondence: Laiss Bertola. Universidade Federal de Minas Gerais. Av. Alfredo Balena, 190, Santa Efigênia – 30130-100 – Belo Horizonte, MG, Brazil.
Telephone: +55 (11) 98424.3212. E-mail: laissbertola@gmail.com

semantic memory subdomains. Initially, all tasks had 20 items each, except the naming test with 65 items and the verbal fluency with six categories. The first version of the BAMS was built with more items considering that a first cognitive health sample would test and improve the selection of the definitive items according to classical and modern psychometric analysis, as item response theory (IRT) and confirmatory factor analysis (CFA). The administration time is approximately 30 minutes. Box 1 shows a description of each task, correction, and scoring system. The supplementary material contains detailed information about item selection and the remained structure of the battery after psychometric analysis.

Some primary criteria defined the items choices according to each task: the frequency of the word according to the Brazilian Portuguese Corpus[19], the expected scholar knowledge for the mean education achievement of the Brazilian older adults population and the nuisance variables available[20]. Items were selected according to a high, medium and low frequency to avoid a ceiling or floor effect for the illiterate and highly educated older adults.

The BAMS have some similar tasks from other semantic memory batteries, including the naming in response to verbal description, picture naming, semantic verbal fluency, and visual categorization based on semantic association[2,3]. This instrument also includes tasks not present at other batteries as general knowledge questions and verbal similarities.

Box 1. BAMS description

Subtest	Description	Correction	Scoring
Verbal Fluency (VF)	Particular semantic category word production.	Correct words produced within each semantic category.	One point for each correct word. All fluencies summed.
Naming by Definition (ND)	Naming items after given definition composed of two or three information.	Right or wrong naming after the full description.	One point for each correct naming.
Naming Test (NT)	Naming black-white line drawing that represents objects, actions, and professions.	Correct or wrong visual naming.	One point for each correct naming.
General Knowledge (GK)	Questions about general knowledge according to national history and culture.	Correct or wrong answer.	One point for each correct answer.
Word Definition (WD)	Meaning of words related to concrete and abstract information.	Correct or wrong definition.	One point for each correct definition.
Categorization (CT)	Pairing one goal picture with one of the three images in the search group.	Correct or wrong pairing.	One point for each correct pairing.
Similarities (SM)	Semantic relation between two words related to concrete and abstract information.	Correct or wrong relation.	One point for each correct relation.

Sample

A hundred and fourteen older adults compose the cognitive health sample. The recruitment involved participants from the community, from physical exercise groups of governmental programs, retirement groups and healthy older adults from a public medical service.

Procedures

All the participants underwent a clinical interview and neuropsychological assessment conducted by a neuropsychologist. All the participants underwent assessment composed by three stages: 1) clinical interview designed to exclude subjects with psychiatric, neurological or other self-related disease, 2) a brief cognitive screening to exclude those subjects suffering from pathological cognitive decline and, 3) a comprehensive neuropsychological assessment to provide data for the assessment of BAMS psychometric properties.

The participants must be 60 years or older, be cognitively intact at the cognitive screening tasks and gave written consent for participation. The exclusion criteria adopted included that none of the patients must have actual or past reported history of neurological diseases; no actual psychiatric symptoms; no severe sensory or motor impairments; no self-reported hormonal or vitamins dysfunctions; and daily dependence.

Cognitive screening

The cognitive screening tasks included the Mattis Dementia Rating Scale (DRS)[21] and the Frontal Assessment Battery (FAB)[22], and the participants should score inside or above the Brazilian normative sample mean according to age and educational achievement. The Ethics Committee in Research of the Universidade Federal de Minas Gerais approved the present study (CAAE-26795714.4.0000.5149).

Neuropsychological protocol

All participants underwent selected neuropsychological tasks. Some of the tasks were grouped into composite scores. The executive function score was composed by Digit Span task[23], and parts three and four of the Five Digits Test[24]. The episodic memory score was composed by the learning, retrieval and recognition parts of the Rey Auditory Verbal Learning Test[25]. The participants also performed the vocabulary subtest of the WAIS-III scale[26] and the identification of common objects task[27]. This configuration of neuropsychological tasks was used to provide psychometric and validity information about the BAMS.

Data analysis

The statistics analyses were performed at Statistical Package for Social Science (SPSS) and MPlus v7 according to the objective. We choose to perform analysis from the classical and modern psychometric theory.

Psychometric analysis was decided according to data type. For the Verbal Fluency tasks we performed a CFA to verify if all six categories could group into a single measure that includes living and non-living. For the last six subtests we followed the steps: (Step 1) We first excluded items with no variability, once these items were very easy and may not be truly informative of the semantic memory average performance. (Step 2) We used the estimated IRT analysis, in a two-parameter logistic model (2PL), to evaluate the psychometric properties of the test and provide a better selection of the items according to each item difficulty and discrimination[28]. We determined that the items selection would respect a minimum of discrimination parameter of 0.65, classified as moderate, and all difficulty items would be considered after the discrimination criteria. If more than ten items passed this first selection criterion, we only kept the best ten. The Naming subtest was an exception to this rule and we kept more items to maintain diversity of nouns and verbs, living and non-living.

We performed this described procedure for each subtest that composes the BAMS. (Step 3) We underwent the selected items into a CFA to evaluate the constructs manifestation throughout a stronger analytics framework accounting for measurement errors, and also performed a Cronbach's Alpha according to the classical test theory. If an item showed Heywood case or a poor fit to the model, it would be excluded. (Step 4) Remain items were summed into composite scores for each subtest and these values underwent an Exploratory Factor Analysis (EFA) and a new CFA to assess a general semantic memory construct (BAMS total), and also another Cronbach's Alpha. Summing the individual item into a composite score for each task

and performing the CFA only with the seven tasks composite scores were done to avoid errors of fit measures according to our sample size.

We performed the subtest CFA with a robust diagonally weighted least square (WLSMV) once the items are categorical, and this estimator does not assume normally distributed variables[28]. The WLSMV does not require the diagonal weight matrix to be positive definite, and requires a smaller sample size than weighted least square (WLS). WLSMV analysis can produce accurate test statistics, parameters estimates and errors with small sample size (100 or higher)[28]. The WLSMV performs accurately also with variables with floor or ceiling effects, although the IRT selection looked to avoid these effects[28]. Correlation analyses were performed to show valuable information about the construct and criterion validity of the BAMS.

Additional BAMS scores

Among the seven tasks that compose the BAMS, we have three subtests that share the influence of executive functions. The tasks of verbal fluency and categorization/similarities involve the frontal lobe network[29-31] and they include compromised performance in clinical groups with dysexecutive syndrome[30,32] even when semantic memory is preserved. We then tested for sub-composite scores built with a division of the BAMS tasks: semantic (SEM) and semantic-executive (SEF). The Naming by Definition, Naming Test, General Knowledge, and Word Definition tests created the SEM score, and Verbal Fluency, Categorization, and Similarities built the SEF score to accomplish findings related to executive and semantic interaction. This clinical division was evaluated using correlation with the composite score of executive functions, episodic memory, vocabulary subtest and the identification of common objects task.

Episodic memory composite score and the WAIS-III Vocabulary subtest were chosen as a convergent validity for the SEM considering that episodic and semantic memory share common long term declarative memory characteristics and the vocabulary measure is also used as a single assessment of semantic memory. The executive composite score and the identification of common objects task were chosen as convergent validity for the SEF score once the composite score was build comprising the theoretical view of three nuclear executive functions[33] and the identification of common objects task is an abstract categorization task.

Results

Sample descriptive characteristics are described in Table 1. BAMS initial and final configurations are reported at the Supplementary material.

The CFA for the Verbal Fluency subtest indicated that the category of birds was not a significant parameter and therefore was excluded, remaining five categories (animals, fruits, household items, tools and clothes). This five categories Verbal Fluency model revealed a good fit (Table 2).

For the Naming Test were selected all items with moderate or higher discrimination. The final task remained with 38 items. The fit measures showed a Chi-square with almost a good fit, but no modification indices were suggested (Table 2). The Root Mean Square Error of Approximation index indicates a good fit (RMSEA = 0.030; CI: 0.008-0.043; p = 0.997), also the CFI (0.992) and TLI (0.991), leading to our decision to keep the task with no more modifications.

After the IRT analysis Naming by Definition, General Knowledge, Categorization, Similarities and Word Definitions subtests remained with ten items each, all showing a good fit model (Table 2). All the subtests with the remained configuration of items also revealed satisfactory internal consistency according to Cronbach's Alpha values (Table 2).

The final selections of items for each subtest were computed into composite scores for each task (standardized estimates of BAMS subtests are shown on Table 3). The EFA analysis revealed a good fit for a unitary latent factor of the BAMS (X^2 = 23.012, df = 14, p = 0.06) and a general CFA for the battery also revealed a good fit in all indices (RMSEA = 0.06, CFI = 0.981, TLI = 0.972, see Table 2 for Chi-square value). The Cronbach's Alpha for the BAMS also indicates a good internal consistency (Table 2).

Considering the subdivision of the BAMS, we tested with the Cronbach's Alpha the internal consistency of the two composite scores SEM (α = 0.822) and SEF (α = 0.755). Considering the possibility of a hierarchical composition, we tested for a CFA hierarchical model build with two latent factors semantic (SEM) and semantic-executive (SEF). This hierarchical model also indicates good fit: Chi-square = 20.089, df = 13, p = 0.093, RSMEA = 0.070, CFI = 0.980, TLI = 0.968.

Correlation results indicated convergent and divergent validity. The BAMS has positive and higher correlation with education (r = 0.647, p < 0.001) than age (r = -0.422, p < 0.001), and also positive correlation with the General Cognition measure (r = 0.778, p < 0.001). The criterion validity is demonstrated through the negative correlation between the BAMS score and the Functional Assessment Questionnaire (Pfeffer Index), indicating that higher semantic memory is related to lower functional impact (r = -0.333, p < 0.001).

Table 1. Descriptive characteristics of the sample (n = 114)

	Mean (SD)	Min-Max
Age	72.69 (8.25)	(60-98)
Education	7.78 (5.50)	(0-26)
Gender (% female)	86 (75%)	-
DRS	131.23 (9.11)	(96-144)
FAB	14.23 (2.76)	(5-18)

DRS: Mattis Dementia Rating Scale; FAB: Frontal Assessment Battery.

Table 2. CFA for each subtest and the battery (n = 114)

	Chi-Square	*df*	*p*	Cronbach's Alpha
Verbal Fluency	0.323	5	0.997	0.846
Naming by Definition	31.591*	35	0.633	0.709
Naming Test	730.737*	665	0.040	0.888
General Knowledge	48.868*	35	0.060	0.870
Word Definition	41.770*	35	0.200	0.751
Categorization	31.618*	35	0.632	0.650
Similarities	36.458*	35	0.400	0.832
BAMS	20.684	14	0.110	0.890

* WLSMV chi-square cannot be used for difference testing in a regular way. BAMS: Semantic Memory Battery.

Table 3. Standardized estimates BAMS by subtests (n = 114)

	B	SE	*p*
Verbal Fluency	0.580	0.071	0.000
Naming by Definition	0.732	0.051	0.000
Naming Test	0.585	0.070	0.000
General Knowledge	0.849	0.034	0.000
Word Definition	0.747	0.049	0.000
Categorization	0.751	0.048	0.000
Similarities	0.842	0.035	0.000

B: standardized estimate; SE: standard error.

The division of the BAMS into SEM and SEF scores also revealed convergent and divergent validity. The SEM score has higher correlations and significant distinct correlation values with education and the vocabulary subtest, and also does not have correlation with the identification of common objects task (Table 4). The SEF score otherwise, has higher correlations and significant distinct correlation values with age and the number of direct questions at the identification of common objects task (Table 4).

Considering the important correlation between BAMS scores with age and education, we choose to divide the sample into two age groups (60 to 75 years old, and 76 thru highest), and three educational groups (0-2 years, 3-8 years, 9 thru highest). The divisions of the educational and age groups were combined and indicated a good homogeneity within each combination. The BAMS scores according to age and educational achievement are shown in Table 5.

Table 4. SEM and SEF correlations with neuropsychological measures (n = 114)

	Age#	Education#	Executive Function	Episodic Memory	ICOT – Direct questions#	VOC – WAIS-III#
SEM	-0.270**	0.692**	0.458**	0.453**	-0.160	0.800**
SEF	-0.455**	0.554**	0.512**	0.432**	-0.248*	0.646**

* p > 0.05; ** p < 0.001; # z test statistic significant difference (p < 0.05). ICOT: Identification of Common Objects Task; VOC: Vocabulary; SEM: Semantic Composite Score; SEF: Semantic-Executive Composite Score.

Table 5. Sample scores of each subtest, SEM, SEF and total BAMS.

Age (years)	60-75			≥ 76		
Education (years)	0-2 n = 11	3-8 n = 30	≥ 9 n = 36	0-2 n = 6	3-8 n = 21	≥ 9 n = 10
Verbal Fluency	56.45 (10.67)	61.64 (11.17)	79.36 (16.76)	49.60 (7.92)	58.25 (11.88)	59.50 (10.18)
Naming by Definition	5.00 (2.56)	7.67 (1.51)	8.67 (1.29)	5.20 (1.78)	7.23 (1.99)	8.50 (1.08)
Naming Test	32.27 (6.57)	36.96 (1.17)	37.70 (0.57)	31.00 (5.65)	36.55 (1.82)	37.10 (1.59)
General Knowledge	0.54 (0.68)	4.39 (2.37)	7.73 (1.81)	2.00 (1.73)	4.28 (2.61)	7.80 (1.54)
Word Definition	1.00 (0.89)	3.14 (1.64)	5.64 (2.01)	0.80 (1.09)	3.09 (1.75)	5.80 (2.39)
Categorization	5.90 (1.44)	8.60 (1.31)	9.47 (0.86)	6.60 (1.51)	8.14 (1.79)	8.60 (1.34)
Similarities	1.09 (0.94)	4.32 (2.27)	6.91 (2.02)	1.00 (1.00)	2.71 (1.82)	7.10 (2.51)
SEM	38.81 (8.50)	52.14 (4.23)	59.78 (4.12)	39.60 (6.84)	51.20 (6.09)	59.20 (5.63)
SEF	63.45 (11.86)	74.56 (11.94)	96.00 (17.51)	57.20 (7.49)	69.05 (13.09)	75.20 (10.45)
BAMS	102.27 (18.11)	126.56 (14.58)	155.83 (19.98)	96.80 (5.26)	120.68 (17.03)	134.40 (14.40)

SEM: Semantic Composite Score; SEF: Semantic-Executive Composite Score; BAMS: Semantic Memory Battery Total Score.

Discussion

The objective of the present study was to analyze the properties of the Semantic Memory Battery (BAMS) using modern and classical psychometrics analysis to better select items and verify the general quality of the proposed battery in a sample of older adults.

The BAMS is composed by seven tasks that evaluate different aspects of semantic memory and showed good fit scores and validities for intra-tasks and overall battery. These results indicate that the selected items and tasks format indeed compose a common semantic score, and therefore, should be considered as a valid measure for this cognitive domain.

The BAMS composition has similar and distinct tasks from the Cambridge Semantic Memory Test Battery (2) and the Nombela 2.0 semantic battery (3) with good acceptance in the field of neuropsychological evaluation. However, the BAMS does not use the same stimulus across tasks, is not equally divided into living and non-living items after the IRT selection, and not all the nuiance variables could be controlled.

The BAMS analysis prioritized the item performance in order to avoid ceiling and floor effects. This analysis will provide more performance variability being also a potential clinical instrument with other conditions despite primary semantic memory decline.

The BAMS is also composed of tasks that are similar to standard measures of semantic memory, even when these tasks just access a specific part of this domain, as the Boston Naming Task[17] and semantic verbal fluency tasks[18]. The use of distinct tasks that evaluates important aspects of semantic memory broadens the assessment of this cognitive domain and raises the possibility of a better clinical diagnosis and intervention.

The BAMS also revealed a good clinical structure when the tasks were divided according to the level of executive function influence. The two composite score variables SEF and SEM also fit an overall score of semantic memory. This division is relevant when assessing patients with executive functions deficits that could drive the total score at the BAMS, and induce the perception of a worse semantic memory[30,34]. This hypothesis needs to be further tested looking for differences at the SEF and SEM division of the battery in clinical groups.

Age and education revealed relations with the semantic measures as expected. The education had higher correlation with the total score and also with SEM score, indicating that the semantic battery is also influenced by schooling process and acts as a crystallized cognition. The correlation with age was higher with the SEF score indicating a more fluid performance influence compatible with the executive function use in tasks of categorization, similarities and verbal fluency.

The BAMS as a total score and as clinical scores SEM and SEF showed good fit measures and also construct and criteria validities, indicating that even though this is the first semantic battery of the Brazilian neuropsychological scenario, it does have good psychometric indicators.

According to the education and age correlations, the sample was split into two age groups and, three education groups, so this influence could be taken into account when evaluating the semantic memory performance older adults. Is notorious the score difference among the fewer educated older adults and the medium to highly educated. We highlight that the BAMS is a battery that can be used with illiterate or semi-literate older adults owing to the fact that items selection took into account distinct educational backgrounds, allowing the assessment of this cognitive domain that is also influenced by cultural insertion.

Beyond the absence of a clinical group, this first study also has a limitation of working with a reduced sample size. Despite the results that the BAMS shows good psychometric properties and will be of relevant use in our neuropsychological evaluation scenario, a bigger sample size will improve the psychometric analysis and also provide parameters to our sample. Once our sample has sociocultural particularities and education has a relation to task achievement, these limitations encourages new perspectives in conducting a normative study with a lager cognitively healthy sample and clinical groups with semantic deficit.

The availability of a better semantic memory assessment is even more important when working with older adults that can have a particular pathological aging process that affects this domain[4,12,13]. The present battery may be a promising instrument for the cognitive assessment and clinical use with older adults.

Acknowledgements

We would like to acknowledge the physical exercise groups of governmental programs, and retirement groups for welcoming the recruitment of participants. We also would like to acknowledge MACB and RTA for allowing us to evaluate some of their participants.

References

1. Ralph MAL, Jefferies E, Patterson K, Rogers TT. The neural and computational bases of semantic cognition. Nat Rev Neurosci. 2017;18(1):42-55.
2. Adlam AL, Patterson K, Bozeat S, Hodges JR. The Cambridge Semantic Memory Test Battery: detection of semantic deficits in semantic dementia and Alzheimer's disease. Neurocase. 201;16(3):193-207.
3. Moreno-Martínez FJ, Rodríguez-Rojo IC. The Nombela 2.0 semantic battery: an updated Spanish instrument for the study of semantic processing. Neurocase. 2015;21(6). Disponível em: http://www.tandfonline.com/doi/abs/10.1080/13554794.2015.1006644. Acesso em: 20 nov. 2017.
4. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1006-14.
5. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256(3):240-6.
6. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-9.
7. Joubert S, Felician O, Barbeau EJ, Didic M, Poncet M, Ceccaldi M. Patterns of semantic memory impairment in Mild Cognitive Impairment. Behav Neurol. 2008;19(1-2):35-40.
8. Balthazar ML, Cendes F, Damasceno BP. Semantic error patterns on the Boston Naming Test in normal aging, amnestic mild cognitive impairment, and mild Alzheimer's disease: is there semantic disruption? Neuropsychology. 2008;22(6):703-9.
9. Willers IF, Feldman ML, Allegri RF. Subclinical naming errors in mild cognitive impairment: A semantic deficit? Dement Neuropsychol. 2008;2(3):217-22.
10. Catricalà E, Della Rosa PA, Parisi L, Zippo AG, Borsa VM, Iadanza A, et al. Functional correlates of preserved naming performance in amnestic Mild Cognitive Impairment. Neuropsychologia. 2015;76:136-52.
11. Bertola L, Cunha Lima ML, Romano-Silva MA, de Moraes EN, Diniz BS, Malloy-Diniz LF. Impaired generation of new subcategories and switching in a semantic verbal fluency test in older adults with mild cognitive impairment. Front Aging Neurosci. 2014;6:141.
12. Joubert S, Brambati SM, Ansado J, Barbeau EJ, Felician O, Didic M, et al. The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. Neuropsychologia. 2010;48(4):978-88.
13. Libon DJ, Rascovsky K, Powers J, Irwin DJ, Boller A, Weinberg D, et al. Comparative semantic profiles in semantic dementia and Alzheimer's disease. Brain. 2013;136(Pt 8):2497-509.
14. Bonner MF, Vesely L, Price C, Anderson C, Richmond L, Farag C, et al. Reversal of the concreteness effect in semantic dementia. Cogn Neuropsychol. 2009;26(6):568-79.
15. Jefferies E, Patterson K, Jones RW, Lambon Ralph MA. Comprehension of concrete and abstract words in semantic dementia. Neuropsychology. 2009;23(4):492-9.
16. Ralph MAL, Patterson K, Garrard P, Hodges JR. Semantic dementia with category specificity: A comparative case-series study. Cogn Neuropsychol. 2003;20(3-6):307-26.
17. Miotto EC, Sato J, Lucia MC, Camargo CH, Scaff M. Development of an adapted version of the Boston Naming Test for Portuguese speakers. Rev Bras Psiquiatr. 2010;32(3):279-82.
18. Fichman HC, Fernandes CS, Nitrini R, Lourenço RA, Paradela EMP, Carthery-Goulart MT, et al. Age and educational level effects on the performance of normal elderly on category verbal fluency tasks. Dement Neuropsychol. 2009;3(1):49-54.
19. Kilgarriff A, Rychlý P, Smrž P, Tugwell D. Itri-04-08 the sketch engine. Inf Technol. 2004.
20. Pompéia S, Miranda MC, Bueno OFA. Brazilian standardised norms for a set of pictures are comparable with those obtained internationally. Arq Neuropsiquiatr. 2003;61(4):916-9.
21. Foss MP, Carvalho VA, Machado TH, Reis GC, Tumas V, Caramelli P, et al. Mattis Dementia Rating Scale (DRS): Normative data for the Brazilian middle-age and elderly populations. Dement Neuropsychol. 2013;7(4):374-9.
22. Beato RG, Nitrini R, Formigoni AP, Caramelli P. Brazilian version of the Frontal Assessment Battery (FAB): Preliminary data on administration to healthy elderly. Dement Neuropsychol. 2007;1(1):59-65.
23. de Paula JJ, Bertola L, Ávila RT, Moreira L, Coutinho G, de Moraes EN, et al. Clinical applicability and cutoff values for an unstructured neuropsychological assessment protocol for older adults with low formal education. PLoS One. 2013;8(9):e73167.
24. de Paula JJ, Ávila RT, Costa DS, Moraes EN, Bicalho MA, Nicolato R, et al. Assessing Processing Speed and Executive Functions in Low Educated Older Adults: the Use of The Five Digit Test in Patients with Alzheimer's Disease, Mild Cognitive Impairment and Major Depressive Disorder. Clin Neuropsychiatry. 2011;6(8).
25. Malloy-Diniz LF, Lasmar VAP, Gazinelli LSR, Fuentes D, Salgado JV. The Rey Auditory-Verbal Learning Test: applicability for the Brazilian elderly population. Rev Bras Psiquiatr. 2007;29(4):324-9.
26. Nascimento E. WAIS-III: Escala de Inteligência Wechsler para Adultos – Manual Técnico. 1ª ed. São Paulo: Casa do Psicólogo; 2005.
27. Fuentes D, Malloy-Diniz LF, Camargo CHP, Cosenza R. Neuropsicologia teoria e prática. 2ª ed. Porto Alegre: Artmed; 2014.
28. Brown TA. Confirmatory factor analysis for applied research. New York Guilford Press; 2006.
29. Costafreda SG, Fu CH, Lee L, Everitt B, Brammer MJ, David AS. A systematic review and quantitative appraisal of fMRI studies of verbal fluency: role of the left inferior frontal gyrus. Hum Brain Mapp. 2006;27(10):799-810.
30. Lagarde J, Valabrègue R, Corvol JC, Garcin B, Volle E, Le Ber I, et al. Why do patients with neurodegenerative frontal syndrome fail to answer: 'In what way are an orange and a banana alike?'. Brain. 2015;138(Pt 2):456-71.
31. Herrmann MJ, Ehlis AC, Fallgatter AJ. Frontal activation during a verbal-fluency task as measured by near-infrared spectroscopy. Brain Res Bull. 2003;61(1):51-6.
32. Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology. 2004;18(2):284-95.
33. Diamond A. Executive Functions. Annu Rev Psychol. 2013;64:135-68.
34. Raposo A, Mendes M, Marques JF. The hierarchical organization of semantic memory: executive function in the processing of superordinate concepts. Neuroimage. 2012;59(2):1870-8.

Review article

Lithium interactions with non-steroidal anti-inflammatory drugs and diuretics – A review

Rui Pedro Nunes[1]

[1] *USF Sete Moinhos – ACES Oeste Sul – ARSLVT, Lisboa, Portugal.*

Received: 10/22/2016 – **Accepted:** 03/08/2018
DOI: 10.1590/0101-60830000000153

Abstract

Background: Lithium is often used in bipolar disorder and occasionally in unipolar depression. Non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics are frequently prescribed and their interaction with lithium is based mainly in few small studies. **Objectives:** Conduct a review, identify different interaction patterns and discuss treatment options. **Methods:** Three searches were made in PubMed in January 2016: 1) using the keywords "lithium" [and] "non-steroidal anti-inflammatory"; 2) using the keywords "lithium" [and] "diuretics" and the filter "title/abstract"; 3) using the terms "lithium" [and] "toxicity" and the filters "title" [and] "review". From the 293 remaining articles, 10 were selected. Another search in Scielo.org was made, using the term "lítio" and the filter "Psiquiatria". Two articles were selected from the initial 53. Six textbooks were added to expand the evidence, achieving a total of 18 references. **Results:** The majority of NSAIDs and diuretics rises lithium levels, specially thiazides. However, some show great variability or no interaction at all, and others even decrease lithium levels. **Discussion:** Lower-doses, shorter durations, lithium adjustments and levels' follow-ups are recommended, especially in elderly and multiple co-morbid patients.

Nunes RP / Arch Clin Psychiatry. 2018;45(2):38-40

Keywords: Lithium, non-steroidal anti-inflammatory drugs, diuretics, drug interactions, safety.

Introduction

Lithium is a mood stabilizer frequently used in bipolar disorder and occasionally in severe or recurrent unipolar depression, reducing also the risk of suicide. Non-steroidal anti-inflammatory drugs (NSAIDs) – for their analgesic, antipyretic and anti-inflammatory effects – and diuretics – for their blood pressure and edema reduction effects – are frequently prescribed, especially in the elderly, who are particularly susceptible to lithium's toxicity[1-11].

The co-administration of this narrowed therapeutic window drug with NSAIDs and diuretics is common, but seldom mentioned. This issue is even more relevant due to the inexistence of robust studies focusing the myriad of possible interactions of lithium with the multiplicity of NSAIDs and diuretics that exist nowadays, with a significant part of the actual evidence coming from case studies and small clinical trials[1-5,10,12].

Therefore, this article intends to make a global review of the matter, having as main **objectives** to identify the different types of NSAID's and diuretics' interactions patterns with lithium and to propose treatment alternatives.

Methods

Three initial bibliographical searches were made in PubMed's database, in January 2016. For the first one, the MeSH terms "lithium" [and] "non-steroidal anti-inflammatory" were used; for the second one were used the terms "lithium" [and] "diuretics" and then the filter "title/abstract" was applied to narrow the search; for the third one were used the terms "lithium" [and] "toxicity", and then were also applied the filters "title" [and] "review". Therefore, the searches resulted in 146, 123 and 24 articles correspondingly (n = 293), from which 10 articles were selected (6, 3 and 1 respectively), accordingly with the objectives of this review.

Afterwards, but also in January 2016, an additional search in Scielo.org database was made, using the term "lítio", resulting in 238 articles. To narrow the search, the filter "Psiquiatria" was applied and from this initial 53 articles' pool, 2 were selected accordingly with the defined objectives.

To expand the scientific evidence found, more sources were added through bibliographic review of 6 textbooks based on strong international scientific evidence, achieving a total of 18 bibliographic references for this critical literature review (Figure 1).

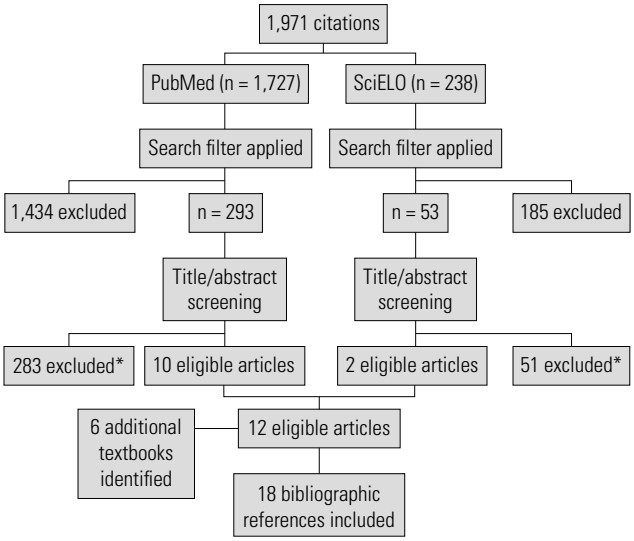

Figure 1. Article selection flow chart. *Reasons for exclusion: did not meet review objectives; not oriented for clinical practice; abstract/full-text could not be obtained; duplicated articles.

Results and discussion

Lithium's pharmacokinetics and pharmacodynamics

Lithium is administrated in the form of lithium's carbonate and its elimination is practically all processed by the kidneys (one half in ≈12h and the other one in 1-2 weeks). This explains why lithium blood measurements are done 4-5 days after the beginning of treatment and 12h after the last dose. About 80% of the lithium filtrate is reabsorbed (≈60% in the proximal tubule and ≈20% in the loop of Henle and collector duct)[1,2,5,9-11].

This way, medications that reduce the glomerular filtration rate (like NSAIDs and hypertension drugs that interfere with the renin-angiotensin-aldosterone system) or that stimulate lithium reabsorption (like NSAIDs and most diuretics) can contribute to lithium levels above the therapeutic window (0,5-1 mmol/L or 0,4-1,5 mmol/L, admitting an extreme interval)[1,2,5,7-11,13].

Address for correspondence: Rui Pedro Nunes. USF Sete Moinhos – ACES Oeste Sul – ARSLVT. Rua José Poman. Telephone: +351 96164-1007. E-mail: rui_nunes22@hotmail.com

It's well established that the **NSAIDs** inhibits prostaglandins' synthesis by cyclogeneses blockage (COX1 and COX2), leading to two processes that can explain the rise of plasmatic lithium levels. On one hand, prostaglandins fall leads to the reduction of renal arteries' flow by vasoconstriction, resulting in decreased glomerular filtrate and consequently decreased renal lithium clearance; on the other hand, theories postulate that low levels of prostaglandins can promote a direct rise in sodium and lithium, because lithium's renal reabsorption is similar to sodium's and because of the presence of several nephron proteins that promote both cations co-transportation[1,5-9,11,12,14].

The **diuretics'** interaction however, differs from class to class. The majority promotes a rise in sodium renal excretion, conditioning a decreased concentration of it and therefore the activation of a compensatory mechanism of increased sodium tubular reabsorption and, as explained, also of lithium. Situations linked to hypovolemia and hyponatremia can also lead to lithium rises by the same mechanism[1,4-6,8,10,11,15,16].

Although, diuretics' effects differ according to the nephron's site of action of each drug class. Thiazides and similar produce and increase in sodium and lithium reabsorption in the proximal convoluted tubule (where their reabsorption is more relevant). Loop diuretics (like furosemide) act mainly in the loop of Henle (where lithium reabsorption is marginal). Differently, osmotic diuretics (like mannitol) and carbonic anhydrase inhibitors (like acetazolamide) increase lithium clearance and consequently diminish lithium levels[1,3-6,10].

Adverse effects of lithium

Common secondary effects (that occur in non-toxic therapeutic doses) can be distinguished from toxic effects (for lithium levels > 1,5 mmol/L)[1,10,11].

The secondary effects can happen in a short or in a long term. At a short term are frequent: nausea, vomits, diarrhea, tremor and in some cases, ataxia, sedation and cognitive impairment. The most frequent long-term effects are: alopecia, acne, hypothyroidism, hyperparathyroidism, weight gain, polyuria, polydipsia (due to nephrogenic diabetes insipidus) and chronic renal insufficiency (mainly due to interstitial nephritis)[1,3,5,9-11].

Several **risk factors** for intoxication are already identified like: old age, drugs (diuretics, NSAIDs), renal insufficiency, renal artery stenosis, hyponatremic and hypovolemic conditions (cirrhosis, cardiac congestive heart failure, nephrotic syndrome, dehydration and low-salt diets) and overdose. Interindividual susceptibility and changes in lithium levels can therefore lead to several adverse effects, described in Table 1[1,3,5,10,11,13].

Therefore, is vital to closely check the lithium levels until stable values are achieved, for instance weekly. Afterwards, a 6-month check is recommended for lithium levels and renal and thyroid functions. Metabolic control (weight, cholesterol and glycaemia) as well as the cardiac function should also be checked more frequently[3,9-11].

Lithium and NSAIDs interaction

The majority of NSAIDs (including COX-2 selective inhibitors) show moderate risk for increasing plasmatic lithium concentrations. This risk is higher for high doses and long-term treatments. Normally, the interaction occurs in the first days of co-administration, despite the description of interaction months later in some cases[6,8,11,17].

Even admitting a class effect, they are still unknown mechanisms of interaction that can be the basis of some exceptions. Acetylsalicylic acid and sulindac are two of those examples without strong evidence of interaction. In other cases, there is a great interindividual variability, as accounts for ibuprofen and naproxen (Table 2). Despite the average increase in lithium levels with NSAIDs of 10%-25%, there are sporadic cases of 100% raise described[1,3-8,12-14,17,18].

Table 1. Toxic lithium effects accordingly with lithium plasmatic levels

> 1,5 mmol/L	> 2 mmol/L
– Nausea and diarrhea – Polyuria e thirst – Psychomotor agitation – Myoclonus and fasciculations – Muscular weakness – Ataxia – Lethargy and sedation – Cognitive impairment	– Acute renal insufficiency – ECG T-wave changes – Seizures – *Delirium* – Coma – Death

Table 2. Sorts of interactions between lithium and different NSAIDs

Well-established interaction (↑ *lithium*)	Celecoxib, diclofenac, flurbiprofen, indomethacin, ketorolac, ketoprofen, lornoxicam, mefenamic acid, meloxicam, niflumic acid, phenylbutazone, piroxicam
Variable interaction (↔ *or* ↑ *or* ↑↑ *lithium*)	Ibuprofen and naproxen
Without proven interaction	Acetylsalicylic acid and sulindac

↔ no change; ↑ slight increase; ↑↑ moderate increase.

Alternatives to NSAIDs for analgesic effect are paracetamol (acetaminophen) and opioids. For Paracetamol there is no evidence of interaction with lithium, but for opioids there is an increased risk for serotoninergic syndrome. Therefore, if there is a need for a NSAID in such cases, one could rather use: 1) acetylsalicylic acid or paracetamol (if analgesic or antipyretic effect is needed and there are no contraindications); 2) low-fixed dose or topic NSAIDs (theoretically less risky, but without studies corroborating that)[1,2,5,6,12,14,18].

Every time there's a strict need to use a NSAIDs, the following **administration recommendations** should be respected:

- To inform the patient of the interaction's risk[11,18];
- To use the minimum effective dose for as less time as possible[6];
- To monitor lithium levels every time a NSAID is started or suspended (4-5 days later on)[6,11,13,14,17];
- It is preferable (if possible) to reduce 20%-25% of lithium dose when a new NSAID is introduced[3,6,14];
- It should be avoided in high risk patients for lithium intoxication, especially in the elderly and renal insufficients[6,10,11].

Lithium and diuretics interaction

The interaction pattern varies with the class of the diuretic and its corresponding pharmacokinetics. Disparity in sodium and lithium renal reabsorption's site can explain why thiazides and analogs have a strong interaction pattern and loop diuretics and sparing-potassium diuretics don't (Table 3)[1,4-6,11,13,15,16].

The report of interaction cases with **thiazides** have accumulated since the 70's, particularly with hydrochlorothiazide and chlorthalidone. These diuretics promote a 25% increase in lithium

Table 3. Sorts of interactions between lithium and different diuretics

↑↑↑ [*lithium*]	Thiazides and analogs	chlorthalidone, hydrochlorothiazide, indapamide*
Variable interaction (↔ or ↑ [*lithium*])	Loop diuretics	furosemide
	K^+-sparing diuretics	amiloride*, spironolactone*, triamterene*
↓↓ [lithium]	Osmotic diuretics	mannitol, urea
	Carbonic anhydrase inhibitors	acetazolamide

*Scarce evidence/class effect assumed. ↔ no change; ↑ slight increase; ↑↑↑ severe increase; ↓↓ moderate decrease.

levels (with some cases reporting up to 4-fold rise). This effect is commonly present in the first days of co-administration. Despite the interaction between lithium and most NSAIDs being so unpredictable, with thiazides that interaction is much more likely (being held as a high-risk interaction). So, its wise to discourage the use of such diuretics in lithium medicated patients[1,4-6,11,13,16].

For **loop diuretics**, the scientific evidence is somewhat conflicting. Although furosemide didn't produce changes in lithium levels in some cases, in others seemed to be responsible for small plasmatic increases, especially in susceptible individuals. Also, furosemide's interaction can occur a little bit latter than with thiazides, but usually in the first month. Despite all that, it is considered a safer diuretic than thiazides, being mentioned as a therapeutic option for nephrogenic diabetes insipidus secondary to chronic treatment with lithium[1,4-6,11,13,15].

For **potassium-sparing diuretics**, the evidence is even more scarce, with no interaction in most studies and small increases in lithium levels on other studies, apparently being amiloride the safest option in the class. Despite not being unanimous, these diuretics can configure an alternative to thiazides[1,3,4,6].

Osmotic diuretics (like mannitol) and **carbonic anhydrase inhibitors** (like acetazolamide) produce an opposite effect comparing to the majority of the other diuretics, decreasing lithium concentration (being therefore classically used to treat lithium's intoxication). Globally, these drugs are not recommended in lithium treated patients, due to high risk for psychiatric unbalance[3,4,6].

However, there are several alternatives to diuretics for anti-hypertension effect, despite the evidence being based mostly on case-control and in class effect extrapolation. The angiotensin converting enzyme (ACE) inhibitors are not recommended because they lead to rises in lithium levels, the same being assumed for angiotensin II receptor antagonists. Calcium channel blockers – most cases mentioning verapamil – can increase sensibility to lithium toxic effects, even though decreases in lithium levels are described paradoxically. Despite β-blockers could decrease lithium's clearance, they seem to be safer and are commonly prescribed to treat accessory effects of lithium (as the common use of propranolol for tremor)[1,3,6,5,9,11,13].

So, in the need of a hypotension effect in a patient already medicated with lithium is probably preferable to use a β-blocker (if no contraindication exists). If a diuretic effect is needed, one could use a loop diuretic (like furosemide) or a potassium-sparing diuretic (like amiloride or spironolactone). These can be administrated in a low-dose basis and following the same administration recommendations as for NSAIDs (with a different advised reduction of lithium dose of 25%-50%). Patients medicated with thiazides should suspend these drugs because of the high risk for lithium intoxication[3-6,11].

Conclusions

The majority of NSAIDs promote an increase in lithium levels and some, like Ibuprofen and Naproxen, show great interindividual variability. Acetylsalicylic acid doesn't show evidence of lithium interaction. Diuretics also promote lithium increments, particularly thiazides, which can be explained by their main action in the proximal convoluted tubule, where lithium absorption is higher. Therefore, they should be replaced by loop and K^+-sparing diuretics, despite the limited evidence for these diuretics. Inversely, osmotic and carbonic anhydrase inhibitors lead to a significant decrease of lithium levels. If it is impossible to remove some NSAIDs and diuretics, they should be used in a lower-dose and shorter duration as possible, with lithium dose adjustments and levels' follow-ups. Elderly and multiple co-morbid patients are considered high risk patients.

Despite these recommendations, more studies are needed to properly assess the probability and severity of these interactions, because an important part of evidence is based on few case studies and small clinical trials.

References

1. Rosa AR, Kapczinski F, Oliva R, Stein A, Barros HMT. Monitoramento da adesão ao tratamento com lítio. Rev Psiquiatr Clín. 2006;33(5):249-61.
2. Oruch R, Elderbi MA, Khattab HA, Pryme IF, Lund A. Lithium: a review of pharmacology, clinical uses, and toxicity. Eur J Pharmacol. 2014;740:464-73.
3. Aprahamian I, Sousa RT, Valiengo LCL, Machado-Vieira R, Forlenza OV. Lithium: a review of pharmacology, clinical uses, and toxicity. Rev Psiquiatr Clín. 2014;41(1):9-14.
4. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. Clin Pharmacokinet. 1995;29(3):172-91.
5. Katzung BG, Masters S, Trevor A. Basic and clinical pharmacology. 12th ed. New York: McGraw Hill; 2009.
6. Aronson JK. Meyler's side effects of psychiatric drugs. Oxford, UK: Elsevier; 2009.
7. Kelly CB, Cooper SJ. Toxic elevation of serum lithium concentration by non-steroidal anti-inflammatory drugs. Ulster Med J. 1991;60(2):240-2.
8. Tonkin AL, Wing LMH. Interactions of non-steroidal anti-inflammatory drugs. Baillieres Clin Rheumatol. 1988;2(2):455-83.
9. Infarmed. Prontuário Terapêutico – 11. Infarmed; 2012.
10. Dale M, Haylett D. Rang & Dale's Pharmacology. 7th ed. Edinburgh: Elsevier/Churchill Livingstone; 2011.
11. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 12th ed. London: Wiley-Blackwell; 2015.
12. Monji A, Maekawa T, Miura T, Nishi D, Horikawa H, Nakagawa Y, et al. Interactions between lithium and non-steroidal antiinflammatory drugs. Clin Neuropharmacol. 2002;25(5):241-2.
13. Mozayani A, Raymon LP. Handbook of drug interactions: a clinical and forensic guide. New York: Humana Press; 2004.
14. Ragheb M. The clinical significance of lithium-nonsteroidal anti-inflammatory drug interactions. J Clin Psychopharmacol. 1990;10(5):350-4.
15. Laville M. Loop diuretics and angiotensin-converting enzyme inhibitors increased risk for hospitalization for lithium toxicity. ACP J Club. 2005;142(1):25.
16. Berkowitz HL. Thiazide diuretics and lithium levels. J Clin Psychiatry. 2001;62(1):57.
17. Phelan KM, Mosholder AD, Lu S. Lithium interaction with the cyclo-oxygenase 2 inhibitors rofecoxib and celecoxib and other nonsteroidal anti-inflammatory drugs. J Clin Psychiatry. 2003;64(11):1328-34.
18. Danion JM, Schmidt M, Welsch M, Imbs JL, Singer L. [Interaction between non-steroidal anti-inflammatory agents and lithium salts]. Encephale. 1987;13(4):255-60.

Evidence-based psychotherapy for treatment of anorexia nervosa in children and adolescents: systematic review

Felipe Alckmin-Carvalho[1,2], Juliana Bergamo Vega[1], Alicia Weisz Cobelo[1], Alessandra Donzelli Fabbri[1], Vanessa Dentzien Pinzon[1], Márcia Helena da Silva Melo[2]

[1] *Eating Disorders Outpatient and Inpatient Program, Child and Adolescent Psychiatry Division (PROTAD/SEPIA), Department of Psychiatry, Institute of Psychiatry, University of Sao Paulo (USP), São Paulo, SP, Brazil.*
[2] *Clinical Psychology Program, Institute of Psychology, University of Sao Paulo (USP), São Paulo, SP, Brazil.*

Institution where the work was conducted: Clinical Psychology Program, Institute of Psychology, University of Sao Paulo (USP). Eating Disorders Outpatient and Inpatient Program, Child and Adolescent, Institute of Psychiatry, University of Sao Paulo (PROTAD-IPq-HC-FMUSP). Rua Dr. Ovídio Pires de Campos, 785. Zip: 05403-903 – Cerqueira César São Paulo, SP, Brazil.

Received: 07/13/2017 – **Accepted:** 02/20/2018
DOI: 10.1590/0101-60830000000154

Alckmin-Carvalho F et al. / Arch Clin Psychiatry. 2018;45(2):41-8

Abstract

Background: Efficacy studies on the treatment of anorexia nervosa (AN) in childhood and adolescence are scarce and systematic reviews are almost non-existent. **Objective:** Systematic review of the literature regarding the modalities of psychological intervention based on evidence used in the treatment of AN in childhood and adolescence. **Methods:** The research was carried out in the databases: PubMed, PsycINFO and Cochrane, using the combined keywords: anorexia nervosa and evidence-based therapy. Articles published between 1990 and 2015 were assessed. **Results:** Of the 139 eligible articles, 14 were selected, of which 10 (71.4%) were conducted in the United States and England. The sample ranged from 9 to 167 participants. Randomized Clinical Trial represented the most frequent design (n = 9; 63.4%), with more than half of the interventions structured in 20 or more sessions (n = 9, 64.3%). Nine types of treatments were tested, with the most tested being Family-Based Treatment (FBT) (n = 7; 50%). Interventions involving the family seem to be more effective, however, the rates for complete remission are modest. **Discussion:** Although evidence of efficacy was verified in the treatments analyzed, the limited number of studies, the various methodological limitations and the methodological heterogeneity between studies make the findings inconclusive.
Keywords: Anorexia nervosa, treatment, adolescence, systematic review, evidence-based psychotherapy.

Introduction

Anorexia nervosa (AN) is an eating disorder often initiated in adolescence, which causes severe disturbances to the eating behavior, resulting in damages that compromise the physical health and the psychosocial functioning of the individual[1]. Its diagnostic criteria are: restriction of caloric intake, which leads to a body mass index lower than the normal minimum expected in terms of age, gender, developmental trajectory and physical health; intense fear of gaining weight, resulting in persistent behavior aimed at weight and body shape control and disturbances in the manner in which weight or body shape is interpreted[1]. Despite the AN prevalence rate being relatively low, ranging from 0.3% to 1%[2,3], the functional and physiological impairments associated with this condition are pervasive. In addition, the mortality rates due to malnutrition and suicide are the highest among all psychiatric disorders[4-6]. Whereby, early psychosocial interventions during adolescence are associated with a positive prognostic impact, by reducing damage and preventing chronic disease[7-9]. The use of proven effective treatments by the respective health care professionals, is therefore fundamental. However, due to the complex interaction of clinical and psychiatric problems, with emphasis on the ambivalent attitudes of patients and their families towards treatment[8,10], there are significant obstacles that moderate the effectiveness of psychotherapeutic interventions and contribute to a limited number of studies in the area[11,12].

Some controlled studies suggest that family-based approaches produce more satisfactory results when compared to individual therapies, among adolescents with AN[13-15]. However, a systematic review with meta-analysis[16] found that at the end of family-based treatment (FBT)[15] no improvement was shown in comparison with the outcome of the individual intervention ($Z = 1.62$, $p = 0.11$). The same study pointed out that the family approach was significantly superior to that of the individual treatment at follow-up ($Z = 2.94$, $p < 0.003$).

Another systematic review conducted in 2005 on the treatment of AN in childhood and adolescence only found five available randomized controlled trials (RCTs)[11]. The analysis of the results of these RCTs showed an intermediate or good outcome[17] ranging from 47%[18] to 90%[19] among participants submitted to family-based treatment (adolescent and family members together) and between 18% and 90% for individual treatment or those involving adolescents and families, separately. Although there is scientific evidence regarding the efficacy of these interventions, the wide variation of the results makes the findings inconclusive.

Despite there being a consensus that AN is associated with high morbidity and mortality rates[4-6], especially when the onset occurs in childhood and adolescence, clinical trials on the subject in young people are scarce, and systematic reviews are almost non-existent. The purpose of this review is to describe the evidence-based psychological interventions in the literature for the treatment of AN in childhood and adolescence. The findings of this study may help specialists to use effective therapies in the treatment of their young AN patients.

Methods

This is a systematic review of the literature, based on the recommendations described by PRISMA[21]. This bibliographic research was carried out in the second semester of 2016, in the databases PubMed, PsycINFO and Cochrane. The following search terms were used in combination: *anorexia nervosa* and *evidence-based therapy*.

In PubMed, each of the search terms were placed, in a separate row on the *Advanced Research* tab, with the option *Any Field* selected along with "AND" being selected between the terms. In the article filter, under the *Article Types* option, the *Randomized Controlled Trial* option was selected. On the *publication date* tab, the period from 1990 to 2015 was selected. On the *ages* tab, the following ages were selected: *Child: 6-12 years and Adolescent: 13-18 years.*

Address for correspondence: Felipe Alckmin-Carvalho. Institute of Psychology of the Universidade de São Paulo, Department of Clinical Psychology. Av. Professor Mello Moraes, 1721, Cidade Universitária, Building F, Room 19 – 05508-030 – São Paulo, SP, Brazil. Telephone: (11) 3091-1961. E-mail: felipealckminc@gmail.com

In PsycINFO, each of the search terms were placed, in a separate row on the Advanced Research tab, with the option Any Field selected along with "AND" being selected between the terms. In the article filter, under the *Methodology* tab, the following study designs were selected: *Treatment Outcome/Clinical Trial*. On the *age* tab, *Adolescence* (13-17 yrs) and *School Age* (6-12 yrs) were selected. In Cochrane the same criteria were used.

The following inclusion criteria were established: articles published between 1990 and 2015; Evidence-based psychological treatment for children and adolescents with a mean age of less than 18 years, exclusive psychological treatment of Anorexia Nervosa (DSM-III, IV or V, depending on the time of publication), treated in outpatient or inpatient units. The following exclusion criteria were adopted: meta-analysis articles, systematic review studies, studies in which the aim involved the development of instruments for the assessment of signs and symptoms of eating disorders, studies involving pharmacological treatment or psychological treatment of other eating disorders.

Bibliographical research was independently performed by two specialists in eating disorders, both with master's degrees, based on the same procedure, to compare the results obtained by each other. In case of disagreement, a third master's degree level researcher refereed in regards to the pertinence of being included in the study.

The categories used to analyze the articles were: study nationality, year of publication, objectives, number of participants, mean age, theoretical perspective, number of intervention sessions, study design, instruments used to assess food symptoms and the family variables, end-of-treatment/follow-up results and methodological limitations.

Results

Of the 139 articles identified, 14 (10%) met the inclusion and exclusion criteria. Figure 1 shows the number of articles identified, selected and analyzed in each of the databases consulted.

Table 1 describes the studies that tested the psychotherapeutic interventions for AN in childhood and adolescence.

Country of study origin and year of publication

A greater predominance of studies in the United States (n = 7; 50%) and in England (n = 3; 21.4%) was observed. Only one article (7.1%) was published in Brazil[22]. No study was found in other Latin American countries. Nor were studies found that were conducted in Asia or Africa. Dividing the period of 1990 and 2015 in two (1990-2002 *vs.* 2003-2015) there is a concentration of publications between 2003 and 2015 (n = 10; 71.4%).

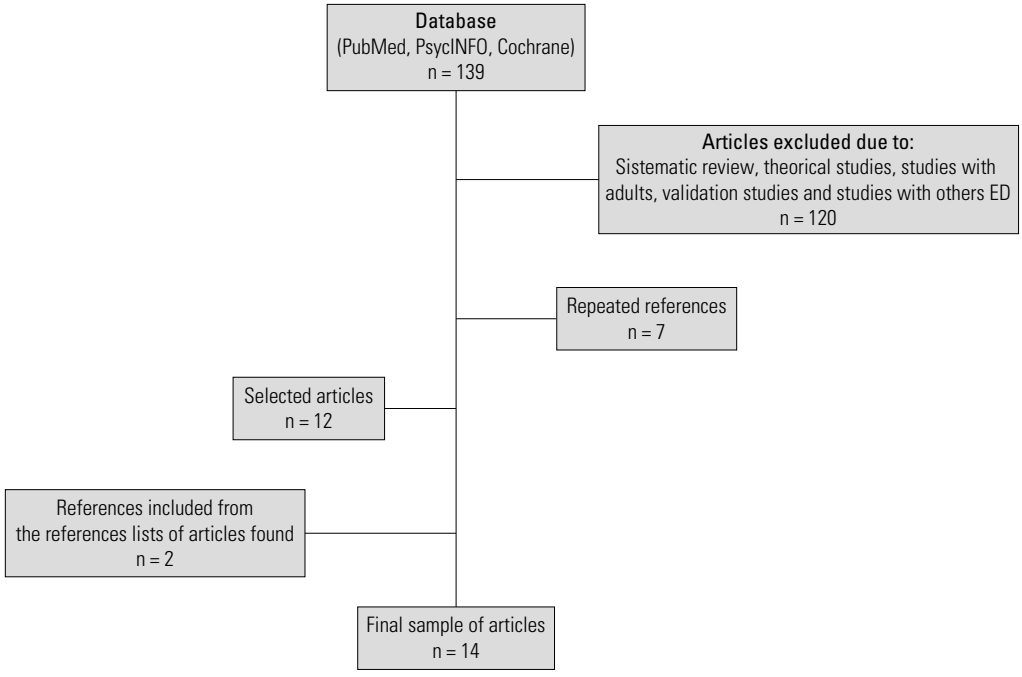

Figure 1. Flowchart of the bibliographic research.

Table 1. Description of the studies' characteristics (n = 14)

Authors/ Country	Objective	N	Age	Theoretical perspective	Design	Sessions	Instruments	Results	
								End of treament	Follow-up
Le Grange *et al.* (1992)[20] (England)	To assess the effects of two modalities of family therapy: CFT and SFT for adolescents with AN in outpatient treatment.	18	15.33 (SD = 1.81)	CFT *vs.* SFT	RCT	9	MRAOS, EAT, RSE, SCFI, FACES-III	Of the 18 participants, 12 (67%) had a good/intermediate outcome, considering both treatments together, and 6 (33%), had a poor outcome. Both treatments showed improvement in terms of weight gain and relief of psychological symptoms, with no differences between groups ($p > 0.05$).	Period: Two years after baseline. Result: There were no changes.

Authors/ Country	Objective	N	Age	Theoretical perspective	Design	Sessions	Instruments	Results	
								End of treament	Follow-up
Robin *et al.* (1994)[29] (United States)	Assess the impact on family relations for BFST vs. EOIT.	22	BFST: 14.7, (SD = 2.7) EOIT: (13.9) SD = 2.1)	BFST *vs.* EOIT (Current name: ASF)	RCT	48	PARQ OFC	55% of the BFST participants and 46% of the IOTR participants recovered in terms of weight and menstruation ($p > 0.05$). Descriptive analysis indicates better results from BFST.	Period: 12 months. Results: 82% of the BFST participants and 50% of the IOTR participants recovered in terms of weight and menstruation ($p > 0.05$).
Robin *et al.* (1999)[30] (United States)	To compare the effectiveness of BFST *vs.* EOIT in the treatment of adolescents with AN.	37	11-20 years	BFST *vs.* EOIT (Current name: ASF)	RCT	40	EAT, EDI, MFPS, BDI YSR, CBCL, PARQ	52.6% of BFST patients and 41.2% of patients in the EOIT group reached a 50th percentile in terms of weight ($p > 0.05$). 94% of the BFST group and 64% of the EOIT group were menstruating regularly ($p < 0.05$).	Period: 12 months. Results: 66.7% of the BFST group and 68.8% of the EOIT group reached the 50th percentile of weight ($p > 0.05$). 92.9% of the girls undergoing BFST and 80% of the EOIT group were menstruating regularly ($p > 0.05$).
Eisler *et al.* (2000)[18] (England)	To assess and compare the efficacy of two psychological interventions for AN: CFT vs. SFT.	40	15.5 SD = 1.6	CFT *vs.* SFT	RCT	15-16	SMFQ, RSE, EAT, EDI, MOCI, FACES III, SCFI	CFT: 5 (26.3%) patients had a good outcome, 4 (21%) intermediate and 10 (52.7%) were poor. SFT: 10 (47.6%) patients had a good outcome, 6 (28.5%) intermediate and 5 (23.8%) were poor. There were no differences between groups ($p > 0.05$).	Did not exist.
Ball & Mitchell (2004)[25] (Australia)	To compare CBT with BFT in the treatment of adolescents with AN.	25	CBT: 18.45 (SD = 2.57) BFT: 17.58 (SD = 3.37)	CBT *vs.* BFT	RCT	21-25	MRS, EDE, ABOS, EDI, BDI, STAI-YI	69.2% of CBT participants completed treatment vs. 75% undergoing BFT. 77.8% of those who completed CBT and BFT treatment, had a "good" or "intermediate" outcome ($p < 0.05$).	Period: 6 months There were no changes.
Lock *et al.* (2005)[27] (United States)	To assess the effects of short term (ST) and long term (LT) of FTB in the treatment of adolescents with AN.	86	15.2 (SD = 1.7)	FBT	RCT	ST: 10 LT: 20	YSR, CBCL, EDE, K-SADS, YBC-ED, FES	There were no differences in primary outcomes (BMI and EDE) in the ST and LT interventions ($p > 0.05$). The indicators of internalizing behavioral problems (CBCL) and the subscale for eating behavior (EDE) were lower in the participants undergoing LT intervention.	Did not exist.
Gowers *et al.* (2007)[28] (England)	To assess the effectiveness of three treatment modalities for AN available in the British healthcare system: CAMHS vs. hospitalization in psychiatric ward vs. outpatient specialty care.	167	12-18 years	CBT and FBT	RCT	20-24	EDI, MRAOS, HoNOSCA, FAD, MFQ	CAMHS: 10 (18.2%) had a good results, 31 (56%) intermediate and 13 (24%) were poor. Specialized outpatient clinic: 8 (15%) had a good outcome, 22 (40%) intermediate and 24 (44%) were poor. Inpatient ward: 12 (21%) had a good results, 18 (32%) intermediate and 26 (46%) were poor.	Period: 2 years after baseline. Results: CAMHS 20 (36%) had a good outcome, 20 (36%) intermediate and 14 (26%) were poor. Specialized outpatient clinic: 13 (24%) had a good outcome, 28 (51%) intermediate and 12 (22%) were poor. Inpatient ward: 19 (33%) good, 17 (30%) intermediate and 17 (30%) were poor.
Paulson-Karlsson *et al.* (2009)[12] (Sweden)	To assess the effects of FTS + CFT for adolescents with AN undergoing outpatient treatment.	32	15.4 (SD = 1.4)	SFT + CFT	Open Trial	20-25	RAB, EDI, YSR, FSC	No results were reported at the end of treatment.	Period: 36 months. Results: 25 (78%) of the participants achieved complete remission, with reduction of eating symptoms, internalizing problems and improvement of family situation. No results were reported in terms of good, intermediate or poor outcomes, nor the results at the end of treatment.

Authors/ Country	Objective	N	Age	Theoretical perspective	Design	Sessions	Instruments	Results	
								End of treament	Follow-up
Lock *et al.* (2010)[26] (United States)	To compare the impact of FBT *vs* AFT (former EOIT) on complete remission in the treatment of adolescents with AN.	121	14.4 (DP = 1.6)	FBT *vs.* AFT	RCT	24	EDE, K-SADS	Complete remission in 22.6% undergoing AFT and 41.8% undergoing FBT, ($p > 0.05$).	Period: 12 months. Results: complete remission in 23.2% undergoing AFT and 49.3% undergoing FBT ($p < 0.05$).
Turkiewicz *et al.* (2010)[22] (Brazil)	To assess the viability, acceptance and efficacy of FBT for AN in adolescents in Brazil.	9	14.64 (DP = 1.63)	FBT	Open Trial	10-12	EDE-Q CGAS	7 (78%) completed the treatment. Six (86%) re-established the target weight, 4 (44%) returned to menstruating regularly. There was no statistically significant reduction in the EDE-Q or CGAS scores.	Period: 6 months. Results: 7 (100%) were assessed. They all regained their weight and returned to menstruating regularly. There was improvement in CGAS ($p < 0.05$), but not in the EDE-Q.
Dalle-Grave *et al.* (2013)[23] (Italy)	To assess the effects of the CBT-e intervention in adolescents with AN and to determine if this type of intervention can be an alternative to FBT.	46	15.5 (SD = 1.3)	CBT-e	Open Trial	44	EDE-q GSI	29 (63%) completed treatment, 9 (32%) reestablished 95% of ideal weight and 28 of those who completed treatment (96.6%) reduced symptoms of eating disorders and other psychiatric disorders compared to the baseline of the treatment.	Period: 12 months. Results: 29 (63%) were assessed at follow-up. Of these, 13 (44.8%) reestablished 95% of the ideal weight. Psychiatric symptoms remained stable.
Agras *et al.* (2014)[24] (United States)	*vs*	158	15.3 (SD = 1.8)	FBT *vs.* SyFT	RCT	16	EDE, BDI, RSES, QLES (short form), SAI, CYBOCS YBCEDS	All participants completed both treatment modalities. Remission rate of 33.1% for FBT and 25% for SyFT ($p > 0.05$) in all endpoints, except for the self-esteem scale, in favor of SyFT.	Period: 12 months. Results: 114 (72%) were assessed. Remission of 40.7% for FBT and 39.0% for SyFT ($p > 0.05$). Faster weight gain in the FBT group, and fewer days of hospitalization, which makes intervention less costly.
Timko *et al.* (2015)[9] (United States)	To assess the feasibility, acceptability and effectiveness of ASFT.	47	14.02 (SD = 1.58)	ASFT	Open Trial	20	CEQ, EDE, EDEq, ABOS, famQ, DERS, AFQ-Y and AAQ-2	of the participants who started treatment, 49% had complete remission and 29.8% had partial remission. The proportion of patients who completed treatment with total remission was 67.7% and, with partial remission, 32.3%.	Did not exist.
Accurso *et al.* (2015)[31] (United States)	To compare FBT-based intervention results achieved in a study with a RCT design, of those obtained in a traditional clinical setting (SCC)	84	14.5 (SD = 2.2)	FBT	Mixt (Open Trial + RCT)	18	EDE-12.0, KSADS, BDI	57% of the total participants had reestablished their weight: RCT (62.5%) and SCC (53.8%). There were no differences between groups ($p > 0.05$). Patients with BMI < 81% of expected had better RCT results ($p < 0.05$).	Did not exist.

ASFT: Acceptance-based Separated Family Treatment; ACT: Acceptance and Commitment Therapy; FBT: Family-Based Treatment; RCT: randomized clinical trial; EDE: Eating Disorder Examination, EDE-q: Eating Disorder Examination questionnaire; ABOS: Anoretic Behavior Observation Scale; famQ: Family Questionnaire; DERS: Difficulties in Emotional Regulation Scale; AFQ-Y: Action and Fusion Questionnaire-Youth; AAQ-2: Acceptance and Action Questionnaire; BDI: Beck Depression Inventory; BFST: Behavioral Family Systems Therapy; EOIT: Ego Oriented Individual Therapy; PARq: Parent Adolescent relationship questionnaire; OFC: Observed Family Conflicts; CBT-E: Cognitive Behaviour Therapy Enhanced; GSI: Global Severity Index; CGAS: Children's Global Assessment Scale; SyFT: Systemic Family Therapy; RSES: Rosenberg Self-Esteem Scale; QLES: Quality of Life and Enjoyment Scale (short form); SAI: State-trait Anxiety Inventory; CYBOCS: Child Yale Brown obsessive Compulsive Scale; YBCEDS: Yale Brown Cornell Eating Disorder Scale; EAT: Eating Attitudes Test; EDI: Eating Disorder Inventory; MFPS: Maturity Fears and Perfectionism Scale; YSR: Youth Self Report; CBCL: Child Behavior Checklist; CAMHS: treatment as usual; KSADS: Kiddie Schedule for Affective Disorders and Schizophrenia; CFT: Conjoint Family Therapy; RAB: Rating of Anorexia and Bulimia Nervosa; FSC: The Family Climate self-rating scale; SMFQ: Short Mood and Feeling Questionnaire; MOCI: Maudsley Obsessional Compulsive Index; FACES III: Family Adaptability and Cohesion Evaluation Scale; SCFI: Standardized Clinical Family Intervention; HoNOSCA: Health of the Nation Outcome Scale for Children and Adolescents; FAD: Family Assessment Device; MFQ: Mood and Feeling Questionnaire; FES: Family Environment Scale; MRAOS: Morgan-Russell Average Outcome Scale.

Design

Regarding the study design, four (28.5%) were open trial[9,12,22,23]; nine with RCT design[18,20,24-30] and one (7.1%) had mixed design (open trial + RCT)[31].

Participants

The number of participants in each intervention ranged from nine[22] to 167[28] with a median of 43 and a mean of 63.7 (SD = 51.8). In all studies, the criterion for the diagnosis of AN was DSM-III, IV or V, depending on the time of the study. The age group selected in the studies ranged from 11 to 20 years, with mean age ranging from 13.9 years (SD = 2.1)[29] to 18.45 (SD = 2.57)[25]. Female adolescents represented the majority in all studies.

Objectives

In general, three trends were verified in relation to the objectives of the studies analyzed: (1) to assess the efficacy of recent interventions in open or randomized clinical trials[9,12,22,23]; (2) to compare the efficacy of two different interventions previously tested[24-26,29,30] and (3) to assess the effect of a previously tested intervention, in different doses or contexts such as the comparison of treatment efficacy in the short *vs.* long term or interventions in private clinics *vs* in the context of research[27,28,32].

Assessment instruments

In order to assess the symptoms of AN the Eating Disorder Examination (EDE), questionnaire or structured interview format, was the most used instrument (n = 8; 57.1%), followed by EDI, which was used in five studies (35.7%). For the assessment of the characteristics of family functioning, the instruments most used were: PARq, a self-reported questionnaire that assesses the quality of the bond between adolescents and their parents (n = 3; 21.5%) and FACES III, a self-completion scale that evaluates the level of cohesion and adaptability of the family (n = 2; 14.3%). A large number of other instruments for assessing family functioning were applied: famQ = Family Questionnaire; FSC = The Family Climate self-rating scale; FAD = Family Assessment Device.

Psychotherapy modalities and protocol characteristics

The following interventions were tested: *Family-Based Treatment* (FBT), *Behavioral Family Therapy* (BFST), *Adolescent Focused Individual Therapy* (ASF; former EOIT), *Cognitive Behavior Therapy* (CBT), *Cognitive Behavior Therapy Enhanced* (CBT-e), *Systematic Family Therapy* (SyFT), *Cojoined Family Therapy* (CFT), *Separated Family Treatment* (SFT) and *Acceptance-based Separated Family Treatment* (ASFT). An attempt was also made to combine two different modalities of psychotherapy (SFT+CFT)[12], as well as an attempt to create a new psychotherapy protocol based on the principles of Acceptance and Commitment Therapy (ACT), a new modality of Cognitive-Behavioral Therapy[9].

The duration of the psychotherapy protocol varied from nine[20] to 48 sessions. More than half of the interventions were structured with 20 or more sessions (64.3%). Certain studies had not predetermined the duration of the psychotherapy protocol. The only study that assessed the differences between short and long-term interventions attributed the first classification to the interventions with ten sessions and the second classification to those with 20 consultations. In this study, the researchers did not find differences between the groups in terms of BMI and dietary symptoms following treatment[27].

Efficacy of the treatment

The research protocol most tested was FBT (n = 7; 50%). In general, the studies comparing the efficacy of the interventions did not find statistically significant differences between groups. Of the eight studies comparing the efficacy of interventions, only two (25%) found statistically significant differences between the groups compared[26,30]. In the first, the BFST was found to produce, at the end of treatment, results superior to the AFT (former EOIT) in terms of biological markers. In the second, it was found that, despite the comparison of the end of treatment for FBT *vs.* AFT not producing statistically significant differences, these differences were found in the follow-up period for the cases.

Methodological limitations

Several methodological limitations were identified in the studies assessed: lack of description regarding the inclusion and exclusion criteria[29,30], loss of a significant number of participants (> 25%) during treatment and follow-up[9,24], lack of clarity regarding the remission criteria or remission assessed exclusively on the basis of biological markers[12,25,29-31], difficulty in randomizing baseline participants[26,31], presence of confounding variables, such as the need for hospitalization, the use of antidepressants for the treatment of comorbidities, which were not necessarily controlled in the analyses[18,22,26,27,30,31] and non-probabilistic samples[20,25,29,30]. In only one study no methodological limitations were found[28].

Discussion

The results indicated the lack of published research in the southern hemisphere, with the exception of Brazil and Australia. This is an important gap in evidence-based psychotherapies for the treatment of AN in childhood and adolescence, to the extent that sociocultural differences, especially in Latin American countries[33], such as stronger and more lasting family ties with the family of origin, parenting styles and socio-educational skills may influence patient adherence to treatment and the efficacy of the intervention. The concentration of articles published in the last decade was verified, which indicates that, although in an incipient manner, studies in the field of ED in childhood and adolescence have recently emerged.

Design

In the present review 9 RCTs were found, a number higher than that found in a systematic review conducted for AN treatment in childhood and adolescence, published in 2005, which found only five studies with this design[11]. Although the RCT design is considered to be the gold standard for evaluating the efficacy of treatments, among the studies analyzed, several methodological limitations have decreased the quality of the scientific evidence produced.

Participants

A large variation in sample size was observed, and most of the studies used non-probabilistic samples, possibly justified by the difficulties inherent in the treatment of AN[34] and by the low prevalence compared to other psychiatric disorders, such as major depression and anxiety disorders[1]; In addition to the negation of the disease, avoidance of treatment and the patients' ambivalence towards the desire to improve, since recovery involves weight gain[10]. All these factors imply low adherence to treatment and a high number of participants being lost after treatment and during follow-up.

Girls represented the vast majority in all studies analyzed. However, recent research points to an increase in the number of boys with AN[35-37], which indicates the need to assess their particularities in terms of clinical presentation, history of being overweight, impact of culture and media on eating behavior, as well as gender and sexuality. These variables have been addressed in qualitative studies[38] and in case studies[35], however, to date, there are few clinical trials with samples of children with AN. In this sense, samples composed by boys are recommended for future studies in order to explore their peculiarities and assess the response to treatment, for the purpose of increasing the efficacy of the services offered to this population.

Psychotherapy modalities and protocol characteristics

With the exception of the ASF[26,29,30], with its psychodynamic approach, and the SyFT[24] with its systemic approach, all other studies (n = 10; 71.5%) are based on the principles of Cognitive, Behavioral or Cognitive-Behavioral Therapies (FBT was included in the cognitive-behavioral therapies group because it has the same basic principles in regards to how the selection, maintenance and management of AN is performed).

In Psychodynamic Therapy[26,29,30] it is the patients with AN were considered to present egoic fragilities associated with difficulty with situations of uncontrollability, alexithymia and intolerance to emotional discomfort, in addition to difficulties with individuation and transitioning from childhood to adulthood. They use the eating control and food restriction, whether consciously or unconsciously, to reduce the contact with negative affections. The food restriction may also serve as a way of communicating through the body, unconscious affects that could not be transmitted via language.

The objective of this modality of psychotherapy is to strengthen the adolescent's egoic functions, develop tolerance to negative affects, including partial uncontrollability and the risks associated with adulthood, while training the ability to recognize and communicate positive and negative emotions. At the beginning of the psychotherapy process, behavioral goals are established for reducing food restriction and increasing weight, while these objectives are worked on in parallel with those described previously.

In the studies assessed[26,29,30] the psychodynamic psychotherapy protocol was offered during 32 sessions, 24 of which were made available to the adolescent individually and eight sessions were given to the parents, without the presence of the adolescent, with the objective being to assess the parental egoic functions, approach to parental behaviors that could assist in the process of changing the their child and to update the parents regarding the progress and difficulties of the psychotherapy process.

In Systemic Psychotherapy, AN is considered to be the expression or attempt to solve a family problem rather than an individual one. The therapist assesses the patterns of family beliefs and behaviors, as well as the individuals' communication skills. The objective of this modality of psychotherapy is to produce a new family functioning in which there is no need for one of its members to be chronically ill. There is no specific focus on decreasing behaviors such as food restriction or weight recovery goals. However, when the family spontaneously brings these aspects up, they must be addressed by the psychotherapist.

In the systemic psychotherapy all 16 sessions are performed with the parents and the adolescent with AN together. Siblings or other people who live in the house are invited to participate in the psychotherapy sessions. The presence of all the members allows the clinician to assess the interaction pattern in the therapeutic setting, which is considered to be a sample of the family's daily functioning.

The Cognitive-Behavioral Therapies, although differing in terms of the setting (for example, number of sessions with the adolescent and parents, content covered, session time), have the following aspects in common: (1) psychoeducation about cognitive and behavioral changes associated with AN and training on the recognition and management of these changes by the parents and adolescents; (2) they consider that the adolescent is momentarily unable to choose how he/she will eat, since his/her judgment about the quantity and quality of food is altered and (3) their main objective is to reduce parents' guilt for having a child with AN and their empowerment as protagonists in the feedback process.

Based on these premises, several behaviors/techniques are trained for providing feedback to the child and how to react consistently in case of refusal, excess anger or attempts to circumvent the treatment. After regaining weight, the focus is on its maintenance. When the adolescent reaches a BMI that poses no risk to his or her life, issues relating to adolescence such as autonomy and new challenges, as well as issues regarding family dynamics are addressed. None of the psychotherapy protocols described assessed the efficacy of the treatment group.

Assessment instruments

A significant number of assessment instruments were used to assess the behavioral profile of the patients, their parents and the ED symptoms. An even greater diversity was used to assess family functioning and family characteristics, such as perceived family support, level of autonomy, and degree of differentiation among the members. The wide variety of instruments used to assess the same family variables makes it difficult to compare the studies. In this sense, an attempt to standardize the instruments used in different research sites can be a promising measure; which would allow, in addition to the comparison between results from different samples, the development of meta-analyses.

Efficacy of the treatment

Most studies did not find a statistically significant difference when comparing the different treatment modalities[18,20,25,29,30]. This can be justified by the reduced sample size of most of the studies, resulting in a possible type II error (not finding differences between groups when they exist).

The two studies[26,30] that found significant differences between groups, compared individual treatment, focusing on the adolescent vs treatment of the adolescent and the family members. It was found that the second modality was more promising, which suggests that interventions that include the family in the treatment have a greater reach than those only involving the adolescent. This finding is corroborated by previous studies[13,14,27].

Apparently, in terms of cost-benefit ratio, FBT is superior to the other treatment modalities, as it is associated with faster regaining of weight and, therefore, less days of hospitalization. Even in FBT, the complete remission rates are not encouraging. This finding points to the need to develop and assess the efficacy of new modalities of research protocols in psychotherapy that integrate FBT interventions with the approach for AN maintaining factors associated with family dynamics, which are already established in the literature.

The combining of good and intermediate outcomes without the presentation of the gross numbers was found, along with the creation of alternative remission criteria, and the presentation of only the participants who finished the treatment, rather than presenting the *drop-out* percentage; thus making it difficult to compare the results between the studies assessed. It is noteworthy that the study with the largest sample size and methodological rigor[28] found some of the lowest complete remission rates among those reported: 18.2% in non-specialized health care, 15% in a specialized outpatient clinic and 21% in an inpatient unit.

Methodological limitations

Interventions with non-probabilistic samples may possibly produce a type II error. This occurred in the great majority of the studies analyzed, and therefore, the findings should be assessed with caution. In this sense, multi-site studies are recommended, in which standardized psychotherapy protocols are used, which can be assessed in multi-site studies, increasing the sample-size and the statistical power of the data.

The lack of clarity regarding the remission criteria makes it difficult to compare the results and the remission assessed exclusively on the basis of biological markers impoverishes the analysis, since it does not consider cognitive and behavioral variables. It was observed that studies that included only biological indicators, such as BMI and menstruation, had more favorable results, with a complete remission of 50% and 60% of the patients who started treatment. Studies that included psychopathological indicators, such as treatment outcome presented less favorable results, reaching 25%, as in the study by Agras *et al.*[24].

Based on this finding, it is verified that the challenge of providing feedback to the patients with AN is met with less difficulty than the approach for the respective psychological components. Disregarding the psychological components associated with AN as a primary

outcome partially explains the modest rates for complete remission and the high rates of relapse found in this population[39,40].

Conclusion

Based on the results of this systematic review it was possible to outline the evidence-based studies for the psychotherapeutic treatment of AN in childhood and adolescence. Although the review did meet its objective, it is necessary to list certain limitations that moderate the quality of the scientific evidence produced; whereby the qualitative methodology used in the data extraction reduces the strength of the analyses, since the results were not submitted to inferential statistical analysis. Another possible limitation is related to the wide variety of objectives, treatments, outcomes, instruments in the assessed studies, a characteristic that hinders the conclusions, but which, on the other hand, points to the need for methodological standardization of the clinical trials in the area so that the studies may be compared.

It has been found that the efficacy of evidence-based treatments available for AN in childhood and adolescence is modest. Psychological interventions involving the family seem to have presented better prognoses when compared to interventions aimed exclusively at the children and adolescents. FBT is the most tested psychotherapy protocol, and in comparison with the others, it seems to be the most appropriate modality of treatment for the child-adolescent population. However, given the limited number of studies and various methodological limitations found, it is not possible to make a conclusion on the efficacy of the interventions. This aspect, as already identified in a previous review[11], remains stable and constitutes an important limitation in the field of ED in childhood and adolescence.

Even in the FBT, the treatment modality that appears to present the best evidence on efficacy, the results are only modest, with positive outcomes in approximately half the cases. Thus, there is a need to improve the content of existing psychotherapy protocols, both in the treatment of parents and adolescents, in individual sessions, in an effort to include the topics described in the literature as being crucial in the approach for patients with AN and their families.

Psychological inflexibility and deficits in social-emotional skills have been repeatedly observed in adolescents with AN and their parents. Along the same lines, inappropriate parenting styles and practices have been reported among the parents of these adolescents. However, to date, these variables have seldomly been investigated in clinical trials for this population. Since these deficits are considered to be risk factors for AN selection and maintenance, studies that include training in social-emotional skills, adolescent psychological flexibility and the training of appropriate parenting styles and practices are necessary.

All the clinical trials selected in this review were exclusively for girls or samples composed mostly of girls. Since the prevalence of boys with AN has increased[42], studies to assess the clinical presentation and the respective response to treatment of these patients are important.

Finally, certain methodological precautions are recommended in the development of clinical trials aimed at assessing the efficacy of psychological treatments for AN in childhood and adolescence, such as the standardization of the instruments used for assessing the outcome of AN symptoms and family functioning; the standardization of the remission criteria, which should be based on both physiological indicators and cognitive symptoms and a clear description of the criteria for inclusion and exclusion of participants. Multicenter studies are recommended to produce trials with probabilistic samples in order to increase the internal validity of the studies.

Acknowledgments

This study was carried out with financial support from Capes, case number 33002010039D4, made available as a scholarship at the doctoral level, to the first author.

Conflict of interest

The authors have no conflict of interest related to the topic of this article. The funding agency had no role in the study design or in the decision to submit the paper for publication.

References

1. American Psychiatric Association (APA). Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-5). Porto Alegre: Artmed; 2013.
2. Swanson SA, Crow SJ, Le Grange D, Swendsen J, Merikangas KR. Prevalence and correlates of eating disorders in adolescents. Results from the national comorbidity survey replication adolescent supplement. Arch Gen Psychiatry. 2011;68(7):714-23.
3. Jaite C, Hoffmann F, Glaeske G, Bachmann CJ. Prevalence, comorbidities and outpatient treatment of anorexia and bulimia nervosa in German children and adolescents. Eat Weight Disord. 2013;18(2):157-65.
4. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch Gen Psychiatry. 2011;68(7):724-31.
5. Franko DL, Keshaviah A, Eddy KT, Krishna M, Davis MC, Keel PK, et al. A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. Am J Psychiatry. 2013;170(8):917-25.
6. Button EJ, Chadalavada B, Palmer RL. Mortality and predictors of death in a cohort of patients presenting to an eating disorders service. Int J Eat Disord. 2010;43(5):387-92.
7. Lock J. Evaluation of family treatment models for eating disorders. Curr Opin Psychiatry. 2011;24(4):274-9.
8. Lock J, Le Grange D. Treatment manual for anorexia nervosa: a family-based approach. New York: The Guilford Press; 2015.
9. Timko CA, Zucker NL, Herbert JD, Rodriguez D, Merwin RM. An open trial of Acceptance-based Separated Family Treatment (ASFT) for adolescents with anorexia nervosa. Behav Res Ther. 2015;69:63-74.
10. Medeiros GC, Sampaio DG, Corchs F. Anorexia nervosa, paternalism and clinical practice. Arch Clin Psychiatry. 2014;41(5).
11. le Grange D, Lock J. The dearth of psychological treatment studies for anorexia nervosa. Int J Eat Disord. 2005;37(2):79-91.
12. Paulson-Karlsson G, Engström I, Nevonen L. A pilot study of a family-based treatment for adolescent anorexia nervosa: 18- and 36-month follow-ups. Eat Disord. 2009;17(1):72-88.
13. Fisher CA, Hetrick SE, Rushford N. Family therapy for anorexia nervosa. Cochrane Database Syst Rev. 2010;(4):CD004780.
14. Hay P. A systematic review of evidence for psychological treatments in eating disorders: 2005-2012. Int J Eat Disord. 2013;46(5):462-9.
15. Lock J. An Update on evidence-based psychosocial treatments for eating disorders in children and adolescents. J Clin Child Adolesc Psychol. 2015;44(5):707-21.
16. Couturier J, Kimber M, Szatmari P. Efficacy of family-based treatment for adolescents with eating disorders: a systematic review and meta-analysis. Int J Eat Disord. 2013;46(1):3-11.
17. Morgan HG, Hayward AE. Clinical assessment of anorexia nervosa. The Morgan-Russell outcome assessment schedule. Br J Psychiatry. 1988;152:367-71.
18. Eisler I, Dare C, Hodes M, Russell G, Dodge E, Le Grange D. Family therapy for adolescent anorexia nervosa: the results of a controlled comparison of two family interventions. J Child Psychol Psychiatry. 2000;41(6):727-36.
19. Russell GF, Szmukler GI, Dare C, Eisler I. An evaluation of family therapy in anorexia nervosa and bulimia nervosa. Arch Gen Psychiatry. 1987;44(12):1047-56.
20. Le Grange D, Eisler I, Dare C, Russell GFM. Evaluation of family treatments in adolescent anorexia nervosa: a pilot study. Int J Eat Disord. 1992;12(4):347-57.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
22. Turkiewicz G, Pinzon V, Lock J, Fleitlich-Bilyk B. Feasibility, acceptability, and effectiveness of family-based treatment for adolescent anorexia nervosa: an observational study conducted in Brazil. Rev Bras Psiquiatr. 2010;32(2):169-72.

23. Dalle Grave R, Calugi S, Doll HA, Fairburn CG. Enhanced cognitive behaviour therapy for adolescents with anorexia nervosa: an alternative to family therapy? Behav Res Ther. 2013;51(1):R9-R12.
24. Agras WS, Lock J, Brandt H, Bryson SW, Dodge E, Halmi KA, et al. Comparison of 2 family therapies for adolescent anorexia nervosa: a randomized parallel trial. JAMA Psychiatry. 2014;71(11):1279-86.
25. Ball J, Mitchell P. A randomized controlled study of cognitive behavior therapy and behavioral family therapy for anorexia nervosa patients. Eat Disord. 2004;12(4):303-14.
26. Lock J, Le Grange D, Agras WS, Moye A, Bryson SW, Jo B. Randomized clinical trial comparing family-based treatment with adolescent-focused individual therapy for adolescents with anorexia nervosa. Arch Gen Psychiatry. 2010;67(10):1025-32.
27. Lock J, Agras WS, Bryson S, Kraemer HC. A comparison of short- and long-term family therapy for adolescent anorexia nervosa. J Am Acad Child Adolesc Psychiatry. 2005;44(7):632-9.
28. Gowers SG, Clark A, Roberts C, Griffiths A, Edwards V, Bryan C, et al. Clinical effectiveness of treatments for anorexia nervosa in adolescents: randomised controlled trial. Br J Psychiatry. 2007;191:427-35.
29. Robin AL, Siegel PT, Koepke T, Moye AW, Tice S. Family therapy versus individual therapy for adolescent females with anorexia nervosa. J Dev Behav Pediatr. 1994;15(2):111-6.
30. Robin AL, Siegel PT, Moye AW, Gilroy M, Dennis AB, Sikand A. A controlled comparison of family versus individual therapy for adolescents with anorexia nervosa. J Am Acad Child Adolesc Psychiatry. 1999;38(12):1482-9.
31. Accurso EC, Fitzsimmons-Craft EE, Ciao AC, Le Grange D. From efficacy to effectiveness: comparing outcomes for youth with anorexia nervosa treated in research trials versus clinical care. Behav Res Ther. 2015;65:36-41.
32. Ciao AC, Accurso EC, Fitzsimmons-Craft EE, Lock J, Le Grange D. Family functioning in two treatments for adolescent anorexia nervosa. Int J Eat Disord. 2015;48(1):81-90.
33. Scott P. A família brasileira diante de transformações no cenário histórico global. Rev Anthropológicas. 2005;16(1):217-42.
34. Watson HJ, Bulik CM. Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines and emerging interventions. Psychol Med. 2013;43(12):2477-500.
35. Alckmin-Carvalho F, Melo MHS. Anorexia nervosa na adolescência: avaliação e tratamento sob a perspectiva analítico-comportamental. In: Fonseca FN, Nery LB (Orgs.). Análise comportamental clínica. 2ª ed. Porto Alegre: Artmed. [no prelo]
36. Campbell K, Peebles R. Eating disorders in children and adolescents: state of the art review. Pediatrics. 2014;134(3):582-92.
37. Rosen DS. Identification and management of eating disorders in children and adolescents. Pediatrics. 2010;126(6):1240-53.
38. Räisänen U, Hunt K. The role of gendered constructions of eating disorders in delayed help-seeking in men: a qualitative interview study. BMJ Open. 2014;4(4):e004342.
39. Herzog DB, Dorer DJ, Keel PK, Selwyn SE, Ekeblad ER, Flores AT, et al. Recovery and relapse in anorexia and bulimia nervosa: a 7.5-year follow-up study. J Am Acad Child Adolesc Psychiatry. 1999;38(7):829-37.
40. Keel PK, Dorer DJ, Franko DL, Jackson SC, Herzog DB. Postremission predictors of relapse in women with eating disorders. Am J Psychiatry. 2005;162(12):2263-8.
41. Alckmin-Carvalho F, Cobelo AW, Melo MHS, Zeni R, Pinzon VD. Age and gender changes in children and adolescent patients of a Brazilian eating disorder program. Arch Clin Psychiatry. 2017.;4(2):33-4.

Flashbulb memories for Paris attacks in Korsakoff's syndrome: a case study

Marie-Charlotte Gandolphe[1], Mohamad El Haj[1,2]

[1] Univ. Lille, CNRS, CHU Lille, UMR 9193 – SCALab – Sciences Cognitives et Sciences Affectives, F-59000 Lille, France.
[2] Unité de Gériatrie, Centre Hospitalier de Tourcoing, Tourcoing, France.

Received: 12/27/2017 – **Accepted:** 01/12/2018
DOI: 10.1590/0101-60830000000155

Gandolphe M-C, El Haj M / Arch Clin Psychiatry. 2018;45(2):49-50

Dear Editor,

Flashbulb memories are detailed, vivid and long-lasting autobiographical memories of attributes of the reception context of surprising and emotionally arousing public events[1-5]. We assessed flashbulb memories for the Paris attacks in a participant with Korsakoff's syndrome (KS).

Method

Participant

We recruited a participant with KS (Mr. T), a male, high-school graduates, right-handed, French native-speakers, living in his own homes with his wife and he had been abstinent for two years. Mr. T was 51 years old and had a 10-year-history of worsening alcohol abuse. He was diagnosed with KS based on the DSM-IV-TR criteria for alcohol-induced persistent amnesic disorder. Even though confabulations and anterograde amnesia persisted after the acute phase, Mr. T showed significant cognitive improvement, in addition to a significant change in volition and motivation for self-care.

Flashbulb memory assessment

Flashbulb memory was assessed using a directed interview technique, including questions on event memory, flashbulb memory, vividness, rehearsal, emotion, surprise, novelty and importance (see Annex).

Verification

To control for Mr. T's recall, we contacted his wife who confirmed that, during the Paris attacks, he was at home watching TV. However, the day of week when he first learned about the attacks was Friday and not Saturday.

Discussion

This is the first study to investigate flashbulb memories in KS. Although our participant tried to retrieve information for event memory, his retrieval was prone to distortion. Indeed, the attacks occurred on 13-November-2015 and not in February-2016, they did not occur at a metro station, nor was there a car bomb, as stated by the patient. These findings are important as they provide evidence on confabulations in KS for memory for real-life events, confabulations that have mainly been observed in laboratory studies. However, confabulations were not observed for flashbulb memories as the answers of Mr. T were confirmed by his wife, except for the day of week when he first learned about the attacks. Thus, flashbulb memories seem to trigger some reliable recall for the reception context. This finding is of interest as it may suggest some positive effect of flashbulb memories on context recall, a type of recall that has been found to be particularly affected in KS patients[6-10].

Interestingly, our KS participant attributed high vividness to his recall. He also reported fair rehearsal and described the attacks as very negative. He further associated his recall with fair feelings, especially shock and sadness, as well as with fair surprise, novelty and importance. Hence, flashbulb memories triggered fair subjective reliving in Mr. T., a finding of interest as, to our knowledge, no published study has assessed subjective reliving of autobiographical memory in KS. The same is true for studies on flashbulb memories in KS.

In closing, our study reveals a positive effect of flashbulb memories on recall of reception context of the Paris attacks in a case with KS. It also demonstrates extensive subjective reliving of flashbulb memories in this patient. By doing so, our work opens a window into the retrieval and subjective experience of emotional and consequential real-life events in patients with KS.

Conflict of interest

None.

Annex

Flashbulb memory assessment

Event memory

- On what date (day/month/year) did the attacks occur?
  Mr. T: February 2016.
- At what time did the attacks occur?
  Mr. T: In the evening.
- Where did the attacks occur?
  Mr. T: At a metro station.
- Do you remember anything else about the attacks?
  Mr. T: There was a car bomb.

Flashbulb memory

- Please describe how you first became aware of the attacks (radio, television, friend etc.).
  Mr. T: I was home watching the TV.
- Please describe where you were when you learned about the attacks.
  Mr. T: I was at home.
- Please describe who you were with when you learned about the attacks.
  Mr. T: I was with my wife.
- Please describe what you were doing when you learned about the attacks.
  Mr. T: Watching TV.
- What day of the week was it when you first learned about the attacks?
  Mr. T: Saturday.
- What time was it when you first learned about the attacks?
  Mr. T: In the evening.

Address for correspondence: Mohamad El Haj. Université de Lille 3, Département de Psychologie, Domaine du Pont de Bois BP 60149 59653, Villeneuve d'ascq, France.
E-mail: mohamad.elhaj@univ-lille3.fr

Vividness

- When you think about the moment when you first learned about the attacks, do you see this moment in your mind? (not at all, a little, moderately, quite a bit, extremely)
  Mr. T: Extremely.
- When you think about the moment when you first learned about the attacks, do you hear this moment in your mind? (not at all, a little, moderately, quite a bit, extremely)
  Mr. T: extremely
- When you think about the moment when you first learned about the attacks, do you feel that you are travelling back to the time it happened? (not at all, a little, moderately, quite a bit, extremely)
  Mr. T: Extremely.

Rehearsal

- Since the announcement of the attacks, how closely have you followed the media coverage? (never, once, once a week, many times a week, every day)
  Mr. T: Many times a week.
- Since its announcement, how many times have you thought about the attacks? (never, once, once a week, many times a week, every day)
  Mr. T: Many times a week.
- Since its announcement, how many times have you talked about the attacks? (never, once, once a week, many times a week, every day)
  Mr. T: Once a week.

Emotion

- Generally speaking, how do you evaluate your emotional reaction when you first learned about the attacks? (very negative, negative, neutral, positive, very positive)
  Mr. T: Very negative.
  When you first learned about the attacks, you were:
- (not at all shocked, a little shocked, moderately shocked, quite a bit shocked, very shocked)
  Mr. T: Very shocked.
- (not at all confused, a little confused, moderately confused, quite a bit confused, very confused)
  Mr. T: Quite a bit confused.
- (not at all sad, a little sad, moderately sad, quite a bit sad, very sad)
  Mr. T: Very sad.
- (not at all angry, a little angry, moderately angry, quite a bit angry, very angry)
  Mr. T: A little angry.
- (not at all afraid, a little afraid, moderately afraid, quite a bit afraid, very afraid)
  Mr. T: Not at all afraid.
- (not at all anxious, a little anxious, moderately anxious, quite a bit anxious, very anxious)
  Mr. T: Not at all anxious.
- (not at all insecure, a little insecure, moderately insecure, quite a bit insecure, very insecure)
  Mr. T: Moderately insecure.

Surprise

- When you first learned about the attacks, you were (not at all surprised, a little surprised, moderately surprised, quite a bit surprised, very surprised)
  Mr. T: Very surprised.

Novelty

- According to you, this event is (very unusual, a little unusual, moderately unusual, quite usual, very usual)
  Mr. T: Very unusual.

Importance

- Is this event important to you? (not at all important, a little important, moderately important, quite a bit important, very important)
  Mr. T: Moderately important.
- Is this event important to your family/friends? (not at all important, a little important, moderately important, quite a bit important, very important)
  Mr. T: Moderately important.
- Is this event important to your country? (not at all important, a little important, moderately important, quite a bit important, very important)
  Mr. T: Very important.
- Is this event important to the international community? (not at all important, a little important, moderately important, quite a bit important, very important)
  Mr. T: Very important.

References

1. Brown R, Kulik J. Flashbulb memories. Cognition. 1977;5(1):73-99.
2. Gandolphe MC, El Haj M. Flashbulb memories of the Charlie Hebdo attack. J Psychol Cogn. 2016;1(1):20-8.
3. El Haj M, Gandolphe MC, Wawrziczny E, Antoine P. Flashbulb memories of Paris attacks: Recall of these events and subjective reliving of these memories in a case with Alzheimer disease. Medicine (Baltimore). 2016;95(46):e5448.
4. El Haj M, Gandolphe MC. Flashbulb memories for Paris attacks in an alcohol-abstinent patient. J Syst Integr Neurosci. 2017;3(2):1-5.
5. Gandolphe MC, El Haj M. Flashbulb memories of the Paris attacks. Scand J Psychol. 2017;58(3):199-204.
6. Kessels RP, Kopelman MD. Context memory in Korsakoff's syndrome. Neuropsychol Rev. 2012;22(2):117-31.
7. Brion M, de Timary P, Pitel AL, Maurage P. Source memory in Korsakoff syndrome: disentangling the mechanisms of temporal confusion. Alcohol Clin Exp Res. 2017;41(3):596-607.
8. El Haj M, Nandrino JL, Coello Y, Miller R, Antoine P. Source monitoring in Korsakoff's syndrome: "Did I touch the toothbrush or did I imagine doing so?" Cortex. 2017;91:262-270.
9. El Haj M, Kessels RP, Matton C, Bacquet JE, Urso L, Cool G, et al. Destination memory in Korsakoff's syndrome. Alcohol Clin Exp Res. 2016;40(6):1321-7.
10. Kessels RP, Kortrijk HE, Wester AJ, Nys GM. Confabulation behavior and false memories in Korsakoff's syndrome: role of source memory and executive functioning. Psychiatry Clin Neurosci. 2008;62(2):220-5.

A rare side effect of escitalopram: bilateral peripheral edema

Taha Can Tuman[1], Bengü Tuman[2]

[1] Birecik State Hospital, Department of Psychiatry, Birecik, Şanliurfa, Turkey.
[2] Birecik State Hospital, Department of Dermatology, Birecik, Şanliurfa, Turkey.

Received: 01/11/2018 – **Accepted:** 03/08/2018
DOI: 10.1590/0101-60830000000156

Tuman TC, Tuman B / Arch Clin Psychiatry. 2018;45(2):51-2

Dear Editor,

Escitalopram, S-isomer of sitalopram is well tolerated, rapid onset efficacy and used in the tratment of depression and other psychiatric disorders in elderly[1-3]. Escitalopram is highly serotonin specific and has minimal effect on the reuptake of other neurotransmitters[4]. Insomnia, headache, tremor, nausea, flushing, sweating, diarrhea, sexual dysfunction have been reported to be adverse drug reaction during escitalopram therapy[3,5,6]. In elderly patients, edema is an important health problem. Heart failure, renal failure, malabsorpsion, liver failure, allergic reactions, local inflammation and infections, burns, lymphatic obstruction increased capillary permeability, venous obstruction and drugs can cause peripheral edema[7]. Antihypertensive medications, nonsteroidal anti-inflammatory agents, calcium channel blockers, corticosteroids, hormones, antibiotics, beta blockers and direct vasodilators are drugs that often cause peripheral edema[7,8]. Edema has been reported rarely with psychiatric medications. Pre-marketing trials have reported peripheral edema as an infrequent adverse event which occured less than 1/100[9]. To the best of our knowladge, there are two case reports that edema associated with escitalopram. First, bilateral ankle edema in 69 year-old female patient after one month therapy with escitalopram 30 mg per day, resolved within first week after discontinuation of the drug[10]. In second case, bilateral pedal edema associated with escitalopram 10 mg per day developed 9th day of the treatment and resolved within 10 days after discontinuation of the drug[11]. Here, we report a case of bilateral leg edema on the 7th day of the treatment with escitalopram 10 mg/day and resolved within 12 days after discontinuation of the drug.

Case

A 71-year-old woman was presented with a three months history of lack of energy, loss of interest, hypersomnia, malaise and anxiety. We diagnosed major depression to the patient according to the DSM-IV criteria and we started escitalopram 10 mg/day as an antidepressant medication. She was admitted to dermatology policlinics with bilateral edema on shins on 7th day after escitalopram was started. On dermatological examination, there was swelling on the shins in both legs. Cellulite was not considered. There was no change of skin redness, ulceration and color. Results of renal function tests, thyroid function tests and liver function tests were within the normal limits. Blood electrolyte levels were normal. Echocardiogram and ECG findings were normal. There was no reason that could be found for edema. Escitalopram was reduced and stopped. After discontinuation of escitalopram, edema decreased. After 12 days, patient's legs were back to normal. Naranjo Adverse Drug Reaction Probability Scale was evaluated as 7 points a probable adverse effect associated with escitalopram[12].

Discussion

Edema has been reported during treatment with various antidepressants such as mirtazapine, trazodone, tranylcypromine, phenelzine and isocarboxazid[13-15]. In literature, edema associated with escitalopram reported in two cases[10-11]. In first case, bilateral ankle edema may be associated with high dosage of escitalopram (30 mg per day)[9]. Higher dosages up to 20 mg per day is not recommended by the pharmaceutical industry. In our case bilateral leg edema was developed in therapeutic doses. In first case with a 69-year-old depressed woman had been receiving atenolol and bromozepam for mild hypertension simultaneously with escitalopram[10]. In second case, 71 year-old patient with bilateral pedal edema had been receiving warfarin, bisoprolol and clonazepam simultaneously with escitalopram for atrial fibrillation and paroxysmal supraventricular tachcardia[11]. We know that drugs such as anxiolytics, antihypertensive drugs and beta blockers and comorbid diseases such as atrial fibrillation, hypertension and paroxysmal supraventricular tachcardia may have contributed to the development of peripheral edema in two cases reported in literature[7]. Therefore, these drugs may have contributed to the development of edema directly or via drug interaction in these cases. Unlike, there was no medication simultaneously with escitalopram and comorbid disease in our patient. Therefore, bilateral leg edema may be directly associated with escitalopram and no drug interactions was observed in our patient.

The possible etiology of edema with escitalopram may be due to increase in vascular permeability[8]. It may be an idiosyncratically drug reaction because of the strong serotonergic effects of escitalopram[11].

Peripheral edema, a rare side effect due to escitalopram is reversible. Clinicians should be careful about this side effect because this side effect may occur at therapeutic doses and even if no medication and comorbid disease in patient's history.

Acknowledgments

Informed consent was obtained from the patient.

Individual contributions

All of the authors have participated and contributed to the treatment and follow-up of the patient and in writing the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

References

1. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. CNS Spectr. 2002;7(4 Suppl 1):40-4.
2. Lepola UM, Loft H, Reines EH. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol. 2003;18(4):211-7.
3. Kasper S, de Swart H, Friis Andersen H. Escitalopram in the treatment of depressed elderly patients. Am J Geriatr Psychiatry. 2005;13(10):884-91.
4. Huska MT, Catalano G, Catalano MC. Serotonin syndrome associated with the use of escitalopram. CNS Spectr. 2007;12(4):270-4.
5. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in

Address to correspondence: Taha Can Tuman, MD. Birecik State Hospital, Department of Psychiatry, Birecik, Şanliurfa,, Turkey. Telephone: +905 330481614. E-mail: tahacantuman@hotmail.com

outpatient treatment of major depressive disorder. Int Clin Psychopharmacol. 2005;20(3):131-7.
6. Wade A, Michael Lemming O, Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol. 2002;17(3):95-102.
7. Cho S, Atwood JE. Peripheral edema. Am J Med. 2002;113(7):580-6.
8. Kaizu K, Abe M. Drug induced edema. Nihon Rinsho 2005;63:102-106.
9. Cipralex. Prescribing information. Disponível em: http://cipralex.com/prescribing_information/default.aspx.
10. Masdrakis VG, Oulis P, Kouzoupis AV, Masdrakis GV, Soldatos CR. Bilateral ankle oedema in a patient taking escitalopram. World J Biol Psychiatry. 2009;10(4 Pt 3):939-41.
11. Ravi PB, Ravishankar GM, Andrade C. Bilateral peripheral edema as a rare adverse effect of escitalopram. Indian J Psychiatry. 2014;56(1):97.
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
13. Kutscher EC, Lund BC, Hartman BA. Peripheral edema associated with mirtazapine. Ann Pharmacother. 2001;35(11):1494-5.
14. Barrnett J, Frances A, Kocsis J, Brown R, Mann JJ. Peripheral edema associated with trazodone: a report of ten cases. J Clin Psychopharmacol. 1985;5(3):161-4.
15. Remick RA, Froese C, Keller FD. Common side effects associated with monoamine oxidase inhibitors. Prog Neuropsychopharmacol Biol Psychiatry. 1989;13(3-4):497-504.