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Letters to the editor

Age and gender changes in children and adolescent patients of a Brazilian eating disorder program

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ABSTRACT

Background: International studies have demonstrated an increase in the prevalence of boys and a decrease of patients' age at the beginning of outpatient treatment for eating disorders (ED). **Objective:** To evaluate if these changes are also present in the Brazilian population participating in the PROTAD, a Brazilian ED program, and to discuss its clinical implication for treatment. **Methods:** Cross-sectional study. We evaluated 150 medical records of patients under 18 years diagnosed with ED (DSM IV-TR). Patients were divided into two groups: G1 (2001-2007) (n = 77) and G2 (2008-2014) (n = 73). The girl/boy proportion and the mean age of patients were compared. **Results:** In G1, six boys (7.8%) were admitted (girl/boy proportion: 11.8:1), while in G2, 16 (22%) boys were admitted (girl/boy proportion: 3.5:1) ($p < 0.05$). The mean age in G1 was 15.6 years (SD = 1.7; 95%CI: 15.2-15.9), whereas the mean age in G2 was 14.9 years (SD = 1.9; 95%CI: 14.4-15.3) ($p > 0.05$). **Discussion:** The increase in the number of boys treated for EDs reported in international studies was also found at the PROTAD. Contrary to what has been reported in international studies, the mean age of patients at the PROTAD did not decrease significantly. Gender and sexual orientation issues, clinical presentation, prior overweight history and culture/media impact on boys should be addressed by the healthcare team to increase the therapeutic efficacy.

Alckmin-Carvalho F et al. / Arch Clin Psychiatry. 2017;44(2):33-4

Keywords: Eating disorders, gender, childhood, outpatient treatment, boys.

Introduction

Eating disorders (EDs) often affect young women[1]. Studies from the 1980s and 1990s have indicated a girl/boy proportion of 10-12:1 among patients with ED admitted to outpatient treatment or inpatient unit[2]. However, international studies have shown that the epidemiology of this pathology has changed in the last decades[3-5].

More recently, studies have found an increase in the frequency of ED among boys[3-5]. A study conducted in Australia with a sample of 101 children and adolescents treated in an ED program found that 25% (1:4) of the participants were boys[6]. In terms of the age of patients treated at ED treatment centers, in the United States, a national estimate indicated that, between the years 2005/2006, of the 28,0155 patients, 1,126 (4%) were children under 12 years old, an increase of 119% in child admissions when compared to the years 1999/2000[7]. Madden *et al.*[6] found that of 79 hospitalized patients, 11 (14%) were children under 10 years old, whereas of the 22 patients in outpatient treatment, four (18%) were younger than 10 years old.

Despite the significant number of children and the increased frequency of boys treated at ED programs shown in international studies, there are few studies in Brazil analyzing this trend. The identification of changes in the mean age and gender proportion of patients with ED is important to understand changes in the psychopathology, improve methods of assessment, and provide more focused interventions in this population to increase the effectiveness of the treatment centers. Therefore, the aim of this study was to evaluate if age and gender proportion changes are also present in a Brazilian ED Program, and to discuss its clinical implication for treatment.

Methods

We conducted a cross-sectional study consisting of the analysis of 150 medical records of patients who sought treatment at the "*Programa de Atendimento, Ensino e Pesquisa em Transtornos Alimentares na Infância e Adolescência*" (PROTAD), based on a Brazilian hospital (Institute of Psychiatry, School of Medicine, University of Sao Paulo (IPq-HC-FMUSP). The PROTAD has provided multidisciplinary outpatient and inpatient care for children and adolescents with EDs and their families since November 2001. Its activities are developed at a public institution, and the target population consists of individuals belonging to lower social classes. All the staff members are volunteers. Patients are referred by health care facilities, but mainly, directly via email.

The patients were divided into two groups according to the year of enrollment in the program: G1, from 2001 to 2007, and G2, from 2008 to 2014. The mean age and the number of boys and girls treated in each period were compared. For data collection, we searched sociodemographic questionnaires filled out by the patient's parents/caregivers upon admission to the outpatient treatment.

Participants under 12 years old were classified as children based on the Brazilian Statute of Children and Adolescents (1990). Student's *t* test for independent samples was used to compare the mean age. To determine gender proportion, we used the Z test to investigate the difference between proportions. The statistical analyses were performed using the SPSS software. Patients/caregivers signed an informed consent form. The study was approved by the Research Ethics Committee for studies involving human subjects of the HC-FMUSP, under the protocol number 0800/08.

Results and discussion

Between 2001 and 2014, 167 children and adolescents diagnosed with ED according to the DSM IV-TR criteria were admitted for treatment at the PROTAD[8]. Seventeen (10.1%) patients were excluded from the study because they were participating in research projects that actively sought girls or age-specific

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participants. The final sample consisted of 150 patients, 22 boys (14.7%) and 128 girls (85.3%) (girl/boy proportion: 6.8:1). G1 was composed of 77 patients, six boys (7.8%) and 71 girls (92.2%) (girl/boy proportion: 11.8:1). G2 consisted of 73 patients, 16 boys (22%) and 57 girls (78%) (girl/boy proportion: 3.5:1). There was a statistically significant difference in terms of proportion of boys between G1 and G2 ($Z = -2.44$, $p = 0.01$).

Between 2001 and 2014, the mean age upon admission to treatment ($n = 150$) was 15.2 (SD = 1.8; 95%CI: 14.9-15.4). G1's mean age of patients was 15.6 years (SD = 1.7; 95% CI: 15.2-15.9) and G2's mean age was 14.9 years (SD = 1.9; 95% CI: 14.4-15.3) ($p > 0.05$). There were three children (3.8%) in G1 and seven children (9.6%) in G2 ($p > 0.05$).

Although there are more girls than boys who are admitted and treated, this difference has been decreasing at the PROTAD. The frequency of boys in G2 is similar to the one found by Madden *et al.*[6] (25%), and much higher than those reported by studies from the 1990s, showing a proportion of 10-12:1[2].

It is worth highlighting the implications of the increase in the number of boys admitted to outpatient treatment at younger ages, as boys with ED have specific characteristics and needs[3,4,9-11]. Strother *et al.*[1] pointed out that health professionals should be aware of the differences in boys' weight history, once a history of overweight or prior obesity is more frequent among male patients when compared to girls. A prior history of overweight or obesity may intensify the fear of gaining weight and impair adherence to treatment. It is useful to ensure patients that after breaking the binge/purge/restrict cycle, eating in quantity compatible with their weight, age, and metabolism will not make them obese.

As a method to control weight, male teenagers and young adults tend to exercise in excess, which is associated with the use of steroids and/or growth hormone. This aspect differs substantially from what have been observed among girls, who resort more frequently to induce vomiting and fasting periods, and therefore it should be considered when evaluating boys with ED[1,5].

Clinicians observe that, especially in cases of anorexia nervosa among boys, ED can be expressed as an avoidance response to difficulties related to acceptance of sexual orientation. In such cases, severe malnutrition conditions produce decreasing testosterone levels, resulting in decreased libido and less contact with sexuality issues[1]. Thus, gaining weight during treatment brings back these difficulties that can hamper recovery and must be concomitantly addressed in psychotherapy.

Analyses of advertising campaigns of products developed for men over recent decades have shown more muscular bodies and, at the same time, less body fat percentage. It is important to be attentive, as developed muscles can hide an ED, giving a false idea of health and hindering diagnosis and treatment[1,10].

Our descriptive analysis showed a slight decrease in the mean age of G2 compared to the global mean and to G1. The number of children in G2 is larger than that found in G1 and close to the 4% reported by Zhao and Encinosa[7]. Early age at admission may be associated with earlier onset of the disease and/or early recognition of signs and symptoms by caregivers and health professionals.

Researchers have pointed out that the clinical presentation of children with ED differs substantially from that of adolescent and adult patients in the following aspects: shorter disease duration, fewer symptoms of ED, lower frequency of binge/purge and physical exercises to control weight, faster loss of weight, and increased risk of growth problems[9,11].

In terms of primary prevention, it is necessary to investigate how obesity prevention campaigns based on fatphobia and stigmatization, as well as the media, influence boys to seek muscular and slim bodies, and what is its relationship with the increased number of ED cases among boys. Further studies are necessary to adapt the assessment and diagnosis methods for boys, and to test the effectiveness of treatment offered to the male population, covering specific issues, such as those addressed in this study.

Our results are unparalleled in Brazil, where there are very few studies on ED during childhood or adolescence. Such results help improve our knowledge in this field by demonstrating changes in the profile of outpatients and by discussing the impact of such changes on the treatment. However, such results must be analyzed with caution due to some limitations of the study. In spite of the statistically significant difference between the proportion of boys in G1 and G2, the reduced absolute number of boys in the sample (six and 16), as well as the exclusion of a significant proportion of the sample, initially (10.1%) imply a low statistical power that impairs the internal and external validity of the study. Although most families of patients with ED contact PROTAD directly by email, the increased number of boys in treatment may reflect more severe cases at a tertiary center of care and not necessarily an epidemiologic change of ED.

The changes found in international studies were also found in the population treated at the PROTAD, although only the difference in the girl/boy proportion showed statistically significant difference. Gaining knowledge about the specific characteristics and needs of children and adolescents with ED helps improve specialized public health services. By focusing on the specific needs of this population, we can increase treatment adherence and promote the effectiveness of the interventions.

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Efficacy of single dose antihistamine vs. single dose valerian-hops in subjective sleep measures among war refugees: a comparison trial

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Abstract

Background: Many sedatives and anxiolytics are used in single dose or chronically to aid sleep. Clinically important sedatives include valerian-hops and antihistamines as they are used over the counter and are highly accessible and safe agents. **Objectives:** To evaluate and compare a single dose of chlorpheniramine versus valerian-hops combination in modulating subjective sleep measures in insomniac war refugees. **Methods:** Insomnia among refugees was screened using the Insomnia Severity Index (ISI). Insomniac subjects were randomized to received a single dose valerian-hops (320/80 mg) (n = 65), or chlorpheneramine (4 mg) (n = 50) or placebo (n = 76) two hours prior sleeping. Participants were instructed to complete Leeds Sleep Evaluation Questionnaire (LSEQ), visual analogue scales of anxiety and sedation. Also sleep latency, total hours slept and self-rated improvement were obtained. **Results:** Almost 75% of screened refugees had insomnia. Chlorpheneramine reduced sleep latency and anxiety significantly, however it resulted in poor sleep quality. Valerian-hops group showed marked anxiolysis one hour after dosing, a sleep quality similar to placebo and better than chlorpheneramine, and better alertness compared to placebo. Participants satisfaction was higher with chlorpheneramine and there was no difference in the total hours slept. **Discussion:** Valerian-hops combination may provide better sleep quality than antihistamines.

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Keywords: Valerian, antihistamines, insomnia, refugees.

Introduction

Insomnia is a primary sleep disorder whereby patients have difficulties falling asleep, with maintaining sleep during the night, or with early wakening[1].

It is estimated that more than 30% of the populations of industrialized countries report sleep disturbances[2,3]. Improper sleep has a negative impact on one's health-related quality of life and impairs patients' social, physical and cognitive functioning[4].

According to the 2012 report of the United Nations High Commissioner for Refugees (UNHCR), there were 15.4 million refugees worldwide[5].

Refugees are highly predisposed to developing neurological and psychological disorders such as anxiety, depression and post-traumatic stress disorder[6,7].

Surprisingly, insomnia prevalence and treatment is seldom studied in refugee populations. Two recent studies reported insomnia prevalence of 38% and 44% among displaced people[6,8].

Benzodiazepines and sedating antihistamines are among the most prescribed sedative hypnotics for both chronic use or when needed as a single dose[9].

Although these synthetic medications have proved their efficacy in sleep induction, they are associated with side effects such as dizziness, headache, dependence and tolerance[10,11]. Therefore, alternative therapeutic options such as valerian root have increased in popularity.

Valeriana officinalis is a hardy perennial flowering plant[12]. It is native to Europe and parts of Asia and has been naturalized in North America for commercial use. Valerian root is formulated as tablets or soft gelatin capsules[13] and is typically administered orally to treat mild insomnia and anxiety in combination with hops. It is assumed to activate GABA through Valerenic acid as the active ingredient[13].

Comparative trials between valerian-hops and synthetic sedatives/anxiolytics are rare. One such study compared the efficacy of a valerian-hops combination to that of diphenhydramine in insomnia over 6 weeks. They revealed modest improvement in sleep outcome measurements in both treatment arms[14]. However, no previous studies have compared the efficacy of single doses of valerian-hops to sedating antihistamine in terms of subjective sleep measures.

Therefore, the objective of the current study is to evaluate and compare the effect of a single dose of valerian-hops against a single dose of a widely used antihistamine, chlorpheniramine, when modulating subjective sleep measures among refugees with insomnia. Subjective sleep parameters were evaluated according to Leeds Sleep Evaluation Questionnaire (LSEQ). Other studied parameters were: sleep latency, sleeping hours, sedation, anxiety and self-rated clinical evaluation.

Methods

Study design and outcome measures

Initially, refugees were screened for insomnia clinically and by using the Insomnia Severity Index (ISI). Afterwards, insomniac refugees were randomly assigned to receive a single dose of valerian-hops, chlorpheniramine or a placebo. The outcome measures were difference in sleep quality according to the (LSEQ), anxiety, sedation, sleep latency, actual hours slept and self-rated clinical improvement. Ethical approval was obtained from the institutional review board (IRB) at King Hussain Hospital. Potential participants were provided with details on the study and had to sign a detailed IRB approved consent form prior to participation. Each participant was informed about his/her right to withdraw from the study at any time.

Sample and sampling method

Adult refugees living in two cities in Jordan (Amman and Mafraq) were approached during their visit to the Caritas Medical Centre.

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At the screening phase, refugees with a prior history of psychological or mental illnesses and ones using anxiolytics or antidepressants or any drugs affecting the central nervous system were excluded. Pregnant or lactating females were also excluded.

Intervention

After screening completion, insomniac refugees were asked about their willingness to participate in the trial. Willing participants were randomly assigned to receive a Cirkulin® Valerian-hops combination (320 mg of valerian root dry extract + 80 mg of hop stabile dry extract), chlorpheniramine 4 mg or a placebo. Randomization was performed by sequencing patients entering to the physician by using numbered closed envelopes. The prescribing physicians asked all the participants to take the single dose two-hour prior to their bed time.

Each participant was asked to complete an LSEQ at awakening. Sedation and anxiety visual analogue scales were filled one hour after the dose, after awakening and 24 hours after dose administration. Data collection and entry was performed by independent researchers blind to the interventions.

Sample size calculations

For the purpose to determine the number of participants need in each study groups, statistical G power calculation was used and revealed the need for at least 44 participants in each group; this was based on 0.07 Eta Squared, and power of 0.80. However, the authors decided to include as much as possible participants equal or greater than 44 in each group.

Study instruments

In addition to demographical and clinical details, the Arabic versions of ISI, LSEQ, the anxiety visual analogy scales, the sedation visual analogue scale, and the treatment evaluation were employed.

The ISI was developed by Morin[15] and consists of seven questions with Likert type choices ranging from 0 to 4; a higher score indicates more sleeping problems. The total possible score for each participant ranged from 0 to 28. Based on a previous literature participants, scoring 10 or more were considered to be insomniacs[16]. Prior research utilized the Arabic version of ISI, which was showed to be reliable with an internal consistency of 0.84[17]. In the current study, ISI was showed to have good reliability with a Cronbach's alpha score of 0.89.

The LSEQ was used to assess sleeping patterns among refugees[18]. The scale was self-reporting and consisted of ten 100-mm visual analogue types of questions, which measure four dimensions of sleep: ease of getting to sleep (GTS) three questions, quality of sleep (QOS) two questions, awakening from sleep (AFS) two questions, and behavior following wakefulness (BFW) three questions. Each participant responded by marking each visual analogue line from 0 to 100 mm. The mark position indicated the changes that occur in sleeping; marks closer to the left indicate improvement, closer to the right indicate impairment, and closer to the middle indicates no changes. The LSEQ was translated to the Arabic language using the standardized back translation method, and each factor showed good reliability with Cronbach's alpha scores ranging from 0.90 to 0.94.

In addition to these measures, a visual analogue scale for each anxiety and sedation that ranged from 0 to 10 was used. The higher score indicates higher anxiety and sedation. Moreover, at 24 hours each participant was asked to mention the minutes they needed to sleep, and the hours of sleeping during that night. Additionally, participants were asked for asked for treatment evaluation, which ranged from one to three (1 for no improvement, 2 for slight improvement, and 3 for marked improvement.)

Statistical analysis

All refugees' continuous data included the LSEQ, with sedation, anxiety and insomnia scores showing as normally distributed. SPSS statistical package version 21 was used to analyze the data. Descriptive statistics were used to analyze frequencies and standard deviations, means and differences in insomnia at screening level.

One-way ANOVA was used to examine the differences in the LSEQ, sedation scores, anxiety, time to sleep, and time of sleeping between the three groups (i.e. valerian-hops, chlorpheniramine and placebo). The Kruskal-Wallis test was used to examine the differences between the three groups in each treatment evaluation. The significant level was less than 0.05 for the statistical tests.

Results

A total of 373 were assessed for their eligibility. A total of 111 candidates were excluded. Therefore, two hundred sixty participants were randomized for the three study groups. A total of one hundred ninety participants successfully completed the study and their data were analyzed. Please refer to the flow chart (Figure 1).

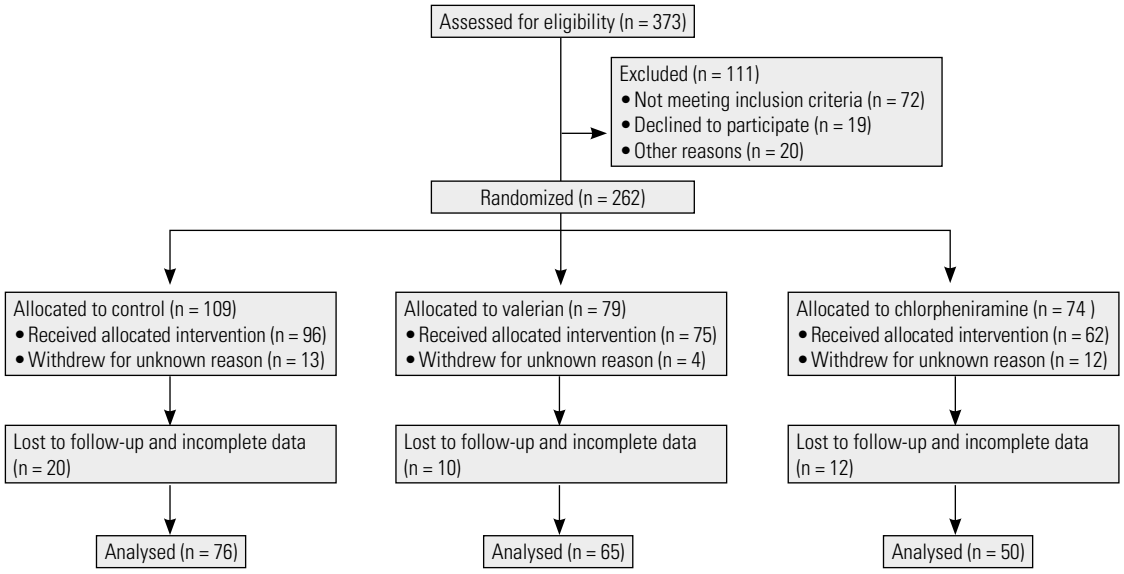

Figure 1. Study flow chart showing participants randomization.

Demographical and clinical details

The mean age of intervention participants was 45.0 (SD = 13.61). As shown in Table 1, the majority of refugees that participated in the study lived in Amman (n = 124, 64.9%), were female (n = 114, 59.7%), married (n = 148, 77.5%), had less than a secondary school education (n = 119, 62.3%), were unemployed (n = 114, 59.7%), had Syrian nationality (n = 131, 68.6%), were non-smokers (n = 113, 59.2%), were not diagnosed previously with any chronic illness namely hypertension, diabetes and cardiac diseases (n = 110, 57.6%), and had medications for chronic illnesses available (anti-hypertensives, oral hypoglycemic agents, etc.) (n = 185, 96.9%).

Table 1. Demographical details of intervention part of study participants

Factors	Categories	Number (percentage)
City	Amman	124 (64.9%)
	Mafraq	67 (35.1%)
Gender	Female	114 (59.7%)
	Male	77 (40.3%)
Marital status	Married	148 (77.5)
	Single	43 (22.5%)
Education level	Less than secondary	119 (62.3%)
	Secondary school or higher	72 (37.7%)
Employment	Yes	161 (84.3%)
	No	30 (15.7%)
Smoking status	Smoker	78 (40.8%)
	Non-smoker	113 (59.2%)
Previous chronic illness (s)	No	110 (57.6%)
	Yes	81 (42.4%)
Medication availability	No	6 (3.1%)
	Yes	185 (96.9%)
Nationality	Syrian	131 (68.6%)
	Iraqi	60 (31.4%)

LSEQ at awakening

As shown in Table 2, the LSEQ was completed at awakening. One-way ANOVA test was used to examine the differences in four factors based on the type of intervention that refugees received.

The ANOVA test showed significant differences in GTS scores between the three groups F (2,189) = 22.64, P = 0.001, QOS scores F (2,189) = 60.19, P = 0.001, AFS F (2,189) = 22.55, P = 0.001, and BFW F (2,189) = 28.52, P = 0.001. The Scheffe *post hoc* test showed that the chlorpheniramine group had a significantly higher score of GTS compared to placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between the placebo and valerian-hops group.

Post hoc showed that there were differences in QOS; the chlorpheniramine group had a significantly higher score of QOS compared to placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between the placebo and valerian-hops groups.

In addition, the chlorpheniramine group had a significantly higher score of AFS compared to placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between the placebo and valerian-hops groups.

Moreover, valerian-hops had a significantly higher score of BFW compared to the placebo group (p = 0.001) and lower scores compared to chlorpheniramine (p = 0.001). In addition, the chlorpheniramine group had a significantly higher score of BFW compared to the placebo group (p = 0.045).

Table 2. Differences in study measures based on the intervention received

Factors	Group	Mean score at 1 hour	Mean score at awakening	Mean score at 24 hours
Leeds (GTS)	Control		4.82	
	Valerian-hops		5.02	
	Chlorpheniramine		6.28	
Leeds (QOS)	Control		4.85	
	Valerian-hops		5.33	
	Chlorpheniramine		6.82	
Leeds (AFS)	Control		4.79	
	Valerian-hops		5.26	
	Chlorpheniramine		6.32	
Leeds (BFW)	Control		4.80	
	Valerian-hops		5.37	
	Chlorpheniramine		6.64	
Sedation	Control	5.25	5.29	5.15
	Valerian-hops	5.18	4.92	4.90
	Chlorpheniramine	5.88	4.98	5.03
Anxiety	Control	5.10	5.01	5.15
	Valerian-hops	4.63	4.76	4.90
	Chlorpheniramine	4.35	4.17	4.62
Sleep latency in minutes	Control		71.83	
	Valerian-hops		64.11	
	Chlorpheniramine		36.08	
Total hours slept	Control		6.80	
	Valerian-hops		6.89	
	Chlorpheniramine		6.58	

Sedation at 1 hour, at awakening and at 24 hours

As shown in Table 2, sedation was measured at 1 hour, after awakening and at 24 hours. One-way ANOVA was performed to examine the differences between the three groups in sedation at one hour, at awakening and at 24 hours.

One-way ANOVA showed that there were significant differences between the three groups in one hour F (2,189) = 25.13, P = 0.001, at awakening F (2,189) = 6.51, P = 0.001 but not in 24 hours F (2,189) = 1.82, P = 0.164.

The *post hoc* test at one hour showed that the chlorpheniramine group had a significantly higher score compared to both placebo (p = 0.001) and valerian-hops (p = 0.001). However, there were no significant differences between valerian-hops and placebo groups at one hour.

Moreover, *post hoc* at awakenings in the placebo group had a significantly higher score compared to both valerian-hops (p = 0.004) and chlorpheniramine groups (p = 0.036). However, there were no significant differences between the valerian-hops and chlorpheniramine group at awakenings.

Anxiety at one hour, at awakening, and at 24 hours

As shown in Table 2, anxiety was measured at 1 hour, at awakenings and at 24 hours. One-way ANOVA was utilized to examine the differences between the three groups' anxiety levels at one hour, at awakenings and at 24 hours.

One-way ANOVA showed that there were significant differences between the three groups in one hour F (2,189) = 8.06, P = 0.001, at awakenings F (2,189) = 10.99, P = 0.001 and at 24 hours F (2,189) = 5.63, P = 0.004.

The *post hoc* test at one hour showed that the placebo group had significantly higher scores compared to both valerian-hops (p = 0.034) and chlorpheniramine groups (p = 0.001). However,

there were no significant differences between the valerian-hops and chlorpheniramine groups at one hour.

Moreover, the *post hoc* test at awakenings in the placebo group had a significantly higher score compared to both the chlorpheniramine (p = 0.001) and valerian-hops groups (p = 0.007). However, there were no significant differences between the valerian and placebo groups at awakenings.

In addition, at 24 hours, the placebo group had a significantly higher score compared to chlorpheniramine (p = 0.004). However there were no significant differences between the Valerian and placebo groups, and between the valerian-hops and chlorpheniramine groups at 24 hours.

Sleep latency and total hours slept

As shown in Table 2, time to sleep and time of sleeping were reported after awakening. For the purpose of examining latency and actual differences in time to sleep in minutes and hours between the three groups, a one-way ANOVA was used. The test showed that there were significant difference between the three groups F (2,189) = 13.11, p = 0.001. The *post hoc* test showed that the placebo group had a significantly higher latency time compared to the chlorpheniramine group (p = 0.001). In addition, the valerian-hops group had longer latency time compared to the chlorpheniramine group (p = 0.001). There was no significant difference between placebo and valerian-hops groups. The results for the time of sleeping differences between the groups showed no significant differences.

Participants' evaluation

As shown in Table 3, each participant in the intervention group was asked to complete a treatment evaluation. There were three options: no improvement, slight improvement and marked improvement.

The Kruskal-Wallis test was used to examine the differences in patients' evaluations. The results indicate that there was a significant difference between them. Between the three groups (Chi square = 12.45, p = 0.002) the higher mean rank was for the chlorpheniramine group (mean rank = 115.62), followed by the valerian-hops group (mean rank = 96.28), and the lowest was for the placebo group (mean rank = 82.86).

Table 3. Treatment evaluation

Group	Participant's self-evaluation		
	No improvement	Slight improvement	Marked improvement
Control	25	50	1
Valarian-hops	22	28	15
Chlorpheniramine	14	13	23
Total number	61	91	39

Discussion

This is the first study that has evaluated and compared the efficacy of valerian-hops and chlorpheniramine among insomniac refugees. Although our results demonstrated that neither valerian-hops nor a chlorpheniramine single dose improved sleep, valerian-hops combination demonstrated a significantly better sleep quality compared to chlorpheniramine.

The efficacy of valerian in improving sleep remains controversial. Previously, some studies have reported improved sleep outcomes with single or multiple doses of valerian[19-21]. On the contrary, our findings are consistent with recent research demonstrating nonsignificant improvement in sleep measures[22,23].

This controversy could be explained by the different study sample, study design, extract type and valerian dose. All previous trials recruited patients with insomnia or healthy volunteers whereas in the current study all participants were recently displaced refugees.

No previous study compared valerian-hops with antihistamine single doses, however, a single study that compared valerian-hops with diphenhydramine demonstrated modest improvements on subjective sleep measures after 6 weeks[24]. Based on our observation that many insomniac subjects use a single dose of sedative/anxiolytics. This is the first study comparing a single dose of valerian-hops combination to antihistamine in improving subjective sleep measures among insomniac refugees.

The anxiolytic and sedative profiles of the two treatments can be explained as follows. Valerian-hops produces an "as needed" anxiolysis that is evident only after one hour compared to the extended anxiolysis and sedative effect of chlorpheniramine. This could be attributed to valerenic acid that is detectable in the serum only within the first hour of administration[25].

This also explains the nonsignificant latency time reduction seen with valerian-hops compared to chlorpheniramine. Moreover, this favorable pharmacokinetic profile prevents residual effects manifested by cognitive and psychomotor side effects with sedating antihistamines.

The study has several weaknesses, as it relied only on subjective sleep measures. Furthermore, the randomization process was not according to standard procedure which could have led to possible bias. Also, the single dose design may not reflect the maximal potential benefit of valerian-hops. A cross-over design was not implemented. Furthermore, refugees are a highly anxiety-prone population, therefore, the results of this study may not be applied to insomniac patients from the normal population. In conclusion, insomnia represents a serious challenge for refugees. Valerian-hops combination revealed better sleep quality than sedating antihistamine. Further studies are needed with multiple dosing design to reveal the potential benefit of this herb among refugees.

Conclusion

Our findings demonstrated that Valerian-hops combination may provide better sleep quality than antihistamines due to its sufficient anxiolytic effect. The study aimed to raise awareness for the need to study over the counter medicines. It may lead to better controlled randomized trials.

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Disclosure

The authors declare no conflict of interest.

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Original article

External validity study of a personality disorders screening test in a community sample

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Abstract

Background: A screening test for personality disorders was recently developed in Brazil, the Dimensional Clinical Personality Inventory – screening version (IDCP-SV). However, no relationship between this screening measure and other scales or external criteria was tested. **Objective:** To seek for validity evidence based on related criteria (*e.g.*, other psychological tests) and external criteria (*e.g.*, sample demographics). **Methods:** Sample comprised 804 participants from São Paulo (Brazil), most female and college students, with mean age equal to 29.65 (SD = 10.73). They answered the IDCP-SV and another screening for personality disorders (IPDS), a depression measure (EBADEP-screening), a scale assessing reasoning for living (EMVIVER), and a self-report for personality disorders categories assessment (SCID-II-PQ). **Results:** IDCP-SV identified 46.4% of community sample as positive for personality disorders. The positive group showed the great mean for almost all comparisions, including psychological tests and the demographics characteristics, including large expressive effect sizes. **Discussion:** Data suggest that the IDCP-SV discriminates a similar percentage of people from the community to what was reported previously using other screening measures; besides, the mean comparisons between groups showed good discriminative capacity by IDCP-SV items.

Carvalho LF et al. / Arch Clin Psychiatry. 2017;44(2):40-4

Keywords: Screening measure, personality test, diagnosis, personality disorders.

Introduction

Personality disorders (PDs) are characterized as persistent and maladaptive patterns of thoughts, feelings, perceptions, and behaviors, deviant from the expectations of the sociocultural group of belonging[1,2]. PDs' prevalence in the general population (US) is from 5 to 10%[3], with a mean of 13% in Western countries[4], and even greater numbers in North and South America[5]. They are linked to clinical diseases, difficulties in adhering to treatment, bad prognoses, risk suicide, and mortality[3,6-11].

Despite the empirical correlations between PDs and harmful outcomes, data indicate that these conditions are underdiagnosed[4,11,12]. Among several factors, greater familiarity of professionals with other psychiatric disorders and limitations on the diagnosis of PDs are possible explanations[4,13]. In Brazil, where the present research took place, the lack of studies in the field and the tiny number of adapted or developed psychiatric and psychological exams for the assessment of personality disorders are indicators of potential underdiagnosis or even poorly stablishment of diagnosis.

The low number of personality assessment tools for PDs in Brasil is real for both, diagnostic and screening tests (*e.g.*, Carvalho *et al.*[14]), but also reflecting problems encountered at an international level (*e.g.*, Tyrer *et al.*[11]; Olssøn *et al.*[15]). The availability of screening tools for PDs are importante for a number of factors[4,16], including help in the PDs diagnosis and lower costs of this process, providing clinicians with a rapid tool of measurement, and allowing investigations in clinical and community samples in relation to PDs occurrence. Not many studies have investigated the occurrence of PDs in community samples, but those who investigated found frequency above 40%, as 44% using the final best-estimate consensus from the IIP Personality Disorder Scales, Iowa Personality Disorder Screen, and Temperament and Character Inventory[17], 54.4% using the IIP-PD 25 items version[18], and 43% using the International Personality Disorder Examination – Screen[19]. Schöttke *et al.*[20] did not present percentages, but considering the cutoff proposed in the study (*i.e.*, > 4) for the Personality Disorder Screening – Short Version (PSS-K) and the mean and standard deviation of the community sample (F = 3.92; SD = 2.8), one can assume occurrences exceeding 40% for personality disorders in the sample sample. We could not find published studies in Brazil concerning screenings tests for PDs.

Recently, a screening test for personality disorders developed in Brazil was proposed[21]. The Dimensional Clinical Personality Inventory (IDCP) screening version (SV) was builded using the full version IDCP items[22] as a starting point. Multiple regression analyzes and item level comparisions were made for items set final composition following a similar empirical approach based on criteria[23] as the one adopted in the development of the Minnesota Multiphasic Personality Inventory (MMPI). Seeking to determine the ideal cutoff for the IDCP-SV, authors applyed the ROC curve reaching a sensitivity equal to 89.5% and a specificity of 67.2%.

The study of Carvalho *et al.*[21] described step by step the development process and diagnostic accuracy indicators of IDCP-SV. However, no relationship between screening measure and other scales or external criteria was tested. As testing for consentaneity of a measure with other variables is a welcome indication of the test score validity[24], in the present study we seek for validity evidence based on related criteria (*e.g.*, other psychological tests) and external criteria (*e.g.*, sample demographics).

Methods

Sample

Using a cross-sectional design, a convenience sample from community was recruited. The total sample comprised 804 participants from São Paulo State, Brazil, most of whom were caucasian (64.9%), female (65.4%), not living in a marital relationship (66%), college students (83%; varying from complete high school to postgraduate). Age ranged from 18 to 69 (M = 29.65; SD = 10.73), and 60.3% reported having attended to psychotherapy and 14.8% reported have attended to psychiatric treatment.

Instruments

Dimensional Clinical Personality Inventory – Screening Version (IDCP-SV[21])

The IDCP-SV was developed based on the full version of IDCP[22], test for measurement of pathological personality traits.

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The instrument aims to conduct personality disorder screening, and consists of 15 items arranged in a Likert 4-point scale, where 1 equals "has nothing to do with me" and 4 "all about me". It is an integrative part of the IDCP-SV's instructions to respond to socio-demographic questions, which were used for analysis in this research. We tested for the Cronbach's alpha internal consistency reliability of IDCP-SV, that was equal to 0.83.

Iowa Personality Disorder Screen[25]

IPDS consists of 11 items, some containing two questions, refering to the diagnostic criteria for personality disorders. The items are answered on a dichotomous scale, yes (1) or not (0). In the case of items containing two questions, the item is scored 1 when both questions are answered with "yes". The authors present data suggesting psychometric adequacy of IPDS, which is corroborated by other studies (*e.g.*, Germans *et al*.[4]). In the present study, Cronbach's alpha internal consistency reliability of IPDS was 0.77.

Baptista Depression Scale – Screening Version (EBADEP-screening[26]*)*

The EBADEP-screening was developed based on the adult version of EBADEP (EBADEP-A[27]), and aims to track symptoms of depression. In the short version of EBADEP-A were selected 15 items, with the descriptors most commonly used in psychiatric manuals (core symptons), *i.e.,* items related to the sad mood, anhedonia, guilt, fatigue, concentration, suicidal ideation and sleep. In the development study, EBADEP-screening was able to discriminate 40 patients diagnosed with depression by SCID-I 40 people without depression with sensitivity equal to 95.0 and specificity of 87.5. In this research, Cronbach's alpha internal consistency reliability of EBADEP-screening was 0.88.

Reasons for Living Scale (EMVIVER[28]*)*

The EMVIVER is a scale developed in order to predict protective factors of risk behavior for life. The instrument has 55 items that show reasons for living divided into three categories: meaningful relationships; attraction for life; plans for the future; and virtues. The EMVIVER has satisfactory psychometric properties evaluated in previous studies[28]. Cronbach's alpha internal consistency reliability of EMVIVER was 0.94.

Structured Clinical Interview for DSM-IV Personality Questionnaire[29]

SCID-PQ-II was developed to assess the 10 personality disorders of DSM-IV Axis II, besides the two personality disorders not included (depressive, passive-aggressive). The instrument is a self-report, consisting of 119 items that should be answered with yes or no. Psychometric properties demonstrated adequacy in the development study. Cronbach's alpha internal consistency reliability of SCID-II-PQ was higher than or equal to 0.60 for some of the scales but varied from 0.06 to 0.52 for obsessive-compulsive, passive-aggressive, paranoid, schizotypal, schizoid, histrionic and narcissist.

Procedures and statistical analysis

This study was approved by an ethics committee. Following approval the data collection was conducted online (n = 546) and live (n = 256), the latter case in particular universities. All subjects read and agree to the Terms of Consent. For data analysis, using the SPSS statistical software, we use the previous cutoffs from the literature for IDCP-SV[21] e para o IPDS[25]. For the interpretation of data, we considered as significant levels equal or less than 0.01, to avoid Type II error. We first presented descriptive statistics, then the group mean comparisions.

Results

Applying the cutoff criteria for dichotomizing, *i.e.*, up to 8 points as negative for PDs and from 9 points as positive for PDs, we found 46.4% as positive. Looking more carefully to the data, we observed a higher rate of people showing score equal to 9 (12.1%), to 7 or 10 (11.3%), to 8 (8.5%), and to 11 (8.3%), presenting 51.1% in total. As the IPDS is also a screening measure, the same procedures were proceed to it, and from the 203 people that responded the test, only 3.9% reached its cutoff, with the higher rate of people at score equal to 1 (32.5%), 0 (23.8%), 2 (18.3%), and 3 (10.3%), representing 85.6% of total.

As we find expressive differences related to people reaching the cutoff in IDCP-SV and IPDS, we verified the correlation btween them, and observed a small to moderate effect size (0.38; $p < 0.001$). The disagreement between the measures, as observed in Figure 1, is located at the high score level of IDCP-SV, ie, there is many people high in IDCP-SV but not in IPDS. In Table 1 comparisons between means are presented, using IDCP-SV classification as criterion for group establishment.

In all cases the IDCP-SV positive group showed the great mean but in Schizoid SCID-II-PQ factor. Together, Schizoid and Antisocial SCID-II-PQ factors were the exception presenting inexpressive effect size, less than 0.20. The highest scores were for depression (total score and almost all factors bur irritability), SCID-II-PQ Cluster C composition, Borderline and Depressive personality disorder factors. Figure 2 helps to observe the main differences between the two groups.

The positive group is clearly distinguished from the negative group on the left side of the figure ($F = 2.795$; $gl = 3.993$; $p = 0.001$); and despite the positive group show almost all means higher than negative group on the right side of the figure, this distinction is a little less obvious, but equally significant ($F = 173.398$; $gl = 4.208$; $p < 0.001$). Table 2 presents again mean comparisons, but now using criteria variables.

All comparisons were significant and the effect sizes were expressive. Current suicide ideation, history of suicide attempt, and participate on both, psychological and psychiatric treatment, were the criteria with the most visible differences between groups.

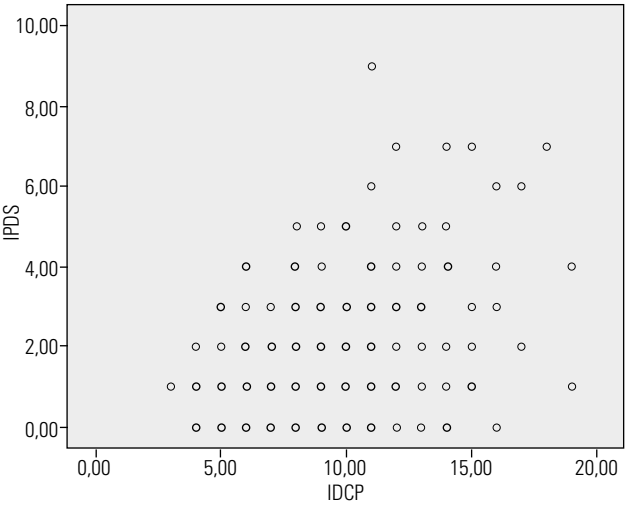

Figure 1. Scatterplot of IDCP and IPDS scores.

Table 1. *t*-test for group comparison in tests based on IDCP-SV classification

Scores	Group	N	M (SD)	*t* (df)	d (p)
IPDS	N	112	1.27 (1.18)	-4.830 (201)	0.68 (< 0.001)
	Y	91	2.38 (2.06)		
EBADEP-screening	N	168	1.66 (0.47)	-9.960 (376)	1.04 (< 0.001)
	Y	204	2.30 (0.71)		
EBADEP humor	N	168	1.75 (0.64)	-7.785 (376)	0.81 (< 0.001)
	Y	205	2.51 (1.12)		
EBADEP somatic	N	169	1.75 (0.59)	-8.328 (376)	0.72 (< 0.001)
	Y	209	2.27 (0.80)		
EBADEP motor	N	169	1.76 (0.87)	-8.087 (376)	0.75 (< 0.001)
	Y	210	2.49 (1.03)		
EBADEP social	N	169	1.63 (0.54)	-7.022 (376)	1.05 (< 0.001)
	Y	209	2.40 (0.84)		
EBADEP cognitive	N	169	1.59 (0.57)	-7.218 (376)	0.85 (< 0.001)
	Y	209	2.18 (0.75)		
EBADEP anxiety	N	169	1.86 (0.83)	-10.136 (376)	0.84 (< 0.001)
	Y	209	2.63 (0.96)		
EBADEP irritability	N	169	1.21 (0.90)	-3.511 (376)	0.36 (0.001)
	Y	210	1.59 (1.12)		
EMVIVER total score	N	109	3.53 (0.34)	4.476 (235)	0.58 (< 0.001)
	Y	128	3.27 (0.52)		
EMVIVER meaningful rel.	N	109	3.47 (0.38)	3.636 (235)	0.49 (< 0.001)
	Y	128	3.24 (0.54)		
EMVIVER attraction life	N	109	3.66 (0.43)	4.285 (235)	0.55 (< 0.001)
	Y	128	3.34 (0.69)		
EMVIVER virtues	N	109	3.47 (0.61)	2.947 (235)	0.38 (< 0.004)
	Y	128	3.21 (0.73)		
SCID Evitative	N	61	2.52 (1,55)	-3.966 (139)	0.68 (< 0.001)
	Y	80	3.71 (1,90)		
SCID Dependence	N	60	2.00 (1.46)	-3.767 (138)	0.64 (< 0.001)
	Y	80	3.08 (1.84)		
SCID Obsessive-compul.	N	59	4.00 (1.85)	-1.228 (139	0.21 (0.22)
	Y	82	4.39 (1.86)		
SCID Passive-aggressive	N	60	2.86 (1.74)	-3.740 (135)	0.65 (< 0.001)
	Y	78	3.92 (1.55)		
SCID Depressive	N	60	2.93 (2.00)	-4.262 (139)	0.73 (< 0.001)
	Y	81	4.34 (1.89)		
SCID Paranoid	N	59	3.08 (2.18)	-1.530 (135)	0.27 (0.13)
	Y	78	3.60 (1.77)		
SCID Schizotypal	N	57	5.59 (2.90)	-3.204 (131)	0.68 (0.002)
	Y	76	7.28 (3.09)		
SCID Schizoid	N	57	2.98 (1.03)	0.485 (134)	0.09 (0.63)
	Y	80	2.87 (1.40)		
SCID Histrionic	N	59	1.52 (1.43)	-1.721 (135)	0.30 (0.09)
	Y	78	2.01 (1.78)		
SCID Narcissistic	N	58	3.89 (2.56)	-1.662 (135)	0.29 (0.10)
	Y	79	4.64 (2.63)		
SCID Borderline	N	57	3.56 (2.69)	-4.512 (137)	0.78 (< 0.001)
	Y	82	6.01 (3.42)		
SCID Antisocial	N	60	1.00 (1.84)	-0.608 (138)	0.10 (0.54)
	Y	82	1.18 (1.77)		
SCID Cluster A	N	55	9.09 (3.44)	-2.346 (127)	0.42 (0.02)
	Y	75	10.58 (3.65)		
SCID Cluster B	N	54	10.29 (6.81)	-3.013 (126)	0.54 (0.003)
	Y	76	14.00 (6.90)		
SCID Cluster C	N	58	14.27 (5.88)	-4.925 (130)	0.86 (< 0.001)
	Y	75	19.39 (5.95)		

N: negative in IDCP-SV; Y: positive in IDCP-SV; EMVIVER meaningful rel.: EMVIVER meaningful relationship; EMVIVER attraction life: EMVIVER attraction for life; SCID Obsessive-compul.: SCID Obsessive-compulsive. For Type II error correction, significance level at 0.01.

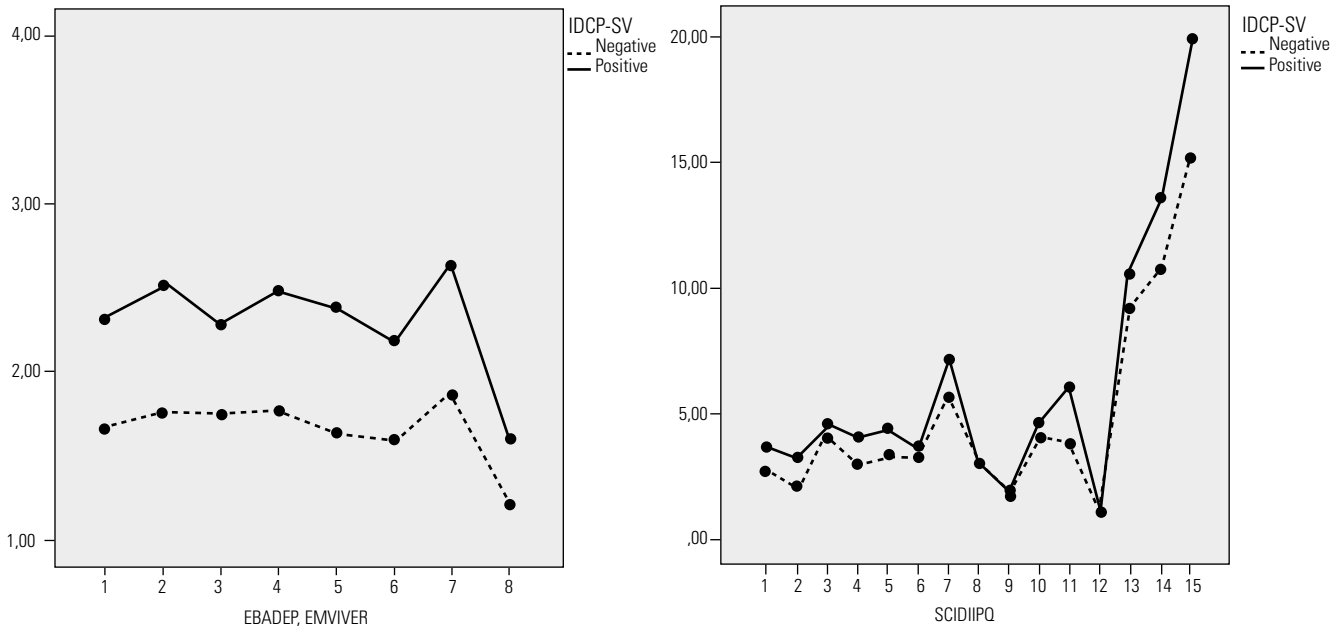

Figure 2. Profile of IDCP-SV groups in administered tests. IPDS scores not included in the figure since it was administered with other part of the sample.

Table 2. *t*-test for group comparison in criteria variables based on IDCP-SV classification

Variables	Groups (N)	M (SD)	*t* (df)	d (p)
Psychological treatment	N (n = 471)	9.09 (3.60)	-6.196 (775)	0.46 (< 0.001)
	Y (n = 306)	10.81 (4.02)		
Psychiatric treatment	N (n = 668)	9.31 (3.59)	-8.443 (770)	0.89 (< 0.001)
	Y (n = 104)	12.60 (4.36)		
Psychological + Psychiatric	N (n = 462)	8.99 (3.48)	-8.581 (556)	0.96 (< 0.001)
	Y (n = 96)	12.47 (4.20)		
Suicide attempt	N (n = 231)	9.70 (3.70)	-5.195 (247)	1.27 (< 0.001)
	Y (n = 18)	14.55 (5.12)		
Suicidal ideation (current)	N (n = 219)	9.30 (3.63)	-3.348 (223)	1.39 (0.001)
	Y (n = 6)	14.33 (3.61)		
Suicidal ideation (past)	N (n = 114)	9.82 (3.61)	-2.966 (133)	0.71 (0.004)
	Y (n = 21)	12.33 (3.26)		

N: negative in IDCP-SV; Y: positive in IDCP-SV; Psychological + Psychiatric: reporting positively to participating on psychological and psychiatric treatment. For Type II error correction, significance level at 0.01.

Discussion

Based on previous research[21] and in the requirement for knowing the strengths and weaknesses of a measure using external criteria[24], this research reports validity evidence based psychological tests and relevant sample characteristics. Data suggest that the screening version of IDCP (IDCP-SV) discriminates a similar percentage of people from the community to what is found in other countries with similar tools for screening of personality disorders. In addition, mean comparisons between groups showed good discriminative capacity by IDCP-SV items.

The proportion of subjects identified as positive by IDCP-SV was higher compared to the expected prevalence in community samples, even considering the data found to America (*e.g.*, Huang *et al.*[5]). This is expected, since screening tests must have high sensitivity and low specificity[17] to ensure that all individuals with particular psychiatric disorder are referred for diagnosis. Compared of the amount of individuals identified by other screening tests for personality disorders, we found very similar data to what is reported in the literature for community samples, ranging from 43% to 54.4%[17,19,20]. This suggests that the IDCP screening version is comparable to screening for personality disorders used in the world, confirming the favorable data found previously[21].

Specifically regarding the observed discrepancy between IDCP-SV and IPDS, it raises questions about whether the IDCP-SV identifies an excessive number of false positives or IPDS identifies an excessive number of false negatives. However, it should be considered that for screening tests, is the most desirable identification of false positives than false negatives. In the study of Morse and Pikonis[17], the authors did not show the percentage of cases identified as positive by the IPDS in the community sample for the score considering the 11 items, but only for subgroups of items, ranging from 17% to 26% cases identified as positive, which is below than observed in the studies with other instruments in community samples and in the study itself, in which consensus was 44% for this sample. The data obtained in the study of Morse and Pikonis seems to be comparable to from the present study in relation to IPDS, since the means obtained are similar ($d = 0.04$; $p = 0.57$). The data suggest that the IPDS for screening in community samples may have lower sensitivity than desired for screening tools, since the percentage of cases identified as positive, are smaller to what has presently found and what is reported in literature. However, future studies should implement an design for comparing the diagnostic accuracy of IDCP-SV and IPDS, also using a gold standard measure.

Furthermore, means comparisons with the different measures (*i.e.*, IPDS, EBADEP, EMVIVER, and diagnostic categories for SCID-II-PQ) pointed to higher scores for the group identified as positive in the IDCP-SV, suggesting that this group tends to have more pathological functioning compared to the group identified as negative. This indicates the discriminative ability of the IDCP-SV for persons with pathological functioning in relation to people with healthier functionings. We observed that the largest discrepancies between groups happened for more general indicators of pathology (*e.g.*, Eaton *et al.*[30]) as the total score of depression and borderline factor of SCID-II-PQ. Along with this, the score on the Cluster C also presented salient difference, which needs to be further investigated, it may reflect a specific tendency of the sample. We also highlight that the groups (positive and negative)

established based on the classification of the IDCP-SV were widely differentiated in criterion variables used, which is highly desirable for measurements with discriminative purpose[24], demonstrating alarming differences for cases of suicide and psychiatric treatment, as would be expected.

The data currently reported must be observed as initial for a Brazilian screening tool for personality disorders. On one hand the data being found with the IDCP-SV seem to be promising, on the other, the limitations of the present research and the need for research with other study designs and samples should be carefully considered. Among the main limitations of this study, is the absence of a clinical sample diagnosed with personality disorders. Another extremely important limitation is the lack of a gold standard measure and the use of other screening tests used worldwide (*e.g.*, IIP-PD). Future studies should seek to embrace these limitations, deepening the knowledge about the applications of IDCP-SV and, equally important, its limitations.

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Efficacy of electroconvulsive therapy augmentation for partial response to clozapine: a pilot randomized ECT – sham controlled trial

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Abstract

Background: Thirty percent of schizophrenia patients are treatment-resistant. **Objective**: This is a single-blinded sham-controlled trial to assess the efficacy of electroconvulsive therapy (ECT) as augmentation strategy in patients with clozapine-resistant schizophrenia. **Methods**: Twenty three subjects were randomly assigned to 12 sessions of ECT (N = 13) or placebo (Sham ECT) (N = 10). The primary outcome was improvement on psychotic symptoms as measured by the mean reduction of the PANSS positive subscale. The assessments were performed by blind raters. **Results:** At baseline both groups were similar, except for negative and total symptoms of the PANSS, which were higher in the Sham group. At the endpoint both groups had a significant decrease from basal score. In the ECT group the PANSS total score decreased 8.78%, from 81.23 to 74.75 (p = 0.042), while the positive subscale had a mean reduction of 19% (19.31 to 16.17, p = 0.006). In the Sham group, the mean reduction of PANSS total score was 15.27% (96.80 to 87.43; p = 0.036), and the PANSS positive subscale decreased 27.81% (22.90 to 19.14, p = 0.008). The CGI score in ECT group decreased 23.0% (5.23 to 4.17; p = 0.001) and decreased 24.31% in the Sham ECT group (5.80 to 4.86; p = 0.004). **Discussion:** In this pilot study, we found no difference between the groups.

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Keywords: Schizophrenia, electroconvulsive therapy, ECT, single-blinded sham-controlled trial, partial response to clozapine.

Introduction

The use of antipsychotics represented a considerable advance in the treatment of schizophrenia but since the introduction of these agents, it was observed that a certain percentage of patients continues to exhibit psychotic symptoms despite adequate treatments either using first or second generation antipsychotics[1]. These patients are termed "refractory" or "treatment-resistant" and various guidelines and algorithms established operational criteria to define these patients as, for example, lack of response to two antipsychotic trials with adequate doses and at least six weeks duration each[2-4]. It is well established that clozapine is the drug of choice for such condition[1,2,4].

Nevertheless, about 30% of patients with treatment resistant schizophrenia (TRS) also do not respond satisfactorily to clozapine and remain predominantly psychotic and such patients are termed incomplete responders, partial responders or having super-refractory schizophrenia (SRS)[4,5].

There is a general agreement that patient with SRS have persistence of psychotic symptoms after adequate treatment with adequate doses of clozapine at least for 6 months[3]. However, to our knowledge, only Mouaffak *et al.*[6] have proposed an operationalized definition, using multidimensional criteria, as follows: 1) At least 8 weeks treatment with clozapine with plasma levels of >350 micrograms/L and failure to improve by at least 20% in total BPRS score; 2) Persistent psychotic symptoms as defined as ≥ 4 (moderate) on at least 2 to 4 positive symptoms items of the BPRS (18 items, graded 1-7); 3) Current presence of at least moderately severe illness on the BPRS score (≥ 45) and a score of ≥ 4 (moderate) on the Clinical Global Impression Scale.

For this population various augmentation strategies have been proposed using compounds such as anticonvulsants, antipsychotics, antidepressants and glutamatergic agents[5] for clozapine augmentation. However, with the exception of the modest effect of lamotrigine, there is no evidence that any pharmacological intervention is really efficacious in terms of clozapine augmentation for such patients[7].

Electroconvulsive therapy (ECT), has been used for treatment of schizophrenia before the advent of antipsychotics[8] and there is evidence of its efficacy when used in combination with antipsychotics, improving patients with schizophrenia who show limited response to medication alone[9]. ECT showed to be effective for patients with TRS in some uncontrolled trials[10,11] as well as retrospective studies[12]. Additionally ECT is recommended in guidelines[3] and algorithms such as the International Psychopharmacology Algorithm Project (www.ipap.org). The use of ECT has been proposed for this population of patients resistant to clozapine with good tolerability in case series with small number of patients, case reports or open label trials which vary considerably in terms of the definition of TRS, ECT techniques and outcome measures[13].

There are only 2 controlled trials which tested the efficacy of ECT in patients resistant to clozapine as is the case of Masoudzadeh and Khalilian[14] who treated 18 patients with TRS. Resistance was defined as lack of response to two antipsychotics trials with 8 weeks duration with adequate doses. Clozapine plasma levels were not evaluated. Eighteen treatment-resistant schizophrenic patients were assigned to three equal groups: one group received clozapine, one group was treated with ECT and one group was treated with the combination of clozapine and ECT. The treatment response was evaluated using the PANSS criteria and results showed that combination therapy was superior to single modality therapy. There were no significant adverse effects with combination treatment.

In another randomized controlled trial[15] patients with partial response to clozapine where assigned to receive ECT and compared

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with patients who received treatment as usual. Patients who were considered non responders to clozapine received an 8-week open trial of ECT (crossover phase). ECT was performed three times per week for the first 4 weeks and twice weekly for the last 4 weeks, 20 sessions. Response was obtained with a 40% reduction in psychotic symptoms on the BPRS[15].

However to the best of our knowledge, there are no studies which tested the efficacy of ECT in comparison with Sham ECT in patients with partial response to clozapine.

Thus, the aim of the present study is to compare clozapine augmentation with ECT as with Sham ECT through a randomized control trial in patients with schizophrenia resistant to clozapine.

Despite the fact that ECT was considered superior to placebo[9] there are no studies which compared ECT versus placebo (Sham) in patients with SRS[13].

Methods

This was a pilot, randomized, placebo-controlled, single blinded, single center trial to assess the efficacy of electroconvulsive therapy (ECT) as augmentation strategy in patients with partial response to clozapine or Super Refractory Schizophrenia (SRS), as compared to placebo (Sham ECT). Patients were recruited at the Institute of Psychiatry of the University of São Paulo Medical School and all the assessments and treatment procedures were carried out at the same site. The study was conducted in accordance with the Declaration of Helsink[16], was approved by the local Internal Review Board of University of São Paulo General Hospital (protocol 0364/09) and was registered in the Clinicaltrials.gov site (NCT02049021). All subjects or a legal tutor signed an informed consent form.

Inclusion criteria: patients of both genders, between 18 to 55 years old were included. Patients fulfilled criteria for a DSM IV-TR[17] diagnosis of schizophrenia or schizoaffective disorder based on clinical interview and follow-up of experienced psychiatrist of the Schizophrenia Research Program of the Institute of Psychiatry of University of São Paulo (Projesq). Severity of symptoms was evaluated by the Positive and Negative Syndrome Scale (PANSS)[18] and Clinical Global Impression scale (CGI)[19]. Generally patients were using clozapine at least for 6 months and had to have a total PANSS ≥ 60 and the CGI ≥ 4. Clozapine plasma levels should be equal or higher than 350 ng/mL[20].

Super refractoriness definition: patients were defined has having an unsatisfactory response to clozapine (super-refractory) using modified criteria[6]: 1) At least 8 weeks treatment with clozapine with plasma levels of > 350 micrograms/L and failure to improve by at least 20% in total BPRS score; 2) Persistent psychotic symptoms as defined as ≥ 4 (moderate) on at least 2 to 4 positive symptoms items of the BPRS (18 items, graded 1-7); 3) Current presence of at least moderately severe illness on the BPRS score (≥ 45) and a score of ≥ 4 (moderate) on the Clinical Global Impression Scale. We used BPRS items contained in the PANSS scale to evaluate patients.

Blindness: raters were blinded for the ECT/Sham procedures and patient's group status.

Medications: all patients were on clozapine either in monotherapy, or in combination with other psychotropic drugs such as antipsychotics, antidepressants or anticonvulsants.

Exclusion criteria: if they showed evidence of any unstable clinical condition in the last three months before the inclusion in the study as well have received ECT treatment for six months before the initiation of study. In case of childbearing potential, women were requested to use contraceptive methods.

Randomization: patients were randomized to either ECT or Sham ECT using tools provided by the researchrandomizer.com site.

Patient's follow-up: patients were assessed at baseline and after 12 sessions by raters who were completely blinded throughout the study. Clozapine serum blood levels were measured before the initiation of the trial, in order to assure that they were within the therapeutic range[20].

ECT procedures: ECT or Sham ECT was administered three times a week, with a total of 12 sessions. ECT was delivered using either a MECTA SpECTrum 5000Q or a MECTA SpECTrum 4000Q (Mecta Corp., Lake Oswego, Oregon, USA). The bitemporal electrode placement technique was used with a standard brief pulse stimulus threshold titration and dosing[21,22]. As routine procedure all patients received anesthesia either by hypnotic induction with Etomidate (0.15 to 0.3 mg/kg) or Propofol (1 to 2 mg/kg), Suxamethonium (0.5 mg/kg) was used for muscle relaxation with Atropine 0,5 mg intravenously. Sham ECT consisted in using the same setting and hypnotic sedation, but without muscle relaxation or electrical stimulus. Therefore all patients received the same procedures.

Measures of efficacy: the primary outcome was the response rate on psychotic symptoms as measured by the mean reduction at PANSS positive subscale. Response rates were defined according to three levels: a 20% reduction, which is generally considered the minimum level of response[23] and 30% reduction, which correspond to "minimally improved" CGI level[24], and 40% reduction, which correspond to the "much improved" CGI level adequate level[24] and considered an adequate level for ECT trials[15]. Secondary outcomes were clinical improvement on other PANSS subscales as well as the CGI.

Statistical analysis

At baseline groups were compared with Pearson's chi-square test for categorical variables or Student's t-test for continuous variables. Response rates were calculated as usual: (Baseline score – Endpoint score)/Baseline score. Pre- and post-treatment comparisons between groups was carried out with a linear mixed effects model to accommodate the dropouts[25]. The goal was to compare the pre and post treatment difference in scores with the interaction effect. Assumption of normality of residuals was assed inspecting the QQ plot. Analyses were carried out on SPSS version 22 and significance level was set at 5%.

Results

Twenty-three patients participated in the study. Only patients with the diagnosis of schizophrenia were included. They were randomly assigned to the ECT group (13 patients) or the Sham group (10 patients). At baseline these groups were comparable in terms of age, gender, educational level, dose of clozapine and blood levels of clozapine. Nineteen patients completed the trial. There were four dropouts: three of them from the Sham ECT group, as can be depicted by the Consort diagram displayed in Figure 1. Reasons for the dropouts: one patient had an infectious orchitis (ECT group) and three other patients could not attend the sections for other reasons not related to the study (Sham group).

Despite the fact that there were more dropouts in the Sham group, demographic variables showed no statistical differences between both completers groups. Patients receiving Sham showed higher degrees of psychopathology than patients receiving ECT as measured by the PANSS and CGI, but only the total score was significantly higher at baseline: PANSS positive subscale (22.9 vs 19.3, p = 0.15), PANSS negative subscale (29.0 vs 23.15, p = 0.08), PANSS General Psychopathology (44.9 vs 38.7, p = 0.13), PANSS total score (98.8 vs 81.2, p = 0.023) and CGI (5.8 vs 5.2, p = 0.14) (Table 1).

In terms of efficacy response rates the 20% reduction on the PANSS positive subscale was achieved by two ECT patients as well as two Sham ECT patients; one ECT patient and two Sham ECT patients had a 30% reduction and only one ECT patient met 40% reduction. Comparing pre and post treatment in terms of the improvement of all other PANSS subscales as well as the CGI no differences were found between active or Sham ECT, since all scores decreased significantly in both groups and no interaction effects were significant, except for the PANSS negative subscale (Table 2 and Figure 2).

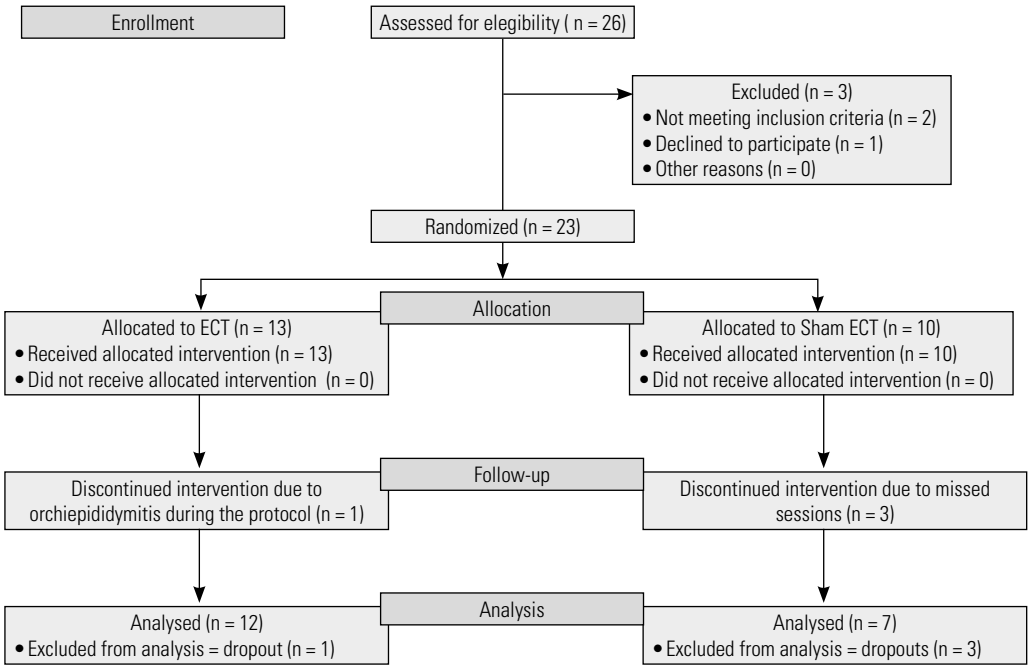

Figure 1. Consort diagram.

Table 1. Baseline data

	ECT	Sham	Statistics	*p*
Gender	9 male; 4 female	7 male; 3 female	$\chi^2(1) = 0.002$	0.97
Age (years)	36.63 (9.95)	37.60 (9.56)	t(21) = -0.24	0.81
Education (years)	10.15 (2.54)	10.00 (2.86)	t(21) = 0.13	0.89
Number of hospitalizations	3.33 (2.74)	4.00 (1.32)	t(21) = -0.70	0.51
Age at first hospitalization	20.15 (5.92)	22.20 (8.51)	t(21) = -0.68	0.50
Clozapine plasma levels (ng/ml)	644.30 (253.71)	747.82 (397.66)	t(21) = -0.76	0.45
Clozapine dose (mg)	532.69 (168.75)	505.00 (130.06)	t(21) = 0.43	0.67
PANSS total	81.23 (14.56)	98.80 (19.86)	t(21) = -2.45	0.023
PANSS positive	19.31 (3.56)	22.90 (6.70)	t(21) = -1.54	0.15
PANSS negative	23.15 (7.69)	29.00 (7.61)	t(21) = -1.81	0.08
PANSS general	38.77 (9.37)	44.90 (9.33)	t(21) = -1.56	0.13
CGI	5.23 (0.60)	5.80 (1.14)	t(21) = -1.55	0.14

Table 2. Comparison between Treatment (ECT) (N = 13) and Placebo (Sham) (N = 10) using Mixed Model Analysis

		Pre-treatment		Post-treatment		*p*-values		
		Mean	SD	Mean		Group	Time	Interaction
PANSS Total	ECT	81.23	14.56	74.75	12.17	0.046	0.006	0.668
	Sham	96.80	19.27	87.43	24.76			
PANSS Positive	ECT	19.31	3.57	16.17	4.11	0.121	< 0.001	0.646
	Sham	22.90	6.71	19.14	6.28			
PANSS Negative	ECT	23.15	7.69	23.42	5.82	0.041	0.995	0.610
	Sham	29.00	7.62	30.14	8.38			
PANSS General	ECT	38.77	9.36	35.17	7.61	0.193	0.023	0.501
	Sham	44.90	9.33	38.14	11.71			
CGI	ECT	5.23	0.60	4.17	0.72	0.149	< 0.001	0.908
	Sham	5.80	1.14	4.86	1.46			

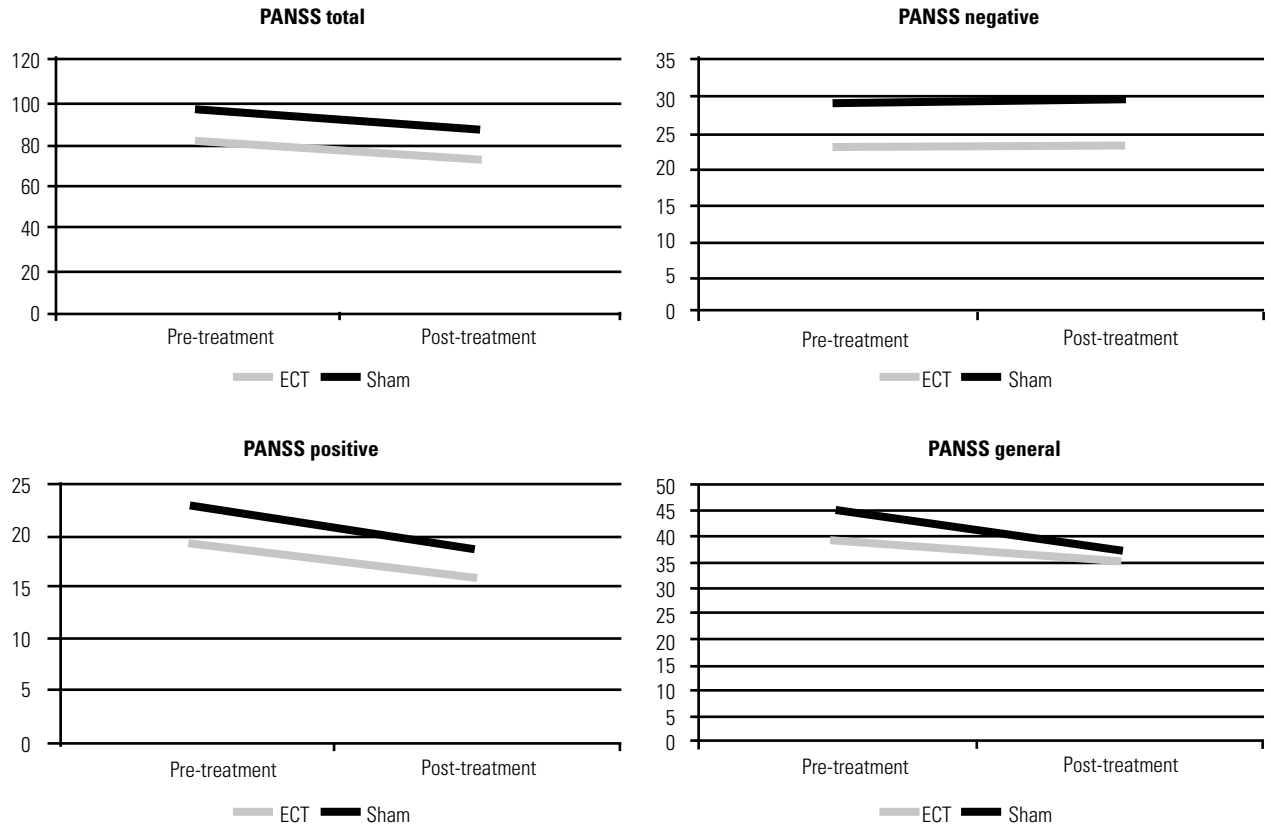

Figure 2. Comparison of PANSS (total and subscale scores) change over time between groups.

Discussion

The present study found that patients with schizophrenia with partial response to clozapine who were treated with ECT as an augmentation strategy showed no benefit when compared with those patients who received Sham ECT either in terms of the primary outcome (i.e. PANSS positive subscale) as well as secondary outcomes (other PANSS subscales and CGI).

As previously mentioned the majority of clozapine augmentation studies with ECT were case reports or open label studies[26] and therefore it is difficult to compare the this study with others, except for the Petrides *et al.*[15] to which the present study bears some similarities such as age range, degree of severity of illness, monitoring clozapine plasma levels and maintenance of concomitant medication with clozapine. However, the mentioned study differs substantially from ours since it was a cross-over trial, employed a higher number and frequency of ECT sessions, used the BPRS which is a scale with less number of items than the PANSS but, mainly, the ECT intervention was compared with treatment as usual.

In fact even in non-pharmacological procedures like ECT, it is well known that the gold standard for the establishment of therapeutic efficacy is the randomized placebo-controlled trial[27] and we think that this aspect represents an important strength of the present study since several reviews have shown that there are no Sham ECT controlled studies of clozapine augmentation strategies in patients with schizophrenia[26,28,29].

The monitoring of adequate plasma levels of clozapine is, to our point of view, another important issue of the present study since it allows to infer that patients are adequately treated and are true clozapine partial responders. This is pointed out by some reviewers who observed that the lack of response to ECT may related to low clozapine oral doses[30] and that the majority of published studies on the efficacy of ECT augmentation strategy for patients with partial response to clozapine did not report their clozapine doses or plasma levels[31].

As reported in other studies the procedure showed to be tolerable and safe since the dropouts in the ECT or Sham groups seems to be not related to the procedure. However there are several limitations that must be considered. The first issue to be considered is the small sample size, of 23 subjects and 19 completers. The high rates of dropouts, three of them from Sham group, (i.e. 50% of the final sample), by no means represents a possible source of bias. We could speculate that lower therapeutic effects associated to difficulties to keep regularity to the complex procedure contributed to these higher rates in this group.

The placebo (or Sham) group had a significant improvement in this study. Indeed, placebo effect was comparable to ECT effect at the endpoint, with no statistical differences (last PANSS and CGI assessments were carried out until seven days after the last procedure)[32-34]. One possible explanation could be the cumulative factors that can increase placebo effect, also described and found in other clinical trials, such as: small sample sizes, smaller placebo groups, higher severity of psychopathology at baseline, lower mean age of participants, as well as the briefness of intervention[32-34].

Moreover, the last structured assessment was carried out until seven days after the last procedure, probably the best point to detect positive symptoms improvements, but still under post-ictal cognitive side effects, which may have an impact on the PANSS scores. Given the short-lived nature of placebo effect, we hypothesize that a long term observation could increase discrimination capacity. Another factor described about placebo effect concerns the nature of intervention itself: complex procedures, using active substances (such as anesthesia), and engaging patients in therapeutic environment, can lead to response rates as high as 70%[35]. This finding of lower differences between control (placebo) and active groups has been reported to be growing, concerning research centers and the industry,

not just in antipsychotic development, but also in mood disorders research[36].

Scales such as the PANSS scale were used as primary outcome measure and CGI as secondary outcome measure. We concluded that these two tools could not confirm that ECT is superior to placebo (Sham ECT) as augmenting therapy to clozapine in SRS, in part due to the small sample size, and other factors discussed above. However the present study is a work in progress. It is an ongoing research and the increasing number of participants we will probably improve statistical power to detect significant effects between groups.

Other aspects should also be considered as for example the fact that recent literature on clinical trials focusing the treatment of schizophrenia have shown a progressive increase in the placebo effect. For example, observing placebo-controlled studies which used the PANSS between 1983 and 2007 studies, it was found a progressive increase of improvement in the placebo group as compared to almost no placebo effect in the earlier decade of the 1980s[34]. In fact the placebo effect of ECT is not understood and may be underestimated[37].

It is well documented that patients with TRS are amongst the most severe cases of schizophrenia[4] and those with partial response to clozapine have higher degrees of psychopathology and current psychopharmacological augmentation strategies showed no superior benefit as compared to placebo[7] while some psychological trials showed small benefits for patients[38]. As previously mentioned contemporary clozapine pharmacological augmentation strategies are considered not better than placebo[7] and in this sense further placebo controlled trials with larger samples are warranted since ECT still represent the single non pharmacological therapeutic alternative for patients with partial response to clozapine.

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Serum cortisol level and depression severity in a sample of Brazilian elders

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Dear Editor,

The recent precision medicine movement has pushed research towards the identification of biomarkers that can be used for early diagnosis. We designed a pilot study that explores the correlation between blood cortisol level (BCL) with depression, depression severity and clinical comorbidities in a sample of aged Brazilian subjects. We hypothesized that BCL will significantly correlate to depression, its severity and with clinical comorbidities in our sample.

Participants were selected from an epidemiological study of older residents of the city of Sao Paulo[1], which screened positive for depression (depression scale-D10-score ≥ 7)[2] and a pool of outpatients who received treatment for depression. Inclusion criteria were 60 years and older, and DSM-IV-TR[3] criteria for major depressive disorder based on a diagnostic interview by geriatric psychiatrists. Controls were 10 adults who were at least 60 years old without depression. Exclusion criteria included dementia, other organic mental disorder, and DSM-IV-TR-criteria-based diagnoses of any psychiatric disorder other than depression. Diagnosis and exclusion criteria were assessed with the CAMDEX interview[4].

We followed 11 depressed subjects. Seven patients (63.6%) began depression after age 60 (late onset depression). Both groups had more female subjects (70% of controls and 54.5% of patients). The groups were similar in terms of marital status, mini-mental score, age and education.

In the initial appointment the subjects were assessed with: Mini Mental State Examination (MMSE)[5]; the CAMCOG version validated for the Brazilian population[6]; Montgomery-Asberg Depression Rating Scale (MADRS)[7], Cumulative Illness Rating Scale (CIRS)[8], Bayer Activities of Daily Living Scale (B-ADL) adapted for the Brazilian population[9], and the Hamilton Rating Scale for Depression (HAM-D)[10]. To ensure that no subjects with incipient dementia would be included in the group we applied MMSE, CAMCOG and the B-ADL. We were unable to standardize the blood sample collection time, but all cases had it collected between 6-10 am (controls 6:29-9:42 am, mean = 8:57:55 am, mdn = 8:57 am; depressed subjects 6:19-9:52 am, mean = 9:23:44 am, mdn = 9:10 am).

It was found that BCL was significantly higher in the depressed aged subjects ($p = 0.049$, $U = 27$, Wilcoxon-Mann-Whitney test), and correlated significantly with severity of both the depressive symptoms (HAM-D: $p < 0.001$, $U = 0$; MADRS: $p < 0.001$, $U = 0$; B-ADL: $p < 0.001$, $U = 10$; Wilcoxon-Mann-Whitney test) and the clinical comorbidities (CIRS-severity, $p = 0.032$, $U = 25$). Finally, depression could be predicted by BCL in a regression model (Table 1).

These findings should be taken with caution, as we did not standardize the collection time for BCL. Nevertheless, they suggest that hypercortisolemic depressed elders comprise a subgroup within depressed subjects. Their clinical course may progress with more morbidity/comorbidities and functional deficits, as shown by the statistically significant relation to all four scales applied. Elevated BCL predicts depression ($p = 0.037$, $df = 1$, $B = 0.34$, $SE = 0.162$, Table 1), which suggests that BCL might be involved in the development of depression in aged patients. The odds of 1.402 means that for each raise of 1 unit (μg/dl) of cortisol level there is 40% increase in risk of depression (95% C.I. 1.020 - 1.926).

Table 1. Logistic regression results for the prediction of diagnostic status from the BCL

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)
BCL	0338	0.162	4.333	1	0.037	1.402	1.020 - 1.926
Constant	-4.155	2.058	4.076	1	0.044	0.016	

BCL: blood cortisol levels; B: the intercept; S.E.: standard error; Wald: Wald chi-square test; df: degrees of freedom; Sig.: significance; Exp(B): odds ratio; C.I.: confidence interval.

Conflict of interest

The authors declare there are no conflicts of interest.

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Melanoma brain metastases presenting as delirium: a case report

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Abstract

Background: Metastatic tumours sometimes present with neuropsychiatric symptoms, however psychiatric symptoms as rarely the first clinical manifestation. Cutaneous melanoma is the third most common cause of brain metastasis, with known risk factors increasing the chance of such central nervous system metastization. **Objectives:** We present a clinical report of delirium as the first clinical manifestation of melanoma brain metastases, illustrating the relevance of an adequate and early differential diagnosis. **Methods:** In addition to describing the clinical case, searches were undertaken in PubMed and other databases using keywords such as "brain metastasis", "melanoma", "agitation", "psychiatric" and "delirium". **Results:** We here report the case of a 52-year-old female patient evaluated by Liaison Psychiatry after sudden onset of delirium while admitted at the Gastroenterology Department to study a hypothesis of pancreatitis. A head CT scan identified brain metastases, and after further examination, including brain biopsy, melanoma brain metastization was confirmed. **Discussion:** Some of the diagnostic challenges of psychiatric symptoms associated with secondary brain tumours are discussed, underlining the importance of an adequate differential diagnosis when working in Psychiatry Liaison.

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Keywords: Brain neoplasms secondary, melanoma secondary, delirium.

Dear Editor,

We report a clinical case of sudden onset of delirium, with psychomotor agitation and behavioural changes, in addition to reported depressive symptoms of subacute onset, as the initial manifestation of melanoma brain metastasis in the right posterior frontal lobe.

Our Psychiatry Liaison Unit was requested to attend a female patient, 52-year-old, that was admitted from the Emergency Department with nausea, vomiting and headache, initiated 2 days before. She had no psychiatry history other than depressive symptoms, about 9 months long, apparently reactive to work conflicts, medicated with paroxetine 20 mg id. Medical history included the excision of an ulcerated malignant melanoma in the right thigh 4 years before, in apparent remission, and hysterectomy for uterine fibroid. Her neurological exam was unremarkable. Blood analysis showed hepatic cholestasis and abdominal ultrasound showed a pancreatic mass; she was hospitalized at the Gastroenterology Department with a hypothetic pancreatitis.

After three days she initiated during the night psychomotor agitation and disinhibited behaviour, motivating Psychiatry Liaison consultation. When interviewed next morning, she was still restless and fidgeting in the sheets, with spatiotemporal disorientation, speaking quickly with a somehow incoherent speech, keeping her eyes closed and stating: "Doctor I have flatulence, but you know me and this is funny..."

An urgent head computerized tomography (CT) scan was performed evidencing an expansive lesion within the right posterior frontal lobe, heterogeneous and hyperdense, conditioning mass effect on adjacent structures. She started oral haloperidol 5 mg id and performed a head magnetic resonance imaging (MRI) (Figure 1).

Later, a chest/abdomen/pelvis CT scan and a whole-body Positron Emission Tomography (PET) scan identified multi-organic metastatic disease affecting the lungs, pancreas and peritoneum. The patient was also medicated with oral dexamethasone and transferred to the Neurosurgery Department. She underwent surgical removal of part of the brain lesion, with a biopsy consistent with melanoma brain metastases.

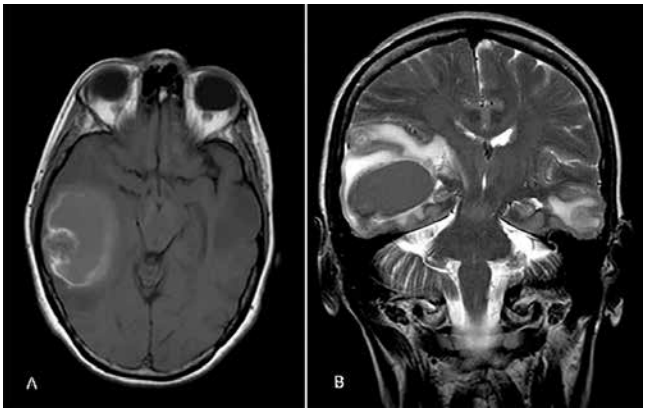

Figure 1. Brain MRI. (**A**) Axial T1-weighted image showing a cortico--subcortical tumoral lesion at temporal lobe with predominant moderate hyperintensity and an irregular halo of higher signal. The spontaneous high signal on T1 is probably due to both a hemorragic component and the melanocytic content. (**B**) Coronal T2-weighted image showing the lesion described in (**A**) and additional two smaller cortico-subcortical masses located at right posterior frontal lobe and at left inferior temporal gyrus. All the lesions had low signal on T2, particularly the inferior solid component of the major tumoral mass, which is also compatible with a melanocytic content. Another milimetric lesion was found at left precuneus (not shown). The hypointensity on T2-weighted image (**B**) may also be associated at lung or gastrointestinal adenocarcinoma metastasis, however with the (**A**) axial T1-weighted image the hyperintense signal is typical of melanoma melanocytic.

Cutaneous melanoma is the third most common cause of brain metastasis, reflecting its distinctive neurotropism[1]. Central nervous system (CNS) metastasis occur in 10 to 40% of melanoma patients in clinical studies and up to 90% in autopsy studies[2]. Nonetheless, to our knowledge, this is the first report in the literature of delirium as a presenting syndrome of melanoma brain metastases.

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Factors that have been shown to increase the risk for development of CNS metastasis in melanoma patients included male sex, thickness or ulceration of the skin lesion, primary site in the head and neck, mucosal or acral lentiginous tumors and nodular primary lesions[3]. Metastatic tumors often present with more neuropsychiatric symptoms[4]. Most brain tumors present with specific neurologic signs due to mass effect, and 78% of patients with brain tumors had psychiatric symptoms, but only 18% presented only with these symptoms as the first clinical manifestation of a brain tumor[5]. Depression was found in 44% of all brain tumor patients, primary and metastatic[6].

We report a rare case associating delirium with the early presentation of brain metastization of melanoma. Clinical suspicion is critical when working in Psychiatry Liaison, and an adequate differential diagnosis is key to the early treatment of potentially fatal CNS conditions.

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