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 44 • NUMBER 3 • 2017

IMPACT FACTORS
0.52 ISI (Thomson Reuters)
0.63 SCImago

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. 44, n. 3 (2017). – 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
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- 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: 21848.6.17

Financial Support

CEIP Centro de Estudos do Instituto de Psiquiatria

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

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VOLUME 44 • NUMBER 3 • 2017

Editorial

Original articles

Letter to the editor

A new editorial board for new challenges

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Received: 5/30/2017 – **Accepted:** 5/30/2017
DOI: 10.1590/0101-60830000000119

Gattaz WF, Crippa JAS / Arch Clin Psychiatry. 2017;44(3):55

It is with mixed feelings of gratefulness and renewed energy that we announce the new editorial board of the *Archives of Clinical Psychiatry*. At the same time that we say goodbye to some of the editors who have given life to our journal over the past years, we cheerfully welcome our newly arrived associate editors, who accepted the challenge of continuing and expanding the fine work done until now.

The entrance of our new Editor-in-Chief, Dr. José A. S. Crippa, from the Medical School of the University of São Paulo in Ribeirão Preto, was the first step to bring together the two centers of research in psychiatry and neuroscience of the University of São Paulo with the purpose of strengthening and expanding the relevance and visibility of the *Archives of Clinical Psychiatry*. Now, each of the five areas covered by our journal will be headed by two associate editors, one from São Paulo and one from Ribeirão Preto.

We would like to express our deepest thanks and appreciation to Dr. Clarice Gorenstein, former Associate Editor of the area of *Instruments and Scales*, Dr. Francisco Lotufo Neto, former Associate Editor of *Human Sciences*, and Dr. Geraldo Busatto Filho, former Associate Editor of the area of *Clinical Psychiatry*. Please receive our deepest gratitude for the time and effort put into the development of our journal over this period.

To share the responsibility for the area of *Child and Adolescent Psychiatry* with Dr. Guilherme Polanczyk (FMUSP), we welcome Dr. Maria Beatriz Linhares (FMRP-USP). Dr. Jaime Hallak (FMRP-USP) now takes over the area of *Clinical Psychiatry* together with Dr. Tânia C. F. Alves (FMUSP). Drs. Elaine Henna (FMUSP) and Flávia Osório (FMRP-USP) are now our associate editors for the area of *Instruments and Scales*, and Dr. Marcos H. N. Chagas (FMRP-USP) has joined Dr. Orestes Forlenza (FMUSP) as associate editor for *Neuroscience*. Finally, we welcome Dr. Clarissa Corradi-Webster (FFCLRP-USP) and Dr. Julio Peres (FMUSP) to head our former area of *Human Sciences*, under the new name of *Psychology and Psychotherapy*.

In its 45th anniversary, the whole staff of the *Archives of Clinical Psychiatry* is happy to rely on the solid basis established by our past contributors and to count on the expertise and enthusiasm of our new editors to become a top-ranking journal in its field and to contribute for the furthering of Brazilian and world science.

Original article

Current alcohol dependence and emotional facial expression recognition: a cross-sectional study

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Received: 11/14/2016 – **Accepted:** 3/9/2017
DOI: 10.1590/0101-60830000000120

Abstract

Background: Several studies have demonstrated that chronic and excessive alcohol use causes social cognition deficits. **Objectives**: Thus, the aim of the current study is to assess the associations between emotional facial expression recognition and current alcohol dependence. **Methods**: The sample consisted of two groups: one was composed by current alcohol dependent individuals (AG = 110); and a control group, composed of healthy individuals (CG = 110) assessed by the Structured Clinical Interview DSM-IV. The instrument to assess the recognition of facial expressions of emotion was a dynamic task at computer. **Results**: The AG showed low accuracy in recognizing emotions as a whole and especially fear and disgust. In addition, the group needed greater emotional intensity to recognize joy, fear, disgust and surprise. It also showed increased reaction time for all emotions ($p < 0.01$). The logistic regression showed the response time for surprise (ODDS = 1.01) and the ability to recognize emotions such as fear (ODDS = 0.68) and disgust (ODDS = 0.70) was significantly associated with alcohol dependence. **Discussion**: These specific associations are of great value to a more refined understanding of alcoholism, and they concern relapse and treatment.

Donadon MF, Osório FL / Arch Clin Psychiatry. 2017;44(3):56-62

Keywords: Alcohol dependence, emotion facial, recognition.

Introduction

It is known that although alcohol consumption is part of the daily habits of many people and that it is linked to prestige and pleasure, alcoholic beverages play an ambiguous role since they lead to serious public health issues worldwide[1]. There is a high percentage of hospitalizations to treat several diseases directly associated with alcoholism (liver cirrhosis, cerebrovascular diseases, cancer, gastritis, esophageal varices, pancreatitis, diabetes mellitus and tuberculosis)[2]. The high percentage of comorbidities such as mood, anxiety and personality disorders is also noteworthy. Such comorbidities increase the losses at different levels and lead to worse prognosis[3].

In addition to the aforementioned damages, the literature indicates that the excessive use of alcohol may cause psychomotor, visuospatial deficits, and neurocognitive deficits. Consequently, it may affect social cognition[4-6], which refers to the ability of decoding emotion signs in the faces of others, mainly when it comes to six basic emotions: anger, disgust, fear, sadness, joy and surprise. Thus, it is a key process to the emotional adaptive functioning[6,7].

Many studies have investigated the hypothesis of the origin of losses that comes along with chronic alcohol dependence and that favors social cognition impairments. Several groups of researchers, among them Jernigan *et al.*[8], Pfefferbaum *et al.*[9], Chen *et al.*[10] state that these changes result from the alcohol neurotoxic effects on the central nervous system. They report losses of white and gray matter in the temporal and in the parietal cortices, mainly in the dorsolateral portion of the frontal and prefrontal cortices, which mediate the emotional processing. On the other hand, another group of researchers[11,12] believe that genetic history may play an important role in the origin of the deficits, since it leads individuals to a greater predisposition to alcohol dependence and to the development of abnormalities in areas of the brain involved in emotion recognition.

Overall, the studies point out interesting findings. The first one to be highlighted refers to the lack of studies in the literature about alcohol dependent individuals who make active use of alcohol, to our knowledge. Therefore, the samples in these studies consist of individuals in the detoxification phase, abstainers, social drinkers or individuals under acute alcohol effect. Moreover, there are many analyzed variables, for example, monitoring of the electrical activity of the brain during the performance of cognitive tasks through electroencephalogram. These studies found that alcohol-dependent individuals showed lower brain activation in areas mediating visual, auditory and visual-motor processes, as well as difficulty to process anger[13,14].

Other studies have focused on investigating facial expression recognition of emotion (FERE) during neuroimaging examinations through functional magnetic resonance techniques. They found that alcohol dependent individuals present low brain activity in the cingulate, orbitofrontal and insular cortices during the recognition of fear[15] and disgust[16]; these areas are emotional processing mediators.

Meanwhile, some studies have focused the performance in tasks involving the FERE by alcoholics (detoxification or withdrawal phase) through the analysis of three outcome variables: accuracy, intensity of emotion and reaction time. According Donadon and Osório[17] the main findings of this review didn't evidenced any marked tendency. Also, an important limitation that deserves to be observed in this field of study was the lack of standard methodology, because the stimuli and procedures show a great diversity, which may influence considerably the results. In contrast, two recent meta-analysis involving subjects with alcohol use disorder (abstinent and/or alcohol detoxification phase) indicate that people with alcohol use disorders show worse FERE than controls, with an effect size of -0.67 IC (-0.95 to -0.39)[18] and also that alcoholics in detoxification, appears to be associated with significant impairment, at the recognition of disgust ($d = 0.62$) and anger ($d = 0.47$)[19].

Considering: a) the widespread damage observed in social cognition in alcoholics and the negative consequences that those may cause to the individual and b) losses in relationships/interpersonal interactions[7] and social coping skills, as the use of alcohol can be a maladaptive way to deal with the lack of behavioral repertoire before stressful situations day-to-day[20,21]. So the aim of the current study is to assess the associations between FERE and current alcohol dependence in a sample composed of male subjects.

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Methods

Individuals

The sample of the current study was selected by convenience and it was calculated the sample size, with an error rate estimated in 5% and the power of the test in 80%, as showed above in two different groups:

a) The current alcohol dependent individuals (AG) was composed by 110 male individuals over 18 years old, who were recruited in a clinic (outpatients) for alcoholic liver disease treatment of a university general hospital. All the individuals were diagnosed with current alcohol dependence by means of the Structured Clinical Interview (SCID-I, for DMS-IV) and across the criterion listed in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The patients did not show hepatic encephalopathy.
b) The control group (CG), composed by 110 male subjects over 18 years old, who were recruited among the general population, mainly in primary health care services and in a non-governmental organization. These individuals had no history of alcohol abuse and/or dependence, according to the SCID-I.

It was decided to use a sample exclusively composed of males, since FERE may suffer influence of gender[22]. The CG and AG sociodemographic variables were paired in the current study, namely: age and education.

The exclusion criterion was the incorrect filling of the instruments or the absence of current alcohol dependence for AG group. Figure 1 shows the flowchart with the sample composition trajectory.

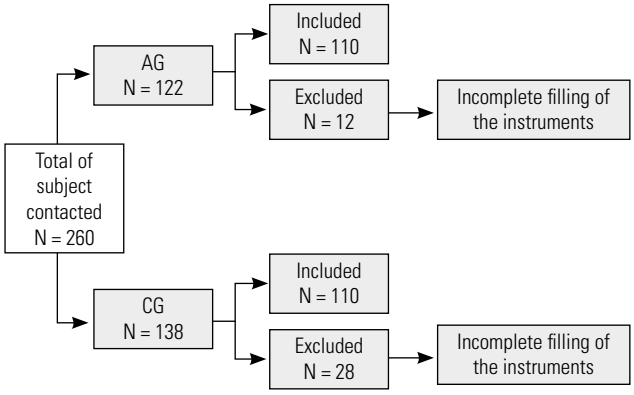

Figure 1. Flowchart of inclusion and exclusion of participants.

Instruments

The following instruments were used to characterize the sample:

Structured Clinical Interview for the DSM-IV (SCID-I – Clinical version) – It was suggested by Frist *et al.*[23] and then translated and adapted to Portuguese by Del-Ben *et al.*[24]. This instrument is used to perform psychiatric clinical diagnoses based on the DSM-IV. It consists of ten modules, which may be applied independently or in combination with other instruments, depending on the desired goals. The current study used Module E in order to diagnose alcohol dependence.

Beck Anxiety Inventory (BAI) – Self-applied instrument composed of 21 items, which assesses the presence and intensity of anxiety symptoms. The current study used the version translated to Brazilian Portuguese and adapted by Cunha[25]. The cutoff point considered to be the pathological anxiety indicator was twenty (20).

Patient Health Questionnaire – 9 (PHQ-9) – This instrument consists of nine self-administered items that assess the presence of depressive symptoms. The current study used the version validated to Brazilian Portuguese by De Lima Osório *et al.*[26]. The cutoff point considered to be the clinical depression indicator was ten (10).

Fagerstrom Test for Nicotine Dependence (FTND) – Self-administered instrument composed of six items to measure the degree of physical nicotine dependence. The current study used the version translated to Brazilian Portuguese and validated by Carmo and Pueyo[27]. The current study used this instrument in order to assess Tobacco dependence indicators.

Clinical and sociodemographic questionnaire – This instrument consists of 18 items and it was developed for the current study, it has the aim to collect complementary data about sociodemographic and clinical features. The current study used this instrument in order to characterize the sample.

Facial Expression Recognition of Emotion Task (FERET) – Computerized task consisting of a series of 24 stimuli composed of photographs of four actors from Ekman and Friesen[28] (two male and two female caucasians, in black and white), who represented features typical of the six basic emotions (happiness, sadness, fear, disgust, anger and surprise). It was created films of images that moved from a neutral 0% of emotion to 100% emotion, dynamically. There was an initial screen with instructions, which was followed by one film of image as an example, which by touching the computer screen, made appear a new screen where there were six options of answers (happy, sadness, fear, disgust, anger, surprise). After the example, the test started and the responses were saved automatically. These procedure was standardized by Arrais *et al.*[29]. The current study used this instrument in order to assess the outcome of variable accuracy and reaction time or intensity of emotion displayed.

Data collection and analysis

The present study was conducted in compliance with the ethical parameters in human research and approved by the Local Ethics Committee (HCRP Process n. 2316/2011).

Data were individually collected and inserted in a database. Subsequently, they were analyzed through: a) descriptive statistics: analysis of the sociodemographic and clinical features of the sample; b) parametric analysis: Student's *t* test (comparison groups); multivariate logistic regression – backward method (the outcome variables were accuracy, intensity of emotion and reaction time), whose p value was less than 0.20 were included in the initial logistic regression model[30].

It was adopted a significance level of $p < 0.05$.

Results

Table 1 shows the main sociodemographic and clinical features of the sample.

As it can be seen in Table 1 that most of the participants were married, with mean age 53 years, and they predominantly had elementary and high school education. No significant differences were found between these variables in the two groups. However, the groups statistically differ from each other in professional status. Most CG members were professionally active, whereas only less than half of the AG members had such professional status, thus it shows job loss in this group.

The AG showed indicators of depression, anxiety symptoms and tobacco dependence symptoms higher than those means of CG, although these average values are not as clinically significant, there was no significant correlations of these FERE variables with psychiatric comorbidities ($p < 0.05$).

Table 2 presents the accuracy indicator features, as well as the comparison between groups.

The AG group presented the smallest number of accuracy for emotions such as fear and disgust, as well as for the total of emotions with statistically significant differences between groups.

Table 1. Sociodemographic and clinical features of the sample according to alcoholics (AG) and control (CG) groups

Variables		AG		CG		Statistics
		N	(%)	N	(%)	
Gender	Male	110	100	110	100	–
Age	*X* *SD*	53.78 (8.24)		53.05 (8.82)		*t* = - 0.47; *p* = 0.52
Marital status	Single Married Widower/divorced	22 64 24	20.0 58.2 21.8	16 79 15	14.6 71.8 13.6	X^2 = 4.60; *p* = 0.10
Children	Yes No	92 18	83.6 16.4	87 24	78.2 21.8	X^2 = 12.32; *p* = 0.26
Education	ES HS HE	62 36 12	56.4 32.7 10.9	60 38 12	54,6 34,5 10,9	X^2 = 0.09; *p* = 0.96
Professional status	Active Inactive	48 62	43.6 56.4	91 19	82.7 17.3	X^2 = 36.13; *p* < 0.001*
PHQ-9/Depression	*X* *SD*	6.69 (6.00)		2.65 (3.54)		*t* = - 6.069; *p* < 0.001*
BAI/Anxiety	*X* *SD*	9.43 (9.50)		4.85 (6.56)		*t* = - 4.151; *p* < 0.001*
FTND/Tobacco	*X* *SD*	2.21 (3.36)		1.05 (2.38)		*t* = - 2.935; *p* = 0.004*
Alcohol doses consumed/day	*X* *SD*	7.64 (4.56)		0.10 (0.12)		*t* = - 17.32; *p* < 0.001*
Alcohol abuse/years	*X* *SD*	29.36 (11.27)		– –		–

N: frequency; (%): percentage; *p*: significance level; X: mean; SD: standard deviation; *t*: Student's *t* test; X^2: Chi-square test; ES: elementary school; HS: high school; HE: higher education; *: statistically significant; AG: alcoholics group composed of individuals diagnosed with alcohol dependence; CG: control group composed of individuals with no diagnosis of alcohol dependence.

Table 2. Groups' mean, standard deviation and percentage of right answers in the emotional facial expressions recognition task

Emotions		AG (N = 110)	CG (N = 110)	Statistics
Happy	Mean (SD) Success rate	3.40 (0.97) 85%	3.62 (0.89) 90%	*t* = 1.72; *p* = 0.09
Sadness	Mean (SD) Success rate	2.01 (1.18) 50%	2.30 (1.31) 57%	*t* = 1.72; *p* = 0.09
Fear	Mean (SD) Success rate	1.33 (1.09) 33%	1.79 (1.07) 44%	*t* = 3.17; *p* < 0.01* d = 0.43
Disgust	Mean (SD) Success rate	1.89 (1.37) 47%	2.32 (1.17) 58%	*t* = 2.48; *p* < 0.01* d = 0.35
Anger	Mean (SD) Success rate	2.05 (1.26) 51%	2.16 (1.11) 54%	*t* = 0.68; *p* = 0.49
Surprise	Mean (SD) Success rate	2.25 (1.42) 56%	2.56 (1.35) 64%	*t* = 1.70; *p* = 0.09
Total	Mean (SD) Success rate	12.93 (4.85) 53%	14.75 (4.24) 61%	*t* = 2.97; *p* < 0.003* d = 0.40

SD: standard deviation; AG: alcoholics group composed of individuals diagnosed with alcohol dependence; CG: control group composed of individuals with no diagnosis of alcohol abuse and/or dependence; *p*: significance level; *t*: Student's *t* test; d: Cohen's; *: statistically significant difference.

Table 3 presents data about the reaction time required to respond in the FERE.

Table 3 shows statistically significance differences between AG and CG individuals in the reaction time during FERET for all the emotions. The differences indicate that AG members needed more time to process all the stimuli.

Table 4 presents the results of the emotional intensity required for FERE.

Table 4 shows that AG members required higher emotional levels to process the emotions of fear and disgust through facial expression. It also shows that there was statistically significant difference between the groups, except for emotions such as sadness and anger.

Is was also carried out analyses of the responses bias (percentage of wrong answer to each emotion). In relation to responses bias we did not found a specific bias to the emotions separately. However, when analysing the total number of responses to emotion, it was clear that the AG has issued more responses of happiness (19.31%, p = 0.003) and anger (19.16%, p = 0.05) when compared to CG, while the CG showed higher responses of fear (17.95%, p = 0.02) and surprise (22.31%; p = 0.02) when compared AG.

A multivariate logistic regression analysis was conducted to assess the associations between the FERE and the current alcohol dependence variables. The initial logistic regression model was not satisfactory and new models were tested by the backward method until reach the final model shown in Table 5.

Results show that the ability to recognize disgust and fear has an influence on current alcohol dependence and also a significant association with the condition of current alcohol dependence.

Table 3. Mean and standard deviation of the different groups according to the reaction time

Emotions		AG (N = 110)	CG (N = 110)	Statistics
Happy	Mean (SD)	11.25 (36.33)	8.66 (28.17)	t = -5.91; p < 0.01* d = 0.07
Sadness	Mean (SD)	13.61 (44.49)	11.50 (40.46)	t = -5.91; p < 0.01* d = 0.04
Fear	Mean (SD)	13.28 (45.00)	11.22 (36.88)	t = -3.70; p < 0.01* d = 0.05
Disgust	Mean (SD)	13.38 (40.67)	11.21 (35.73)	t = -4.19; p < 0.01* d = 0.05
Anger	Mean (SD)	14.26 (52.80)	11.92 (38.74)	t = -3.74; p < 0.01* d = 0.05
Surprise	Mean (SD)	12.90 (41.29)	10.69 (36.92)	t = -4.18; p < 0.01* d = 0.05
Total	Mean (SD)	13.07 (35.96)	10.81 (29.92)	t = -5.05; p < 0.01* d = 0.32

SD: standard deviation; AG: alcoholics group composed of individuals diagnosed with alcohol dependence; CG: control group composed of individuals with no diagnosis of alcohol abuse and/or dependence; *p*: significance level; *t*: Student's *t* test; d: Cohen's; *: statistically significant difference.

Table 4. Mean and standard deviation of the different groups in relation to the intensity of the emotion (percentage) required to recognize the emotion itself during the facial expression recognition task

Emotions		AG (N = 110)	CG (N = 110)	Statistics
Happy	Mean (SD)	91.86 (13.39)	80.20 (18.50)	t = -5.35; p < 0.01* d = 0.72
Sadness	Mean (SD)	96.10 (11.21)	93.42 (13.92)	t = -1.57; p = 0.11 d = 0.21
Fear	Mean (SD)	95.45 (12.89)	91.27 (14.23)	t = -2.28; p = 0.02* d = 0.30
Disgust	Mean (SD)	96.71 (8.98)	92.55 (17.80)	t = -2.18; p = 0.03* d = 0.33
Anger	Mean (SD)	96.66 (10.62)	94.16 (12.47)	t = -1.60; p = 0.11 d = 0.47
Surprise	Mean (SD)	94.66 (12.58)	89.40 (16.52)	t = -2.65; p < 0.01* d = 0.35
Total	Mean (SD)	97.12 (8.62)	91.76 (12.85)	t = -3.63; p < 0.01* d = 0.48

SD: standard deviation; AG: alcoholics group composed of individuals diagnosed with alcohol dependence; CG: control group composed of individuals with no diagnosis of alcohol abuse and/or dependence; *p*: significance level; *t*: Student's *t* test; d: Cohen's; *: statistically significant difference.

Table 5. Final logistic regression model to predict alcoholism

Variables	B	SE	P	OR	CI = 95%	
					Lower	Upper
Accuracy – Fear	-0.38	0.16	p = 0.02*	0.68	0.49	0.94
Accuracy – Disgust	-0.34	0.15	p = 0.02*	0.70	0.52	0.95
Reaction Time – Surprise	0.16	0.00	p < 0.001*	1.01	1.00	1.02

B: beta value; CI: confidence interval; OR: *odds ratio;* SE: standard deviation of the estimate; *p*: significance level; * Statistically significant difference.

Discussion

The aim of the current study was to evaluate possible associations between the FERE and current alcohol dependence, being observed overall damages at accuracy rate, reaction time, and intensity necessary for the recognition of emotions, with an effect size considered (d > 0.32).

The results from this study are unprecedented since, to our knowledge, this is the first to assess current alcohol use in dependent subjects. Prior studies at the literature conducted with abstinent and/or subjects at alcohol detoxification phase and they also pointed to global losses[31,32], in the same way that was observed in this study, signalling the convergence of results, regardless of the current or previous use of alcohol. In addition, a recent meta-analyses involving subjects with alcohol use disorder (abstinent and/or alcohol detoxification phase) also indicate more specific deficits, showing impairments at the recognition of disgust and anger[19].

The understanding of deficits in FERE in alcohol dependent individuals has two distinct possibilities: a) the deficits have been caused by etiological factors associated with alcohol use disorder and/or b) the possibility of the deficits had been caused by the consequences of excessive alcohol use. As the present study was not a longitudinal design, we will discuss the findings by taking both possibilities into account.

Several studies suggest that chronic alcohol use may *under-activate, over-activate* and even reduce the volume of the brain

in some areas of the prefrontal and anterior cingulate cortices, of limbic structures, among others. Consequently, it would impair several cognitive functions such as the emotional information processing speed, the attention level during the task, memory, and the psychomotor skills, among others. These functions may lead alcoholic individuals to spend more time focusing on the task in order to respond to it, to need longer response times and to make more misjudgements mistakes[30,31,33-37]. In addiction, a recent meta-analyse[19] pointed out that toxic effects of alcohol on neuronal integrity could explain the deficits in emotion recognition, by changes at structural and connectivity in brain regions are consequence of excessive use of alcohol.

On the other hand, other studies also suggest that neurocognitive deficits may have a genetic origin and lead individuals to greater predisposition to alcoholism and to the development of abnormalities in areas of the brain used to process emotions[11,12,32,33]. This studies indicated that the predisposition may lead to the development of abnormalities in areas of the brain used to process emotions/cognitions, as well as may lead individuals to use alcohol[11,12]. Schandler *et al.*[32] found that pre-school children from families with alcohol-dependent individuals already present deficits in visuospatial information processing. In addition, D'Hondt *et al.*[33] reported that the changes found in FERE may be linked to changes in areas of the brain related to vision and/or to visual recognition prior to alcohol use. These changes are not directly linked to the excessive use of alcohol. It reinforces the necessity to find the intermodal aspect of express emotions (body posture or emotion auditory aspects) and not just through the use of visual stimuli.

Independent of the deficits origin, the literature points out several consequences such as losses at social and interactional contexts, losses at interpersonal relationships and interactions, since both the interpersonal relationships and the interactions are influenced by complex factors that involve, among others, non-verbal cues[7]. In addition, the presence of deficits in social coping skills, may be a maladaptive way to cope with the lack of behavioural repertoire against stressful daily situations[17,18].

The specific changes highlighted at current study, pointed to impairments at the recognition of fear and disgust. It is known that theses emotions are related to adaptive functions in the body. The adaptive value of fear is associated with the anticipation of danger, since fear triggers protective avoidance or escape behaviors in individuals facing imminent danger. Thus, by the correctly identifying of fear in people's faces, the individual becomes aware of the presence of nearby threats, and it helps them mobilizing resources to deal with danger[32,33].

The AG members showed low accuracy rate to recognize fear. They also needed longer response time and stronger emotional intensity to process the facial expressions. There were significant differences between the groups. This finding is corroborated by the previous literature, which also identified losses in individuals with prior use of alcohol during the FERE, mainly in the faces showing negative emotions such as fear[7,9,12,15,34-38]. It is mentioning by the literature that the recognition of fear, i.e., the ability to anticipate dangers (and to trigger protective behaviors), was associated with alcohol dependence[35,37].

According to the literature, the aforementioned changes were found in alcohol dependent individuals, because the excessive use of alcohol led to altered function of the prefrontal cortex, as well as of the limbic structures, with emphasis on the amygdale. Consequently, they harmed the processing and the accurate recognition of fear, since the limbic structures are involved in aggressiveness control, emotional memory, avoidance and escape responses, and in fear conditioning, among others[40,41].

These data are corroborated by Calder *et al.*[42] and Townshend and Duka[7], who pointed out that alcohol dependent individuals show less brain activation in the limbic region during the emotion (fear) processing task. In addition, O'Daly *et al.*[16] showed that alcohol dependent individuals were less able to recognize fear expressions than the control individuals, since they showed less activation in the prefrontal areas, including in the orbitofrontal cortex and in the insula, which also mediate emotional processing.

Another interpretation available in the literature points out that the lack of skill to recognize non-verbal signs of fear may be a path leading to alcohol dependence. Since alcohol dependent individuals do not accurately interpret signs of fear during social interactions, not even in possible conflicting (dangerous) social situations, favouring greater exposure and vulnerability, which may also be one of the factors triggering the beginning and/or the continuity of alcohol consumption[35-37].

Current alcohol dependent individuals also showed quite impaired recognition of disgust. This emotion, as well as fear, play a role at adaptive function, since it may refer to aversion or repulsion to things and/or objects that taste or smell bad, or that even have a rotten aspect. In addition, aversion or repulsion may appear in interpersonal relationships, as in the case of morally objectionable behaviours or inappropriate scenes. Therefore, their basic function is to keep individuals away from repulsive things[38].

The AG and CG members showed statistically significant differences between them. The AG members were less successful in recognizing disgust, and required more time and emotional intensity to process the facial expressions. This finding also corroborated by the previous literature, which identified losses in individuals with alcohol dependence (abstinent and/or detoxification alcoholics) during the emotional facial recognition task in expressions related to disgust[33-35,39-41] and also in agreement with a recent meta-analysis[19]. In addition, the study by Salloum *et al.*[15], which involved neuroimaging examination during FERE, found that alcohol dependent individuals had lower activation in the anterior cingulate cortex while processing disgust and sadness than the healthy controls. It indicated that the lower activation in this area of the brain may have been caused by the excessive use of alcohol, thus resulting in the less accurate recognition of such emotions.

It is worth highlighting that the accurate recognition of disgust also has negative association with alcohol dependence. Therefore, it is hypothesized that the accurate recognition of disgust works as protection against the disorder, because it makes individuals aware of threats and mobilizes them to avoid what is disgusting or even repulsive to them and/or to their culture[27,36,37].

The deficits found in the current study, in relation to surprise, were related to the need of longer reaction time and of greater emotional intensity in the recognition of surprise, and to the tendency of obtaining less correct answers in AG than in CG. Similarly, some authors have found that alcoholic individuals showed less accuracy in the recognition of surprise[38-40] they needed longer response time[32] and even greater emotional intensity[38,39] than the control group. However, other authors found no differences between groups in any of the aforementioned variables[7,15,40].

It is worth highlighting that the reaction time to process surprise was positively associated with alcohol dependence. Among the basic emotions, surprise lasts a few seconds and its valence may be either positive or negative. Thus, it is hypothesized that the quick recognition of surprise is a way to avoid something that is interpreted as threatening, dangerous or uncertain. Philippot *et al.*[40] pointed out that alcohol dependent individuals have difficulty to deal with positive emotions, since they anticipate these emotions as negative consequences (threat, danger, rejection), because the excessive use of alcohol has possibly caused greater activation in limbic structures such as the amygdala[7].

The current study did not find significant changes regarding sadness, anger or happy. These emotions were associated with longer reaction times in AG in relation to CG, and they showed statistically significant differences, as well as the trend of less accuracy rate for sadness and happy. In addition, biases of total responses were found for happiness in AG in comparison to CG. Such results corroborated some studies in the field showing little alterations at the bias responses[38,39,41]. On the other hand, and different from the present study, the meta-analyses[19] found that abstinent or detoxification alcoholics present deficits in the recognition of anger, which may

be directly related to differences in sample characteristics or time of alcohol consumption.

Thus, the results of the present study overall suggest the worse performance of AG than that of CG, and it corroborates data found in the literature relative to the individuals who were not in current use of alcohol.

The fact that the individuals were not assessed for the presence or absence of possible cognitive and/or intellectual deficits may be seen as a limitation of the current study, since the literature indicates that alcohol dependent individuals may develop a range of cognitive impairments, such as dementia and/or encephalopathies, due to 0the use of alcohol[37-40]; fact that could directly and negatively affect FERE establishment and performance. This limitation is not specific to the current study, but it regards a gap in the literature, since only few studies have assessed the intellectual functioning[34,40,41]. Another limitation of the study involves the possibility of the presence of other psychiatric comorbidities, especially with personality disorders, which are not evaluated. The control of these confounding variables is important for future studies.

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Translation, cultural adaptation, and content validity index of the Juvenile Love Scale to the Brazilian context

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Received: 11/22/2016 – **Accepted:** 3/9/2017
DOI: 10.1590/0101-60830000000121

Abstract

Background: Passionate love involves physiological, emotional, and cognitive features that greatly changes behavior. This phenomenon seems universal or near universal. Even other animal species choose partners. An intense state of passionate love is associated with activity in dopamine pathways of the brain 'reward system', and recently has been regarded as a 'natural addiction'. Instruments or tools to evaluate romantic love during childhood is still scarce. **Objective:** To perform the translation and cultural adaptation of the Juvenile Love Scale (JLS) for use in the Brazilian context targeted for adolescents between 14 and 18 years old. **Methods:** The translation and cultural adaptation of JLS followed international recommendations, and its content validity was analyzed by a panel of experts in different areas of knowledge. **Results:** The final version of the JLS for use in the Brazilian context showed high content validity (> 90%). **Discussion:** To our knowledge, this is the first scale for measuring romantic or passionate love in adolescents adapted to the Brazilian context. This instrument is a significant contribution to the study of the dimensions of love, as well as to understand the impact of love on the psychiatric phenomena that pervade life in this stage of development.

Soares LS et al. / Arch Clin Psychiatry. 2017;44(3):63-6

Keywords: Romantic love, passionate love, Juvenile Love Scale (JLS), psychometrics, adolescence assessment.

Introduction

Romantic love, or passionate love, is associated with an intense desire for union towards another person[1]. Passionate love involves physiological, emotional and cognitive features that greatly changes behavior. Although some consider romantic love as a cultural construct promoted by the European historical context, there is evidence that this phenomenon is universal or near universal. Jankowiak and Fischer[2] analyzed 166 different societies and found reports of passionate love in 147 (88.5%) of them. These results are endowed by evidence that behaviors related to romantic love are also observed in other animal species through partners' choice mechanisms[3]. Altogether, passionate love seems to have an evolutive component, which is related to motivation towards a preferred mating partner[4].

An intense state of passionate love is associated with activity in dopamine pathways of the brain 'reward system' (*e.g.*, ventral tegmental area, caudate, and accumbens), and recently has been regarded as a 'natural addiction', though with mainly positive effects[5]. However, individuals passionately in love often express non-adaptive behaviors when expressed in extremes such as euphoria, obsession, and risk-behavior, which may lead to harmful consequences, particularly for those experiencing love withdrawn/rejection[5,6]. In fact, intense romantic infatuation was proposed as a model for studying "normal" alteration of the mechanisms related to reward processing[6], and has become an increasing topic of study[7]. Therefore, it is of extreme importance to be able to measure 'passionate love' reliably.

Hatfield *et al.*[8] found 33 instruments measuring romantic love over the last 70 years approximately. These measures were elaborated by different areas of expertise such as Sociology, Psychology, Anthropology, Medicine, Biology and Neurosciences. However, two scales stand out as the most used to measure human love, namely the Sternberg's Triangular Love Scale and the Hatfield & Sprecher's Passionate Love Scale (PLS). From the PLS, Hatfield and Sprecher also elaborated the Juvenile Love Scale (JLS)[9]. The purpose of the JLS is to measure romantic love in children and adolescents from 3 to 18 years-old. The juvenile version contemplates cognitive, physiological, and behavioral aspects of love. Despite the adult version had been translated into more than 12 languages and adapted to many other cultures and countries such as Germany, France, India, Italy, and even Brazil[8], measures that consider the state of romantic love during childhood and adolescence are still scarce. Nevertheless, adolescence may be a critical sensitive period for the experience of love, a time when love intensity may be lived as in no other point in life, especially in late adolescence[10,11]. Puberty brings a cascade of changes putting adolescents at a higher risk of reckless behavior, especially in the face of social situations, making them especially driven by passions[12,13]. Therefore, to expand cross-cultural research on passionate love in adolescents is of relevance for its better characterization and further investigation of its influence on a range of adaptive and non-adaptive behaviors.

In this study, we present the translation and cultural adaptation of the Juvenile Love Scale-JLS for use in the Brazilian context. The Content Validity Index (CVI) is also shown for the JLS Brazilian version. The target population for the present adaptation was adolescents between 14 to 18 years.

Methods

Juvenile Love Scale (JLS)

Thirty items compose the JLS, which also has a reduced version with 15 items. The items are rated on a 9 points-Likert scale (from one to nine) with higher scores indicating higher love intensity. It can be used to assess romantic love intensity in children and adolescents from 3 to 18 years. Hatfield and Young[13] reviewed evidence published in different studies and found high internal consistency with indexes ranging from 0.94 to 0.98. The correlation between the JLS and the Passionate Love Scale, the adult version, is 0.88 for children and 0.87 for adults[14].

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The JLS was designed to assess cognitive, emotional and behavioral signs of passionate love[8,10]. *Cognitive components* consist of [1] intrusive thought or concern for the partner; [2] idealization of the other or the relationship; and [3] desire to get to know each other and be known by him/her. The *emotional components* are [1] attraction to the partner, especially sexual; [2] positive feelings when things are going well; [3] negative feelings when things go wrong; [4] yearning for reciprocity; [5] desire for a whole and permanent union; and [6] physiological arousal (sexual). Finally, the *behavioral components* consist of [1] actions to determine the feelings of others; [2] studying the other person; [3] be at the disposition for the other; and [4] the maintenance of physical proximity.

Translation and adaptation

The adaptation process of the original instrument to the Brazilian context occurred in six stages as recommended by Sousa and Rojjanasrirat[14].

Stage 1. The translation of the original scale into Brazilian Portuguese was elaborated by two independent bilingual translators (T1 and T2).

Stage 2. A preliminary version was synthesized combining the best cultural translation of each item between T1 and T2. This first synthesis was performed by a third independent bilingual individual who was knowledgeable about the instrument and its theoretical foundation.

Stage 3. Two independent native English-speakers back-translated the preliminary version from Brazilian Portuguese to American English.

Stage 4. The two back-translated versions were examined by a committee composed of bilingual clinical psychologists, English native speakers, and English teachers and translators in Brazil. They assessed the initial conceptual, semantic and content equivalence of both back-translated versions until reaching a final agreement. In this stage, only item 26 ("_____ *can make me feel bubbly, like coke.*") had to go through the earlier stages again in order to be considered equivalent in both languages.

Stage 5. Twenty-two adolescents between 14 and 18 years participated in a pilot testing of the scale for assessment of the clarity of the instructions and items regarding language. Participants were asked to rate the instrument on a dichotomous scale (i.e., clear vs. unclear).

Stage 6. The preliminary final version was submitted to an expert committee of scholars and professionals to assess the content validity of the scale to elaborate a final version. Data regarding content validity was collected trough a questionnaire developed following the model suggested by Polit and Beck[15]. The items in the preliminary version of the scale were rated in a 4 point-Likert scale (1-irrelevant, 2-little relevance; 3-relevant; and 4-extremely relevant). Ten judges among scholars and professionals in the Psychology and Neuroscience fields answered the content validity questionnaire. We then calculated the Content Validity Index (CVI) *per* item and of the scale, i.e., the degree of agreement of the judges about the classification of the items[15]. For analysis, the rates were merged into two categories, so items ranked as 1 and 2 were considered irrelevant for the scale, while those scored as 3 and 4 were considered relevant. First, we calculated the CVI individually for each item (proportion of experts rating the item as relevant). The CVI of the whole scale was then obtained as the mean of the CVI of the items. Polit and Beck[15] recommended values above 0.90 to achieve significant content validity.

All participants consented to have their data used in the research. The project was approved by the local ethics board (CAAE: 57272416.1.0000.5149).

Results

The pilot testing sample (stage 5) was composed by 22 adolescents from 14 to 18 years old (15.7 ± 1.2; 3 males, 19 females). All adolescents were students (9.8 ± 1.03 years of education). The interrater agreement for the instructions and all items was higher than 80%. Therefore, no item had to be reconsidered in this stage.

The expert committee was composed of ten individuals among four University professors (neuroscientists in university departments of Psychology [n = 2], Pediatrics, and Physical Education), four Clinical Psychologists coursing post graduation (one Ph.D. student in Neuropsychology, and three master students in Molecular Medicine), and two Clinical Neuropsychologists coursing their Ph.D. in Molecular Medicine. Table 1[1] shows the Content Validity Index (CVI) *per* item and of the whole scale. Thirteen out of 30 items were rated as relevant by a 100% of the experts. The agreement in the remaining, but two items, ranged between 80% and 90%. A CVI of 78% or higher is considered ideal for the item judgment[15]. Therefore, the items 4 (*Sometimes I think it is fun just to see _____ move*) and 22 (*I want _____know me, know what I am thinking, what scares me and what I desire*) were considered poor in content validity. The version of 30-items of the scale obtained a 91% CVI, while the 15-items version reached a 93% CVI. Therefore, overall, the complete and short versions had a satisfactory CVI. Table 2 presents the original item and its final cultural adaptation for the Brazilian population. Both versions are available to download in www.labepneuro.com or by the authors on demand.

Discussion

The translation and cultural adaptation of the Juvenile Love Scale (JLS) for use in the Brazilian context were executed under a rigorous methodological approach known to improve reliability and validity of cross-cultural instruments or scales[16]. The Brazilian version of the JLS showed good language clarity considering a

Table 1. Content Validity Index (CVI) of the Juvenile Love Scale items, complete version, and short version in the Brazilian context

Item	CVI	Item	CVI	Item	CVI
Item 1	80%	Item 11[a]	100%	Item 21	90%
Item 2[a]	100%	Item 12	90%	Item 22[a]	70%
Item 3	90%	Item 13	100%	Item 23	100%
Item 4	40%	Item 14[a]	90%	Item 24[a]	89%
Item 5[a]	90%	Item 15[a]	100%	Item 25	90%
Item 6[a]	100%	Item 16	100%	Item 26	100%
Item 7[a]	100%	Item 17[a]	80%	Item 27[a]	90%
Item 8[a]	100%	Item 18	90%	Item 28	90%
Item 9	80%	Item 19[a]	100%	Item 29	100%
Item 10[a]	100%	Item 20	90%	Item 30[a]	90%
Scale-CVI	30 itens	91%			
	15 itens	93%			

[a] Indicates inclusion on the JLS-15 short form.

Table 2. Juvenile Love Scale items – Brazilian Portuguese version

Item	Original Version	Brazilian Version
1.	When _____ is around I laugh and cry more often.	Quando _____ está por perto eu sorrio e choro mais vezes.
2.	I feel like things would always be sad and gloomy if I had to live without _____ forever.	Eu sinto que as coisas são sempre tristes e sombrias se eu viver sem _____ para sempre.
3.	Sometimes I feel shaky all over when I see _____.	Algumas vezes, eu me sinto bambo quando vejo _____.
4.	Sometimes I think it is fun just to watch _____ move around.	Às vezes, eu acho divertido apenas ver _____se mover.
5.	Did you ever keep thinking about _____ when you wanted to stop and couldn't?	Você já continuou pensando em alguém, mesmo quando você queria parar e não conseguiu?
6.	I feel happy when I am doing something to make _____ happy.	Eu me sinto feliz quando estou fazendo algo que faz _____ feliz.
7.	I would rather be with _____ than anybody else.	Eu prefiro estar com _____ do que com qualquer outra pessoa.
8.	I'd feel bad if I thought _____ liked somebody else better than me.	Eu fico triste se penso que _____ gosta de outra pessoa.
9.	No one else could like _____ as much as I do.	Ninguém poderia gostar de _____ tanto quanto eu.
10.	I want to know all I can about _____.	Eu quero saber tudo que eu puder sobre _____.
11.	I'd like _____ to belong to me in every way.	Eu gostaria se _____ fosse minha (meu) de todas as formas.
12.	I will always like _____.	Eu sempre vou gostar de _____.
13.	I feel all happy inside when _____ looks at me and I look at _____.	Eu me sinto todo feliz por dentro quando _____ olha para mim e eu olho para _____.
14.	I'd like it a lot if _____ played with me all the time.	Eu realmente adoraria se _____ brincasse comigo o tempo todo.
15.	If I could, when I grow up I'd like to marry (live with) _____.	Se eu puder, quando crescer, gostaria de me casar (viver) com _____.
16.	_____ is the person who can make me feel the happiest.	_____ é a pessoa que me faz mais feliz.
17.	When _____ hugs me my body feels warm all over.	Quando _____ me abraça, eu sinto todo meu corpo se aquecer.
18.	I feel all soft and happy inside about _____.	Eu me sinto leve e feliz por dentro quando penso em _____.
19.	I am always thinking about _____.	Estou sempre pensando em _____.
20.	If I were alway from _____ for a long time I would be very lonely.	Se eu ficasse longe de _____ por muito tempo, eu me sentiria muito sozinho.
21.	Sometimes I can't do my school work because I am thinking about _____.	Às vezes, eu não consigo fazer meu dever de casa porque estou pensando em _____.
22.	I want _____ to know me, what I am thinking, what scares me, what I am wishing for.	Eu quero que _____me conheça, conheça o que estou pensando, o que me assusta e o que eu desejo.
23.	Knowing that _____ cares about me makes me feel more like I am OK.	Saber que _____ se importa comigo faz eu me sentir bem.
24.	I look at _____ a lot to see if he/she likes me.	Eu olho bastante para _____ para ver se ele/ela gosta de mim.
25.	If _____ needed help from me, I'd stop what I was doing, even if it was lots of fun and go help him (her).	Se _____ precisasse da minha ajuda, eu pararia o que estivesse fazendo, mesmo que fosse muito divertido, para poder ajudá-lo(a).
26.	_____ can make me feel bubbly, like coke.	_____ faz eu me sentir radiante, nas nuvens.
27.	When _____ is around I really want to touch him/her and be touched.	Quando _____ está por perto eu quero muito tocá-lo/a e ser tocado.
28.	Living without _____ would be very, very sad.	Viver sem _____ seria muito, muito triste.
29.	I want to hug _____ very, very tight.	Eu quero abraçar _____ muito, muito apertado.
30.	When I think _____ might be mad at me, I feel really sad.	Quando eu penso que _____ pode estar bravo(a) comigo, eu fico muito triste.

target population of adolescents between 14 to 18 years with the straight approval of all 30 items and the instructions. The expert panel evaluating the content-related validity of the scale found the JLS to be a conceptual measure of romantic love in children and adolescents and an equivalent measure of the original instrument with a Content Validity Index (CVI) higher than 90% for both the complete and the short forms of the JLS. Overall, the results suggest that the Juvenile Love Scale, translated and adapted to the Brazilian context, is pursuant to its proposal and suitable for application in the population of adolescents aged 14 to 18 years.

The use of the JLS can contribute to academic research and the widening understanding of various aspects of children and adolescent lives. Romantic love in adolescence is a recent topic of scientific interest with studies on the subject only becoming more significant in the last two decades. It is no longer possible to ignore such an impressive part of the lives of the young. According to a study conducted with American teenagers, about 25% of people in early adolescence affirmed they had a romantic relationship in the past 18 months, increasing for 53% in the 15-year-olds, and reaching more than 70% of adolescents by age 18[17]. So, romantic love is a central topic of human development with adolescence being a critical age.

Being in a loving relationship in adolescence was associated with well-being in the short and the long term with benefits to the self-esteem and social integration[18,19]. On the other hand, young people who were involved romantically manifest more symptoms of depression than those who were not, with the probability of a first episode of major depression during adolescence being higher if a break-up had recently been reported[18-20]. Similarly, a conflictual relationship heightens an already stressful phase in life, a critical period for the development of various psychiatric disorders, especially concerning emotional disorders[5,21-23]. Therefore, a reliable and valid measure of the intensity of romantic love in adolescence is pivotal for a better understanding of the impact of love on several aspects of the adolescent life and their potential consequences.

By a clinical perspective, instruments such as the JLS can be useful to evaluate possible altered states and behaviors related to passionate love in adolescence. Brand *et al.*[24], for example, says that adolescents' early-stage of intense romantic love can be highly comparable to hypomania, changing sleep patterns, mood, daily concentration, and daily activity. Also, especially in psychotherapy contexts, adolescents have a chance to talk about their feelings and thoughts about love, sex, and intimacy during the time they use to complete the scale. Besides, it allows therapists to have a chance to evaluate some skills that adolescents must come to develop[9].

It is noteworthy to acknowledge some limitations in this translation and cross-cultural adaptation process. There is no consolidated or consensual theory on romantic love in children and adolescents. Therefore, the evaluation of the judges may be somewhat

biased by their impressions and observations of passionate love. Moreover, some key expressions on the original content of the scale have no equivalent in Brazilian Portuguese, which hampered the translation process. In such cases, new expressions were developed to ensure the semantic quality issues. However, the translation process requires specific care in linguistic terms since it must preserve the idiosyncrasy of the language in which the scale will be translated to and have in mind the target community of interest. Moreover, the semantic adaptation of any scale or test is necessary to the extent that ensures language understanding to the population for which it is intended to[25,26]. Additionally, though the JLS was originally developed for children from 3 to 18 years, we have assured language clarity only for adolescents from 14 to 18 years. Thus, future studies are needed to ensure the adequacy of the Brazilian version of the JLS for a younger population. Also, the scale should be administered to a large sample of teenagers so that psychometric properties can be verified.

For the first time, a scale measuring romantic or passionate love in adolescents was adapted to the Brazilian context in this study. The JLS is a significant contribution to the study of the dimensions of love in the Brazilian population, as well as to understand the impact of love on the psychiatric phenomena that pervade life in this stage of development. After all, "few phenomena reflect the euphoria and the despair of this stage of life more poignantly than romantic relationships"[27].

Acknowledgments

We thank professor Elaine Hatfield of the University of Hawaii for kindly agrees with the translation and cultural adaptation of the Juvenile Love Scale for the Brazilian context. This study was supported by INCT-MM that is financed by the Brazilian agencies for research development: *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq), *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Capes), and *Fundação de Amparo à Pesquisa do Estado de Minas Gerais* (Fapemig).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Pain-related quality of life related to mental health and sociodemographic indicators in adolescents

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Received: 11/28/2016 – **Accepted:** 5/4/2017
DOI: 10.1590/0101-60830000000122

Abstract

Background: A total of 6150 junior and senior high school students aged 11–18 years participated in this study. Their level of pain-related QOL was assessed using the pain subscale of the Taiwanese QOL Questionnaire for Adolescents. The severities of depression, suicidality, anxiety, and alcohol abuse were also examined. **Objectives:** This study examined the associations between pain-related quality of life (QOL) and sociodemographic characteristics and those between pain-related QOL and mental health problems such as depression, suicidality, anxiety, and alcohol abuse. **Methods**: The association of sociodemographic factors with pain-related QOL was examined through multiple regression analysis. The association of pain-related QOL with mental health problems was examined through logistic regression analysis. **Results**: The boys exhibited a higher level of satisfaction with pain-related QOL than did the girls. Older age was significantly associated with a lower level of satisfaction with pain-related QOL. Residential background, parental marital status, and parental education levels were not significantly associated with the level of satisfaction with pain-related QOL. Increased risks of depression, suicidality, anxiety, and alcohol abuse were significantly associated with a low level of satisfaction with pain-related QOL. **Discussion:** A low level of satisfaction with pain-related QOL is significantly associated with the risk of poor mental health. Adolescents with the correlates of low satisfaction with pain-related QOL should be monitored for the risk of mental health problems.

Lee PH et al. / Arch Clin Psychiatry. 2017;44(3):67-72

Keywords: Quality of life, pain, mental health, adolescent.

Introduction

Mental health problems are prevalent in adults with chronic nonmalignant pain[1]. Headache and joint, back, and neck pain increase the risks of depression–anxiety spectrum disorders and the chronic depression–anxiety course in adults[2,3]. Chronic nonmalignant pain, such as back pain and headache, is prevalent among adolescents[4]. However, to the best of our knowledge, few studies have examined the association between pain and mental health problems in adolescents.

An examination of the correlates of pain and their association with mental health problems in adolescents is warranted for the following reasons. First, adolescents undergo considerable biological changes with puberty[5], and fast-growing muscles and bones may increase the likelihood of experiencing pain[6]. Second, high-technology devices and systems, such as computers, the Internet, and smartphones, have become important in the lives of adolescents[7]. The use of these high-technology devices and systems may reduce adolescents' engagement in physical exercise and increase their sedentary time, thus increasing their risk of pain[8]. Third, the construction of an emancipated identity is a major developmental task of adolescence[5]; therefore, pain and mental health problems developed during this stage may affect a person's identity in the long term. Hence, it is crucial to investigate pain and its association with mental health problems in adolescents.

Quality of life (QOL) is defined as people's perceptions of their own positions in life in the context of culture and value systems in which they live[9]. QOL is a multidimensional concept comprising psychological, physical, and social well-being[10]. Few studies have examined pain-related QOL and its sociodemographic correlates in adolescents. A previous study found that pain intensity is associated with a relatively poor functional status and poor psychological and somatic functioning in adolescents aged 12–18 years; pain-related QOL and the effect of pain on the families of the adolescents remained unchanged during the 3-year follow-up period in that study[11]. Additional studies should survey the sociodemographic correlates of pain-related QOL in adolescents to provide a reference for developing prevention and intervention strategies.

Although many studies have examined the association of malignant pain with depression and anxiety in adolescents in clinical units[12,13], to the best of our knowledge, few studies have examined the association between nonmalignant pain and mental health problems in adolescents in communities. Pain, depression, and anxiety may exhibit bidirectional relationships. Although a recent study investigating Norwegian adolescents determined that depression symptoms increased the risk of neck and shoulder pain[14], another study investigating adolescents with cancer found that pain increased the risk of depression and anxiety[15]. Additional studies are necessary to investigate the association between nonmalignant pain and mental health problems in non-referred adolescents in communities.

A previous study reported a significant association between pain and suicidality in adults[3]; the lifetime prevalence of suicide attempts in people with pain is approximately 5%–14%, and the prevalence of suicidal ideation is approximately 20%[3]. Chronic nonmalignant pain, such as migraines, increases the risk of suicidal attempts[16]. Other medical conditions, such as human immunoviral infection and multiple sclerosis, are also associated with suicidality[17,18]. A survey of the members of a chronic nonmalignant pain self-help organization revealed that the proportion of members considering suicide at the time of the survey was as high as 50%[19]. However, most studies have not specifically focused on adolescents.

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Researchers have also investigated the association between pain and alcohol use. Moderate alcohol consumption, as defined by The United States Department of Health and Human Services (2010), is associated with positive pain-related outcomes (*e.g.*, higher QOL), whereas excessive consumption is associated with negative pain-related outcomes (*e.g.*, higher pain severity)[20]. Zale *et al*. proposed that alcohol consumption can relieve acute pain, but pain can motivate alcohol consumption[20]. In addition, pain is a significant predictor of heavy drinking lapses during treatment[21]. Most studies have not focused on the association between pain and alcohol consumption in adolescents, except for a recent study that reported that chronic pain may not increase the risk of alcohol use in adolescents[22].

The present study examined the sociodemographic correlates of pain-related QOL in adolescents and the correlation of pain-related QOL with depression, suicidality, anxiety, and alcohol abuse. Examining adolescents' pain-related QOL may provide information on their perception of pain and its effects on their daily lives. We hypothesized that differences exist in pain-related QOL among adolescents with various sociodemographic factors. We also hypothesized that pain-related QOL is significantly associated with depression, suicidality, anxiety, and alcohol abuse in adolescents.

Methods

Participants

Participants in this study were recruited from the 2009 Project for the Health of Children and Adolescents in Southern Taiwan, a research program examining the mental health status of children and adolescents living in four counties and three metropolitan areas in southern Taiwan[23]. In 2009, 254,130 students were studying in 205 junior high schools and 202,883 students in 143 senior high/vocational schools in this area. A stratified random sampling strategy was developed on the basis of the definitions of urban and rural districts in the *Taiwan-Fukien Demographic Fact Book* and school and grade characteristics and applied to ensure proportional representation of districts, schools, and grades. Five junior high schools and five senior high/vocational schools were randomly selected from urban districts. Similarly, five junior high schools and four senior high/vocational schools were randomly selected from rural districts. Furthermore, classes in these schools were stratified into three levels on the basis of grade: primary, junior high, and senior high/vocational school. Subsequently, 6703 high school students in grades 7–12 were randomly selected on the basis of the ratio of students in each grade. This study was approved by the Institutional Review Board of Kaohsiung Medical University.

Instruments

Pain subscale of the Taiwanese QOL Questionnaire for Adolescents

We used the self-reported pain subscale of the Taiwanese QOL Questionnaire for Adolescents (TQOLQA) to measure the levels of pain-related QOL in participants[24]. The pain subscale of the TQOLQA comprises three items: (1) "Do you worry about pain or discomfort?" (2) "Do you have any difficulty in managing or coping with pain or discomfort?" and (3) "Does your pain or discomfort interfere with things you need to do?" This instrument focused on both aspects of well-being and functionality. After the conversion of raw scores for reverse questions, a higher total subscale score indicates improved pain-related QOL over the preceding 2 weeks. The subscale is then standardized to range from 0 (lowest level of functioning) to 100 (highest level). In the present study, Cronbach's α coefficient of the pain subscale was 0.74.

Sociodemographic characteristics

Data on characteristics such as age, sex, residential background (urban or rural), and paternal and maternal education levels were collected. In Taiwan, the duration of compulsory fundamental education is 9 years. Therefore, participants were categorized as those with parents with a high level of education (father or mother completed 9 years of compulsory fundamental education) and those with parents with a low level of education (father or mother did not complete 9 years of compulsory fundamental education).

Mandarin Chinese version of the Center for Epidemiological Studies-Depression Scale

The Mandarin Chinese version of the Center for Epidemiological Studies-Depression Scale (MC-CES-D) is a 20-item self-administered questionnaire that entails using a 4-point evaluation scale to assess the frequency of depressive symptoms in the preceding week[25,26]. Higher MC-CES-D scores indicate higher depression severity. In the present study, Cronbach's α coefficient of the MC-CES-D was 0.92. Moreover, participants whose total MC-CES-D score was 1 standard deviation (SD) higher than the mean score of the study population were classified as the group with significant depressive symptoms.

Suicidality

The 5-item questionnaire derived from the epidemiological version of the Kiddie Schedule for Affective Disorders and Schizophrenia[27] was used to assess the occurrence of suicide attempts and four forms of suicidal ideation in the preceding year[28]. Each question elicited a "yes" or "no" response. Cohen's kappa coefficient of agreement (κ) between participants' self-reported suicide attempts and their parents' reports was 0.541 ($p < 0.001$)[28]. Participants who responded "yes" to any of the five items were classified as having suicidal ideation or attempts.

Taiwanese version of the Multidimensional Anxiety Scale for Children

The Taiwanese version of the Multidimensional Anxiety Scale for Children (MASC-T) consists of 39 items that are answered on a 4-point Likert scale to evaluate participants' self-reported general anxiety symptoms[29,30]. A higher total MASC-T score represents a more severe level of general anxiety. Participants whose total MASC-T score was 1 SD higher than the mean score of the study population were classified as the group with significant general anxiety symptoms.

CRAFFT Alcohol Abuse Screening Test

The self-reported CRAFFT Alcohol Abuse Screening Test was developed to assess problematic alcohol use in adolescents[31,32]. A previous study[31] demonstrated that a cutoff score of 2 on the CRAFFT Alcohol Abuse Screening Test can be used to identify adolescents with alcohol use disorder or problematic alcohol use on the basis of the Diagnostic and Statistical Manual of Mental Disorders[33]. In this study, we classified adolescents with a score of 2 or more on the CRAFFT Alcohol Abuse Screening Test as those having "problematic alcohol use".

Statistical analysis

A total of 6,445 students (96.2%) agreed to participate in this study. Of the 258 students who did not participate in this study, 68 did not participate because of parental objections, 128 returned blank questionnaires, and 62 were absent when research assistants

visited their classes. We recruited five research assistants with educational backgrounds of nursing, social work, or psychology. All research assistants received training to ascertain consistency and accuracy in the process of performing data collection of self-reported questionnaires. Research assistants explained the purpose and procedure of this study in each classroom during school hours and invited students to complete the research questionnaire anonymously. Participants could ask research assistants to answer them if they had questions regarding the contents of the research questionnaire. Participants who changed their mind could return blank questionnaires along with those from other students. All students received a gift worth NT$33 (US$1) at the end of the assessment.

Data analysis was performed using SPSS statistical software, version 18.0 (SPSS Inc., Chicago, IL, USA). The association of sociodemographic factors with pain-related QOL was examined in the two-step analysis. First, the association of sociodemographic factors with pain-related QOL was examined using Pearson's *r* correlation and t test. Second, factors that were significantly associated with pain-related QOL were further incorporated (independent variables) into a multiple linear regression analysis to examine their association with pain-related QOL (dependent variable). In addition, we used the standard criteria proposed by Baron and Kenny (1986)[34] to examine whether the associations of some sociodemographic correlates with pain-related QOL were different in terms of other sociodemographic correlates. According to the criteria, moderation occurred when an interaction term for a predictor (sociodemographic correlate A) and a hypothesized moderator (sociodemographic correlate B) were significantly associated with a dependent variable (pain-related QOL) after controlling for the main effects of both predictors and hypothesized moderator variables. The associations of pain-related QOL (independent variable) with mental health problems (dependent variables) were examined using logistic regression analysis after controlling for the effects of sex and age. Two-tailed $p < .05$ was considered statistically significant.

Results

Table 1 lists the sociodemographic characteristics, level of pain-related QOL, and mental health indicators of the participants. Of the participants, 3216 were girls and 2934 were boys; their mean age was 14.8 years (SD: 1.8 years), and the mean score of pain-related QOL was 64.1 (SD: 17.2), ranging from 0 to 100.

Table 2 shows the associations of sociodemographic factors with pain-related QOL examined using Pearson's r correlation and t test. Age was negatively associated with pain-related QOL ($p < .001$). The boys had a higher level of satisfaction with pain-related QOL than did the girls ($p < .001$). The adolescents with mothers with a high level of education reported a higher level of pain-related QOL than did those with mothers with a low level of education ($p = .048$).

Age, sex, and maternal education level were further incorporated into multiple regression analysis to examine their association with pain-related QOL (Table 3). The condition index was 19.766, indicating the absence of a multicollinearity problem. The results of Model I indicated that male sex and old age were significantly associated with a lower level of satisfaction with pain-related QOL. Maternal education was not significantly associated with the level of satisfaction with pain-related QOL. Furthermore, we examined the moderating effect of sex on the association between age and pain-related QOL by including the interaction between sex and age in the regression analysis (Model II). However, the interaction between sex and age did not significantly moderate pain-related QOL.

Table 4 demonstrates the correlations of pain-related QOL with mental health problems. After the effects of age and sex were controlled for, a high level of satisfaction with pain-related QOL was significantly associated with reduced risks of depression, suicidality, anxiety, and alcohol abuse.

Table 1. Sociodemographic characteristics, the level of pain-related QOL, and mental health indicators (N = 6150)

	n (%)	Mean (SD)	Range
Sex			
Girls	3216 (52.3)		
Boys	2934 (47.7)		
Age (years)		14.8 (1.8)	11-18
Residential background			
Urban	3146 (51.2)		
Rural	3004 (48.8)		
Parental marriage			
Widowed, separated, and divorced	919 (14.9)		
Married and not separated	5231 (85.1)		
Paternal education			
High	4853 (78.9)		
Low	1297 (21.1)		
Maternal education			
High	4796 (78.0)		
Low	1354 (22.0)		
Pain-related QOL		64.1 (17.2)	0-100
Mental health indicators			
Depression	630 (11.0)[a]		
Suicidality	1977 (32.3)[b]		
Anxiety	739 (13.9)[c]		
Alcohol abuse	811 (13.2)[d]		

[a]: *n* = 5708; [b]*n* = 6127; [c]*n* = 5327; [d]*n* = 6126.

Table 2. Association of sociodemographic factors with pain-related QOL

	Pain-related QOL			
	Pearson's *r*	Mean (SD)	*t*	*p*
Age	-0.094			< 0.001
Sex				
Girls		61.8 (16.3)	-11.066	< 0.001
Boys		66.6 (17.8)		
Residential background				
Urban		64.0 (17.3)	-0.404	0.686
Rural		64.1 (17.4)		
Parental marriage				
Widowed, separated, and divorced		63.8 (17.3)	-0.431	0.666
Married and not separated		64.1 (17.2)		
Paternal education level				
High		64.2 (17.3)	1.504	0.133
Low		63.4 (16.8)		
Maternal education level				
High		64.3 (17.4)	1.974	0.048
Low		63.2 (16.6)		

Table 3. Association of sociodemographic factors with pain-related QOL: multiple regression analysis

	Model I			Model II		
	Beta	*t*	*p*	Beta	*t*	*p*
Sex[a]	0.134	10.654	< 0.001	0.284	2.748	0.006
Age	-0.088	-6.970	< 0.001	-0.070	-4.053	< 0.001
Maternal education level[b]	-0.021	-1.640	0.101	-0.021	-1.679	0.093
Sex x Age				-0.151	-1.460	0.144
R square	0.028			0.028		

[a]: 0: girls; 1: boys; [b]: 0: high; 1: low.

Table 4. Association of pain-related QOL with mental health problems: logistic regression analysis

	Depression				Suicidality				Anxiety				Alcohol abuse			
	Wals	*p*	OR	95% CI	Wals	*p*	OR	95% CI	Wals	*p*	OR	95% CI	Wals	*p*	OR	95% CI
Pain-related QOL	295.026	< 0.001	0.957	0.952-0.962	235.615	< 0.001	0.974	0.971-0.977	421.331	< 0.001	0.946	0.941-0.951	5.963	0.015	0.995	0.990-0.999
Sex	18.193	< 0.001	0.678	0.568-0.811	22.015	< 0.001	0.766	0.686-0.856	63.546	< 0.001	0.485	0.406-0.579	9.711	0.002	1.269	1.092-1.474
Age	3.448	0.063	1.046	0.997-1.098	0.004	0.950	0.999	0.969-1.030	26.886	< 0.001	0.884	0.844-0.926	24.010	< 0.001	1.108	1.064-1.155

QOL: Quality of life.

Discussion

The results of the present study showed that the boys had a higher level of satisfaction with pain-related QOL than did the girls. Previous studies have also reported sex differences in pain experience[35,36]. Compared with men, women usually reported more frequent, severe, and persisting pain[36]. A study reported differences in central pain processing, including the magnitudes and locations of μ-opioid system activation, between men and women[37]. Men have higher activation in the right dorsolateral prefrontal cortex, insula, and dorsal pons, whereas women have higher activation in the ventromedial prefrontal cortex, right anterior cingulate cortex, and left amygdala[37]. Additional studies should investigate whether these sex differences in central pain processing account for the sex difference in pain-related QOL found in this study. Moreover, hormonal changes during the menstrual cycle in women may partially account for the sex difference in pain-related QOL, because the sex difference in pain is mainly observed during reproductive years and is observed to a lesser extent in children or older adults[38]. In women, the various phases of the menstrual cycle may exert different effects on pain. A study reported that the luteal phase of the menstrual cycle is related to higher pain sensitivity, and higher rates of back pain, temporomandibular joint pain, and migraines occur at the end of the luteal phase[36]. Another study indicated that the reproductive status of women may influence the overall function of central opioid systems[39].

Our study results revealed that older age (from the range of 11–18 years) was significantly associated with a lower level of satisfaction with pain-related QOL. Adolescents may encounter more physical conflicts and accidents as they become older; thus, they may also experience more pain. Cognitive and behavioral reactions to pain may also partially account for the association between age and pain-related QOL. Piira *et al*. reported that compared with younger children and adolescents, older children were more likely to use internalizing or catastrophizing coping strategies for pain[40]. Ineffective coping strategies for pain may further compromise their pain-related QOL. However, Myers *et al*. found that older adolescents may have higher pain tolerance than do younger adolescents[41]. Compared with younger adolescents, older adolescents may have higher self-confidence and are more well-equipped with appropriate skills to cope with pain. Additional studies should examine the association between age and pain-related QOL.

The results of this study indicated that a high level of satisfaction with pain-related QOL was significantly associated with a decreased risk of depression. Although many studies have explored the association between pain and depression[42,43], it is difficult to establish the precise direction of causation. At the brain circuit level, mesolimbic dopamine system dysregulation has been proposed to be associated with both pain and depression[44]. At the physiological level, short-term stress activates dopaminergic neurotransmission in the ventral tegmental area and nucleus accumbens and drives motivation to cope with stress[43,45]. By contrast, chronic stress causes sustained activation and ultimately dysregulates the mesolimbic dopamine system[46]. These observations may partially account for the association between pain and depression. Although this cross-sectional study did not determine the causal relationship between pain-related QOL and depression, we speculate that a high level of satisfaction with pain-related QOL indicates less susceptibility and more flexibility in the mesolimbic dopamine system and is hence associated with a decreased risk of depression.

In the present study, a high level of satisfaction with pain-related QOL was significantly associated with a decreased risk of suicidality. Previous studies have reported that chronic pain increased the risk of suicidality in adolescents[47,48], even after controlling for depression[49]. At the brain circuit level, both pain and self-injurious acts are associated with the altered function of the endogenous opioid system, particularly β-endorphin and enkephalin neurotransmitters[50]. Chronic pain may result in endogenous opioid system dysfunction, and self-injurious acts may increase its functions[51]. Thus, we can reasonably speculate that a high level of satisfaction with pain-related QOL may reduce the need for endogenous opioid actions and is hence associated with a decreased risk of suicidality. Moreover, Cohen's kappa coefficient of agreement between participants' self-reported suicide attempts and their parents' reports evaluated using the 5-item questionnaire derived from the epidemiological version of the Kiddie Schedule for Affective Disorders and Schizophrenia was 0.541, indicating a moderate agreement[52]. Detecting suicidal ideation of adolescents is a clinical challenge. Information from multiple sources, including adolescents themselves, families, peers, teachers, and social workers, is necessary for clinicians to evaluate the risk of suicidality among adolescents.

We observed that a high level of satisfaction with pain-related QOL was significantly associated with a decreased risk of anxiety. Although several studies[53,54] have explored pain and anxiety in adolescents, extremely few studies have focused on pain-related QOL. A study reported that higher anxiety sensitivity correlates with a higher fear of pain, which is associated with increased pain disability[55]. Another study indicated that pain is related to functioning at a low, but not high, level of anxiety[56]. This finding provides an alternative perspective that anxiety may moderate the relationship between pain and QOL.

The present study found that a high level of satisfaction with pain-related QOL was significantly associated with a decreased risk of alcohol abuse. A previous study reported a curvilinear association between alcohol consumption and pain[20]. Moderate alcohol consumption was associated with positive pain-related outcomes, such as higher QOL, whereas excessive consumption was associated with negative pain-related outcomes, such as higher pain severity[20]. Another study showed that alcohol dependence and chronic pain share common neural circuits; therefore, pain sensitivity and alcohol use may exert reciprocal effects[57].

Potential prevention strategies related to mental health problems are available. Clinicians should be more alert and pay more attention to psychiatric comorbidities when treating patients with pain. Awareness-raising activities and community psychoeducation are crucial to deliver accurate information regarding pain and mental health problems to the public. The incorporation of related psychoeducation into school programs can be more effective considering our targeted group of adolescents.

This study has several limitations. First, the cross-sectional research design of this study limited our ability to draw conclusions regarding the causal relationship between pain-related QOL and

mental health problems examined in this study. Second, data in this study were exclusively self-reported. The use of one data source may have influenced our findings and resulted in shared-method variance. In addition, we did not specify the types of pain measured, which can be essential in further data analysis. Moreover, pain and discomfort are different aspects with different implications for prevention, assessment, and treatment; however, the design of questions in the questionnaire did not differentiate them. Third, although we examined the sociodemographic correlates of pain-related QOL, we did not examine the relationship of other factors, such as domestic violence or school bullying, with pain-related QOL. Therefore, taking into account of the limitations, additional studies should be conducted in the future not only to examine the relationship of these factors but also to explore the reasons underlying the association of pain-related QOL with depression, suicidality, anxiety, and alcohol abuse.

Conclusion

Sex and age are significantly associated with pain-related QOL. Thus, prevention and intervention programs for pain problems in adolescents should consider sex and age. A low level of satisfaction with pain-related QOL is significantly associated with increased risks of depression, suicidality, anxiety, and alcohol abuse, indicating that pain-related QOL is a clinical issue that deserves routine survey among adolescents.

Funding

This study was partially supported by grant NSC 97-2410-H-037-003-SSS awarded by the National Science Council, Taiwan (ROC).

Disclosure

None declared.

Ethical approval

This study was approved by the Institutional Review Board of Kaohsiung Medical University.

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Paraoxonase (PON1) L55M and Q192R polymorphisms in major depression and bipolar affective disorder

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Received: 12/15/2016 – **Accepted:** 4/3/2017
DOI: 10.1590/0101-60830000000123

Abstract

Background: Oxidative and nitrosative stress pathways, along with immune-inflammatory response, might play an important role in the pathogenic mechanisms underlying major depression and bipolar disorder. **Objective:** The aim of the present study is to investigate paraoxonase 1 polymorphisms and its correlations with disease parameters in patients with major depression and bipolar affective disorder. **Methods:** PON1 L55M and Q192R single nucleotide polymorphisms were analyzed in a group consisted of 100 patients with major depression, and 100 patients with bipolar affective disorder and 96 healthy controls. Polymorphisms were analyzed by using polymerase chain reaction. **Results:** Our findings reported no association between Q192R and L55M polymorphisms of PON1 and major depression and bipolar disorder. Additionally, there was no association between the PON1 genotypes and disease variables in both depressed and bipolar patients. **Discussion:** Evaluating the different stages of patients with affective disorders and and investigating the connection between PON1 polymorphisms and treatment outcomes will help us to clarify the relationship between PON1 and mood disorders.

Yildiz M et al. / Arch Clin Psychiatry. 2017;44(3):73-6

Keywords: Major depression, bipolar affective disorder, paraoxonase (PON1), polymorphism, association study.

Introduction

Mood disorders are thought to be caused by a combination of environmental, psychological, biological and genetic factors. It was shown that oxidative and nitrosative stress pathways, along with immune-inflammatory response, might play an important role in the pathogenic mechanisms underlying major depression and bipolar disorder[1]. Reactive oxygen species affect both the immune-inflammatory pathways and the expression of key neurotransmitters which are involved in the pathophysiology of depression[2]. Studies demonstrated discrepancies in antioxidant enzyme levels in different stages of bipolar affective disorder[3,4]. Additionally, adding antioxidant agents to treatment of patients with bipolar affective disorder caused a substantial decrease in depressive symptoms and and increase in clinical functioning or quality of life measures[5].

Paraoxonase is a calcium-dependent esterase that catalyzes the hydrolysis of neurotoxins such as organophosphates and aromatic carboxylic acids[6]. The paraoxonase (PON) gene family has three members, PON1, PON2, andPON3. Human paraoxonase 1 (PON1) is a high-density lipoprotein (HDL)-associated serum enzyme that exhibits a broad substrate specificity[7]. The PON1 enzyme has both paraoxonase and arylesterase activity and show antiinflammatory and antioxidative properties[8]. The PON1 gene contains two common polymorphisms found in the PON1 coding region, leading to a glutamine (Q) → arginine (R) substitution at position 192 (Q192R; rs 662) and to a leucine(L) → methionine (M) substitution at position 55 (L55M; rs 854560)[9]. The L55M polymorphism affects the enzyme concentration and the Q192R polymorphism is responsible for the hydrolytic activity of the enzyme[10,11]. Studies concerning the relationship between PON1 polymorphism and mood disorders exhibited inconsistent results. It was reported that PON1 Q192R polymorphism may be associated with symptoms of depression in older women[12]. Another study demonstrated that PON1 Q192R-smoking interaction predicted the odds of depression[13]. Contrarily, no associations were detected between mood disorders and any of the Q192R genotypes[14]. In a genome-wide association study, thew authors reported no associations between major depression and the Q192R polymorphism or any other polymorphism in the PON1 gene[15]. Also, no significant association was found between PON1Q192R polymorphism and depression in population-based studies[16]. While some studies found no differences in terms of PON1 activity between patients with depression and controls[17]; others demonstrated a diminished PON1 activity[13,18,19]. Furthermore, it was indicated that antidepressant treatment increased the lowered paraoxonase/arylesterase levels[19].

It was demonstrated that carrying homozygote or heterozygote mutated alleles of L55M and Q192R might cause susceptibility to bipolar I disorder[9]. The odds of bipolar disorder were increased by the QQ genotype of Q192R in smokers[13]. In a genome-wide association study, no associations between bipolar disorder and the Q192R polymorphism or any other polymorphism in the PON1 gene was detected. Two studies investigated PON1 activity in bipolar patients. The first one presented normal PON1 activity but the other showed decreased PON1 activity in bipolar patients[13,20]. In a study consisting of both depressed and bipolar patients; lowered PON1 activity was found to be associated with comorbid mood disorders and tobacco use disorder[14]. In terms of polymorphisms, there were no significant associations between the patient groups and any of the three PON1 Q192R genotypes in the same study.

The aim of the present study is to investigate paraoxonase 1 polymorphisms and its correlations with disease parameters in patients with major depression and bipolar affective disorder.

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Methods

This study used the DNA specimens of a former study entitled: "Investigation of Dopamine-β-hydroxylase Polymorphism in Patients with Major Depression, Bipolar Affective Disorder and Schizophrenia". The study group consisted of 100 patients with major depression (83 females and 17 males), and 100 patients with bipolar affective disorder (49 females and 51 males) and 96 healthy controls (48 females and 48 males). All depressed and bipolar patients were followed up at the Outpatient Clinic of the Psychiatry Department of Gaziosmanpasa University, School of Medicine. Diagnoses of major depression and bipolar disorder were made according to the DSM-IV (Diagnostic and Statistical Manual-IV) criteria (American Psychiatric Association, 1994)[21]. The control subjects were recruited from hospital staff. The study protocol was approved by the Clinical Researches Ethics Committee, and the written informed consents were obtained from the study participants.

Genotyping

Genomic DNA was extracted from peripheral leukocytes from EDTA-anticoagulated blood using the High Pure Polymerase Chain Reaction Template Preparation Kit (Roche Molecular Biochemicals, Mannheim, Germany) according to the manufacturer's instructions. To identify PON1 L55M and Q192R singlenucleotide polymorphisms (SNPs), genotyping was performed using commercially synthesized primers and fluorescently labeled probes (Metabion, Martinsried, Germany) and the LightCycler 480 II Real-Time Polymerase Chain Reaction System (Roche Diagnostics). The genotyping method was based on methods developed previously for genotyping both PON1 55 and 192 polymorphisms using LightCycler real-time polymerase chain reaction technology, which relies on fluorescence resonance energy transfer[22]. Target fragments of the human PON1 gene were amplified with specific primers. To detect the PON1 L55M polymorphism, 10 pmol of the forward primer 5'-CCTGCAATAATATGAAACAACCTG-3' and the reverse primer 5'-CTAGAACACAGAAAAGTGAAAGAAAAC-3' and 3 pmol of the sensor probe 5'-CTCTGAAGACATGGAGATACTGCC-fluorescein-3' and the anchor probe 5'-LCRed640-ATGGACTGG CTTTCATTAGCTCTGTGAGT-3' were added to genomic DNA. To detect the PON1 Q192R polymorphism,we also used 10 pmol of the forward primer 5'-ATTGTTGCTGTGGGACCTGAG-3' and the reverse primer 5'-CCTTCTGCCACCACTCGAAC-3' and 3 pmol of the sensor probe 5'-CCCCTACTTACAATCCTGGGAGAT-fluorescein-3' and the anchor probe 5'-LCRed705-ATTTGGGTTTAGCGTGGTCGTATGTTG-3'. Melting curves were transformed to melting peaks by plotting the negative derivative of the fluorescence signal versus the temperature. The genotypes were identified by creating a melting curve with specific melting points.

Statistical analysis

Descriptive analyses were performed to provide information on general characteristics of the study population. One way ANOVA test was used to compare the continuous data among groups. The continuous data were presented as the mean ± standard deviation. Chi-Square test was used to compare the categorical data between/among groups. Categorical variables were presented as a count and percentage. A p-value < 0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY)[23].

Results

The baseline clinical and demographics features of patients with major depression and bipolar disorder are shown in Table 1 and Table 2. The mean age of the depressed group, bipolar group and controls were 38.21 ± 12.07, 41.19 ± 12.25 and 37.34 ± 10.21 respectively. No significant difference in the mean ages and gender was observed between the bipolar patient group and the control group. The mean age was not different between depressed group and controls but the depressed group was different from controls in terms of gender. Namely, the the majority of the depressed group consisted of females. All the PON1 gene polymorphisms analyzed were in Hardy–Weinberg equilibrium. Allele and genotype frequencies were not different between patients with depression and controls in with regard to L55M and Q192R polymorphisms of PON1 (Table 3). Likewise, there was not a significant difference of to L55M and Q192R polymorphism between patients with bipolar disorder and controls (Table 4). Additionally, there was no association between the PON1 genotypes and disease variables in both depressed and bipolar patients.

Table 1. Baseline clinical and demographics features of the 100 study patients with major depression

Characteristic	Depressed patients group
Gender, no. male/female (male %/female %)	13/87 (13.0/87.0)
Age, mean ± SD (range) years	38.21 ± 12.07

Table 2. Baseline clinical and demographics features of the 100 study patients with bipolar disorder

Characteristic	Bipolar patients group
Gender, no. male/female (male %/female %)	49/51 (49.0/51.0)
Age, mean ± SD (range) years	41.18 ± 12.27
Age of onset, mean ± SD (range) years	25.21 ± 9.86
Bipolar disorder subtype, n (%)	
Type 1	87 (87%)
Type 2	13 (13%)
Rapid cycling, n (%)	17 (17%)
Seasonal pattern, n (%)	59 (59%)
Alcohol/drug use, n (%)	10 (10%)
Suicidal behavior, n (%)	26 (26%)
Psychotic feature, n (%)	55 (55%)
Hospitalization, n (%)	69 (69%)
Family history of BPD, n (%)	33 (33%)
Family history of suicide, n (%)	13 (13%)

Table 3. PON1 polymorphisms in patients with major depression and healthy controls

PON locus	Healthy controls n = 96 (%)	Major depression patients n = 100 (%)	*P*
PON55L/M			0.56
L/L	40 (41.7)	37 (37.0)	
L/M	42 (43.7)	43 (43.0)	
M/M	14 (14.6)	20 (20.0)	
Alleles			0.15
L	122 (63.5)	117 (58.5)	
M	70 (36.5)	83 (41.5)	
PON192Q/R			0.61
Q/Q	43 (44.8)	47 (47.0)	
Q/R	39 (40.6)	43 (43.0)	
R/R	14 (14.6)	10 (10.0)	
Alleles			0.24
Q	125 (65.0)	137 (68.5)	
R	67 (35.0)	63 (31.5)	

Table 4. PON1 polymorphisms in patients with bipolar affective disorders and healthy controls

PON locus	Healthy controls n = 96 (%)	Bipolar patients n = 100 (%)	*P*
PON55L/M			0.89
L/L	40 (41.7)	39 (39.0)	
L/M	42 (43.7)	47 (47.0)	
M/M	14 (14.6)	14 (14.0)	
Alleles			0.41
L	122 (63.5)	125 (62.5)	
M	70 (36.5)	75 (37.5)	
PON192Q/R			
Q/Q	43 (44.8)	44 (44.0)	0.95
Q/R	39 (40.6)	40 (40.0)	
R/R	14 (14.6)	16 (16.0)	
Alleles			0.41
Q	125 (65.0)	128 (64.0)	
R	67 (35.0)	72 (36.0)	

Discussion

The present study examined the L55M and Q192R polymorphisms of PON1 gene in patients with depression and bipolar disorder. We did not find any association between the L55M and Q192R polymorphisms and major depression and bipolar disorder. Also, no association was found between the PON1 genotypes and disease variables in both patient groups.

The lack of association between the L55M and Q192R polymorphisms and major depression in the present study is in line with Nunes et al's report[14]. Although, they did not distinguish depressed and bipolar patients and they only looked for the Q192R polymorphisms but not for the L55M polymorphisms; but they found no association between patients with mood disorders and any of the three PON1 Q192R genotypes. In a similar manner, no associations between major depression and the Q192R polymorphism or any other polymorphism in the PON1 gene have been found in a genome-wide association study[15]. However, there are some contradictory findings. In a study exploring the PON Q192R polymorphism in major depression in relation to nicotine dependence, it was demonstrated that PON Q192R-smoking interaction might play a role in depression[13]. A different study including British women aged 60–79 years, R allele of PON1 Q192R was found to be associated with increased odds of depression[12]. Large differences between ethnic populations are known in the PON1 genotype distribution[24]. So, it may be the reason for differences among studies. The majority of the subjects in the depressed group were female and it was significantly different from controls. As it was shown that gender had no impact on PON1 polymorphism[25], it was thought that the gender difference in the present study did not confound the results. The contradictive results are also present for PON1 activity. No differences were found in terms of PON1 activity between patients with depression and controls[17]. A diminished PON1 activity was also reported[13,18,19]. In addition, long-term AD treatment seems to increase the paraoxonase/arylesterase levels in patients with depression[19]. In the present study, we did not measure PON1 activity. As in our study, the vast majority of the studies in the literature did not include any measure of PON1 activity.

We did not find any association between any association between the L55M and Q192R polymorphisms and bipolar disorder. Ezzaher *et al*. demonstrated that carrying homozygote or heterozygote mutated alleles of L55M and Q192R might cause susceptibility to bipolar I disorder[9]. It was indicated that the QQ genotype of Q192R in smokers increased the risk of bipolar disorder[13]. Our findings are consistent with a genome-wide association study reporting no associations between bipolar disorder and the Q192R polymorphism or any other polymorphism in the PON1 gene[26]. In terms of PON1 activity in bipolar patients; one study demonstrated normal activity[13] but the other showed decreased PON1 activity[20]. The results of the present study and the discrepancies between the other studies might be associated with the distinct genotypic distribution of PON1 across different ethnic populations.

We also found no association between clinical variables of depression and bipolar disorder and the L55M and Q192R polymorphismS of PON1. Diminished serum paraoxonase and arylesterase activities and polymorphisms of PON1 in humans have been have been linked to heightened systemic oxidative stres[8,27]. So, it could be expected that, the more serious forms of mood disorders might be associated with lower levels or lower activity of antioxidant properties.

Polymorphism regarding PON1 have not been studied too much in other psychiatric disorders. In a study including patients with schizophrenia, their relatives and healthy controls; authors suggested that the subjects carrying R allele or RR genotype of Q192R polymorphism might be susceptible to schizophrenia and subjects with QQ or LL of L55M polymorphism might be protected against schizophrenia[28]. Another study looked for an association between Q192R and L55M polymorphisms of PON1 and autism spectrum disorders, but they found no association[29].

The results of the present study must be interpreted within the limitations of the study. Firstly, larger sample size of groups would be beneficial and the sample of our depressed and bipolar patients may not be representative of the whole patient populations. Secondly, our work is a cross sectional study that does not permit to follow-up of biological parameters. We did not measure PON activity but it is the common limitation of such association studies. Another limitation of the study is that reports from association studies constitute tentative knowledge and must be interpreted with caution[30].

In conclusion, our findings reported no association between Q192R and L55M polymorphisms of PON1 and major depression and bipolar disorder, suggesting that this polymorphism might not play a role in the physiopathology of mood disorders. There were also no significant associations between the polymorphisms of the PON1 gene and the clinical and the demographic characteristics of patients. Prospective studies with larger sample sizes evaluating the different stages of patients investigating the connection between PON1 polymorphisms and treatment outcomes will help us to clarify the relationship between PON1 and mood disorders.

Acknowledgments

This study was supported by the Gaziosmanpasa University (project no: 2015/28). The authors would like to thank the patients and the controls for their participation.

Conflict of interest

The authors do not have an affiliation with or financial interest in any organization that might pose a conflict of interest that are directly relevant to the contents of the paper.

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Patterns of psychiatric diagnoses in inpatient and outpatient psychiatric settings in Saudi Arabia

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Received: 1/21/2017 – **Accepted:** 4/20/2017
DOI: 10.1590/0101-60830000000124

Abstract

Objective: This study aimed to explore the current patterns of psychiatric diagnoses in inpatient and outpatient psychiatric settings in Saudi Arabia. **Methods:** Cross-sectional study was conducted on patients seeking psychiatric advice at six hospitals in the five main regions of Saudi Arabia. The data were primarily obtained by reviewing patient charts. **Results:** Total of 1,205 patients were recruited. The majority was unemployed (71.4%), had a low level of education (85.5%), and had low income (61.9%). The most common psychiatric diagnoses among inpatients were schizophrenia (55.8%), bipolar disorder (23.3%) and major depressive disorder (7.2%). The most common psychiatric diagnoses among outpatients were major depressive disorder (29.3%), schizophrenia (28.9%), generalized anxiety disorder (15.6%) and bipolar disorder (11.5%). Primary psychotic disorders and secondary psychiatric disorders were significantly more frequent among men whereas primary bipolar disorders and depressive disorders were significantly more frequent among women in both inpatient and outpatient settings. Psychotic and bipolar disorders were significantly more frequent among younger patients whereas depressive disorders were significantly more frequent among older patients; anxiety disorders were of similar frequency in all age groups. **Discussion:** The most common psychiatric diagnoses among inpatients were schizophrenia and bipolar disorder whereas the most common psychiatric diagnoses among outpatients were major depressive disorder and schizophrenia.

Alosaimi FD et al. / Arch Clin Psychiatry. 2017;44(3):77-83

Keywords: Patterns, psychiatric disorders, inpatients, outpatients, Saudi Arabia.

Introduction

Mental and substance use disorders are the leading causes of disability-adjusted life years (DALYs), accounting for 7.4% of all DALYs worldwide[1]. The burden of mental and substance-use disorders increased by 37.6% between 1990 and 2010; for most disorders, this increase was driven by population growth and aging[1]. Approximately 14.3% of deaths worldwide each year and approximately 10 years of potential life lost are attributable to mental disorders[2]. In the Global Burden of Disease Study 2013 (GBD 2013), major depressive disorder was the leading cause of Years Lived with Disability (YLDs) in every country[3]. Anxiety disorders, alcohol- and drug-use disorders, schizophrenia, bipolar disorder, and dysthymia also rank among the 20 conditions that contribute the largest global share of YLDs. The aggregate burden of YLDs resulting from mental and behavioral disorders (22.7%) continues to be higher than the burden resulting from any other disease category[4].

The treatment gap for mental disorders is universally extremely large although the gap varies across regions[5,6]. Of serious psychiatric cases, 35.5% to 50.3% in developed countries and 76.3% to 85.4% in less developed countries received no treatment in the 12 months prior to the interview[7]. Compared with the general population, people with serious mental illnesses (SMI) exhibit higher rates of undiagnosed and untreated medical illnesses and higher morbidity and mortality from physical illnesses, primarily because of modifiable lifestyle risk factors[8]. The poor psychiatric and medical health outcomes in people with SMI may primarily be attributed to disparities in access to, utilization of, and provision of health care[9-12].

However, consultations with mental health professionals throughout the world remain inadequate, partially because of the stigma that prevents people with psychiatric illnesses from taking the medical advice of professionals[13]. A WHO study observed that the prevalence of having any psychiatric disorder in the previous year varied widely, from 4.3% in Shanghai to 26.4% in the United States[7]. Even among similar European nations, the prevalence of some mental illnesses differs from one country to another[14]. One US study indicated that no more than 41% of mature Americans who had a mental illnesses received mental health services in 2012[15]. Not surprisingly, treatment conditions are even worse in developing countries, including the Arab countries; the literature indicates that the treatment of mental disorders in such countries is uncommon[16]. In Saudi Arabia (SA), the stigma of visiting professionals in mental health hospitals remains a deterrent. Instead of considering mental health professionals' opinions, people may visit non-experts in the field of mental health, *e.g.*, faith healers, traditional healers and specialized non-psychiatrists physicians, to obtain help to overcome their psychiatric symptoms[13,17].

An obvious worldwide shift from inpatient management of psychiatric disorders to outpatient management has occurred[6]. The 'deinstitutionalization' of mental health services and the establishment of services in primary care facilities, community centers and general hospitals are a response to patient and family needs and are intended to minimize psychiatric stigma[6]. Conversely, inpatient services account for the majority of the cost of mental health services[18]. The decision-makers in the kingdom of Saudi Arabia have emphasized the improvement of the mental health care

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system; consequently, mental health care has developed in recent decades[19]. Currently, the mental health services in SA are organized on a regional basis; each region has a mental health hospital that delivers basic outpatient, inpatient, and emergency services. Private mental health services paid for out of pocket or by insurance also contribute substantially to mental health care services[20]. However, the majority of the patients with chronic mental illnesses continue to be hospitalized for long periods because of institutions' inability to refuse the patient's family's request to care for the patient, the presence of residual psychiatric symptoms, the necessity for rehabilitation, a lack of public facilities, the lack of halfway houses, and legal concerns related to early discharge, all of which render physicians reluctant to discharge patients from the inpatient unit[13].

To the best of our knowledge, there have been no large-scale nationwide studies that describe the distribution of inpatient and outpatient psychiatric illnesses across all regions of Saudi Arabia (SA). Therefore, the present study sought to explore the current patterns of psychiatric diagnoses in patients in psychiatric settings throughout Saudi Arabia and to compare the patterns of psychiatric diagnoses between inpatient wards and outpatient clinics.

Methods

Study design

A cross-sectional observational study was conducted between July 2012 and June 2014. The study received all of the required ethical approvals from the institutional review board at the Faculty of Medicine at King Saud University in Riyadh as well as the appropriate administrative approvals from the respective hospitals.

Study setting

The current study was conducted among patients seeking psychiatric help at major hospitals in Saudi Arabia. Patients were recruited from a number of hospitals located in central, eastern, western, northern, and southern Saudi Arabia. The hospitals included King Khalid University Hospital in Riyadh and Zulfi General Hospital (central region), Jeddah Mental Health Hospital (western region), Al Amal Complex for Mental Health – Dammam (eastern region), Aljouf Mental Health Hospital (northern region), and Abha Mental Health Hospital (southern region). King Khalid University Hospital is a university-affiliated governmental hospital whereas the other hospitals are government-funded service hospitals under the authority of the Ministry of Health. All of the included hospitals provide free psychiatric inpatient and outpatient healthcare services.

Study population and sampling

Consecutive adult patients (18 years and above) seeking psychiatric help in the included hospitals during the study period were invited to join the study. Those patients who signed the informed consent regardless of their psychiatric diagnosis, duration of disease, or recent use of psychotropic medications were included. Patients whose records and interviews indicated an absence of psychiatric disease were excluded.

Data collection

A mini-interview form was developed that included socio-demographic characteristics, medical history, current psychiatric diagnosis, and recent use of psychotropic medications. Data were obtained primarily by reviewing the patients' charts. The diagnosis of psychiatric disorders in this study was based on routine clinical interviews. The psychiatric consultants in charge in each study site made psychiatric diagnoses of their patients using the DSM-IV-TR criteria. The psychiatric diagnoses were confirmed by the treating teams, primarily following longitudinal evaluation and follow up in the psychiatric setting. Unclear or missing information was verified by interviewing the patient and/or his or her family. Trained psychiatric residents and staff were responsible for the chart review and for conducting interviews with the patients and/or their families.

Classification of psychiatric diagnoses

For the purpose of analyzing the data, the psychiatric diagnoses of the studied patients were classified into 7 categories. *Primary psychotic disorders* included schizophrenia, schizoaffective disorder, delusional disorder and brief psychotic disorder. *Primary bipolar disorders* included bipolar disorders, type I and type II. *Primary depressive disorders* included major depressive disorder and dysthymic disorder. *Primary anxiety disorders* included generalized anxiety disorder, obsessive-compulsive disorder, social anxiety disorder, specific phobia, panic disorder, post-traumatic stress disorder, and acute stress disorder. *Personality disorders* included mixed personality disorder, paranoid personality disorder, antisocial personality disorder, and borderline personality disorder. *Secondary psychiatric disorders* included psychotic disorders due to another medical condition, depressive disorder due to another medical condition, dementia, substance-use disorder, and substance-induced depressive disorder. *Other disorders* included somatic symptom disorder, mental retardation, conversion disorder, attention deficit hyperactivity disorder, dissociative disorder, primary insomnia, adjustment disorder, enuresis disorder, trichotillomania, and anorexia nervosa.

Statistical analysis

Data are presented as frequencies and percentages for categorical data and as the mean and standard deviation (SD) for continuous data. Individual psychiatric diagnoses and psychotropic medications were categorized into standardized groups. Statistically significant differences between inpatients' and outpatients' sociodemographic, clinical, and therapeutic characteristics were tested using either Chi-square tests or Fisher's exact tests (as appropriate) for categorical data and Student's *t*-tests for continuous data. All P-values were two-tailed. A P-value < 0.05 was considered statistically significant. SPSS software (release 20.0, SPSS Inc., Chicago, U.S.) was used for statistical analysis.

The study was funded by the Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia, Research Group no. RG–1435-087.

Results

A total of 1,205 patients (443 inpatients and 762 outpatients) were included in the current analysis, and their demographic characteristics are presented in Table 1. The average age was 38.1 years, 54.4% were unmarried but majority had children. Two thirds of patients had pre-university education, and an additional 21.4% of the patients were illiterate. The majority (71.5%) of the patients was unemployed and 62% of them had a family income of 6,000 SR (1600 US$) or less per month. Compared with outpatients, inpatients were more likely to be male, unmarried, have fewer children (1-3), be unemployed, have a lower (< 3,000 SR = 800 US$) family income, and be living in rural communities. There were no statistically significance differences with regard to age or educational level.

The clinical characteristics of the included patients are presented in Table 2. The average body mass index (BMI) was 28.7 kg/m^2, and 45.2% of the patients were either currently or previously smokers. The average age at onset of psychiatric diagnosis was 28.3 years and the average duration of psychiatric diagnoses was 9.7 years. Compared with outpatients, inpatients were more likely to have a lower BMI, be smokers, have a single psychiatric diagnosis, present a longer disease duration, younger age of onset of psychiatric disorder, and have diabetes, epilepsy, or a substance abuse disorder.

Table 1. Demographic characteristics according to patient psychiatric settings in Saudi Arabia (N = 1205)

	Inpatient (N = 443)	Outpatient (N = 762)	Total (N = 1,205)	*p*-value
Age				
Mean ± SD	37.4 ± 12.0	38.4 ± 13.6	38.1 ± 13.0	0.185
< 40	271 (61.3%)	442 (58.3%)	713 (59.4%)	
40-60	154 (34.8%)	272 (35.9%)	426 (35.5%)	
> 60	17 (3.8%)	44 (5.8%)	61 (5.1%)	0.270
Gender				
Male	252 (56.9%)	379 (49.7%)	631 (52.4%)	0.017
Female	191 (43.1%)	383 (50.3%)	574 (47.6%)	
Marital status				
Married	116 (28.0%)	410 (55.5%)	526 (45.6%)	< 0.001
Single	235 (56.8%)	272 (36.8%)	507 (44.0%)	
Divorced	61 (14.7%)	47 (6.4%)	108 (9.4%)	
Widowed	2 (0.5%)	10 (1.4%)	12 (1.0%)	
Number of children				
Mean ± SD	3.2 ± 2.9	3.6 ± 3.3	3.5 ± 3.2	0.089
None	36 (20.5%)	116 (24.9%)	152 (23.7%)	0.002
1-3 children	78 (44.3%)	138 (29.6%)	216 (33.6%)	
> 3 children	62 (35.2%)	212 (45.5%)	274 (42.7%)	
Educational level				
Illiterate	88 (20.9%)	163 (21.6%)	251 (21.4%)	0.534
Secondary or less	284 (67.5%)	487 (64.7%)	771 (65.7%)	
University/other	49 (11.6%)	103 (13.7%)	152 (12.9%)	
Work type				
Private	35 (8.1%)	62 (8.3%)	97 (8.2%)	0.001
Governmental	49 (11.4%)	149 (19.9%)	198 (16.8%)	
Own business	13 (3.0%)	28 (3.7%)	41 (3.5%)	
Jobless	334 (77.5%)	510 (68.1%)	844 (71.5%)	
Monthly family income*				
≤ 3000	150 (36.1%)	195 (26.2%)	345 (29.7%)	< 0.001
3001-6000	126 (30.3%)	247 (33.2%)	373 (32.2%)	
6001-9000	93 (22.4%)	149 (20.0%)	242 (20.9%)	
> 9000	47 (11.3%)	153 (20.6%)	200 (17.2%)	
Residence				
City	351 (80.0%)	614 (80.7%)	965 (80.4%)	< 0.001
Village	88 (20.0%)	120 (15.8%)	208 (17.3%)	
Desert	0 (0.0%)	27 (3.5%)	27 (2.3%)	

* Income is shown in Saudi Riyal. (1 U.S. dollar = 3.75 Saudi Riyals).

Table 2. Clinical characteristics according to patient psychiatric settings in Saudi Arabia (N = 1,205)

	Inpatient (N = 443)	Outpatient (N = 762)	Total (N = 1,205)	*p*-value
Body mass index (BMI)				
Mean ± SD	27.8 ± 7.7	29.3 ± 7.6	28.7 ± 7.7	0.001
Underweight	34 (8.2%)	34 (4.5%)	68 (5.8%)	
Normal	122 (29.5%)	193 (25.6%)	315 (27.0%)	
Overweight	128 (30.9%)	214 (28.4%)	342 (29.3%)	
Obese	130 (31.4%)	313 (41.5%)	443 (37.9%)	0.001
Smoking status				
Current	175 (40.4%)	227 (29.9%)	402 (33.7%)	
Past	62 (14.3%)	75 (9.9%)	137 (11.5%)	
Never	196 (45.3%)	458 (60.3%)	654 (54.8%)	< 0.001
Number of psychiatric diagnoses				
1	419 (94.6%)	672 (88.2%)	1,091 (90.5%)	
2	23 (5.2%)	89 (11.7%)	112 (9.3%)	
3	1 (0.2%)	1 (0.1%)	2 (0.2%)	< 0.001
Age at onset of psychiatric diagnosis				
Mean ± SD	25.4 ± 9.0	29.9 ± 13.1	28.3 ± 11.9	< 0.001
< 25	226 (52.6%)	268 (35.7%)	494 (41.9%)	
25-50	197 (45.8%)	435 (58.0%)	632 (53.6%)	
> 50	7 (1.6%)	47 (6.3%)	54 (4.6%)	< 0.001
Duration of psychiatric diagnoses (years)				
Mean ± SD	11.7 ± 10.2	8.6 ± 8.7	9.7 ± 9.4	< 0.001
≤ 1	60 (14.0%)	125 (16.7%)	185 (15.7%)	
2-5	85 (19.8%)	246 (32.9%)	331 (28.1%)	
6-10	93 (21.6%)	176 (23.5%)	269 (22.8%)	
> 10	192 (44.7%)	201 (26.9%)	393 (33.4%)	< 0.001
Medical history				
Diabetes mellitus	53 (12.0%)	59 (7.7%)	112 (9.3%)	0.015
Hypertension	37 (8.4%)	57 (7.5%)	94 (7.8%)	0.586
Asthma	3 (0.7%)	5 (0.7%)	8 (0.7%)	1.000
Hyperthyroidism	12 (2.7%)	13 (1.7%)	25 (2.1%)	0.239
Epilepsy	10 (2.3%)	4 (0.5%)	14 (1.2%)	0.007

The prevalence of individual psychiatric diagnoses is depicted in Table 3. The most common psychiatric diagnoses among inpatients were schizophrenia (55.8%), bipolar disorder (23.3%) and major depressive disorder (7.2%) while the most common psychiatric diagnoses among outpatients were major depressive disorder (29.3%), schizophrenia (28.9%), generalized anxiety disorder (15.6%) and bipolar disorder (11.5%). Compared with outpatients, inpatients were more likely to have schizophrenia, bipolar disorder, schizoaffective disorder, and delusional disorder but were less likely to have major depressive disorder, generalized anxiety disorder, substance-induced psychotic disorder, obsessive compulsive disorder, dementia, panic disorder, social anxiety disorder, adjustment disorder, and somatic symptom disorder. Similarly, as shown in Figure 1, inpatients were more likely than outpatients to have primary psychotic disorders and primary bipolar disorders ($p < 0.001$ for each) but less likely to have primary depressive disorders ($p < 0.001$), primary anxiety disorders ($p < 0.001$), secondary disorders ($p = 0.009$), multiple disorders ($p = 0.003$), and other disorders ($p = 0.004$).

Some diagnoses were associated with age and/or gender in both inpatients and outpatients. For example, primary bipolar disorders were significantly more frequent among younger patients in both groups. However, primary psychotic disorders were significantly more frequent among younger patients whereas primary depressive disorders were significantly more frequent among older patients in outpatient but not inpatient settings. With regard to gender, primary psychotic disorders and secondary psychiatric disorders were significantly more frequent among men in both groups although primary bipolar disorders and primary depressive disorders were significantly more frequent among women in both groups.

More than 90% of the patients were currently using psychotropic medications, and medications were used more frequently among inpatients than outpatients. This was true for antipsychotics, mood stabilizers, and anti-anxiety medications; antidepressants were used more frequently in outpatients than in inpatients. Both groups had a similar history of using psychotropic medications. Previous psychiatric hospitalizations were significantly more common among inpatients than outpatients (4.3 ± 5.0 *vs.* 2.8 ± 2.7, $p < 0.001$).

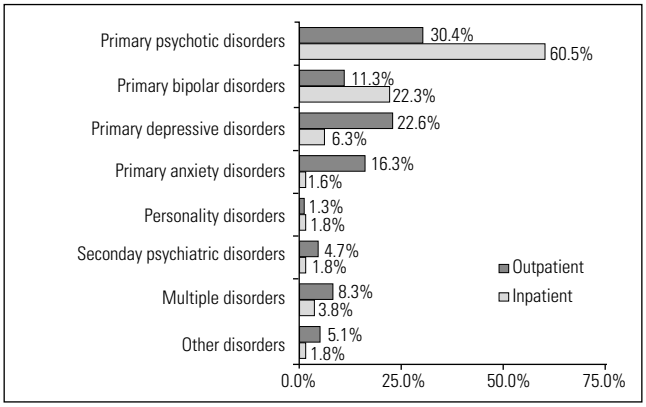

Figure 1. The prevalence of psychiatric diagnostic groups according to patient psychiatric settings in Saudi Arabia (N = 1,205).

Table 3. The prevalence of individual psychiatric diagnoses according to patient psychiatric settings in Saudi Arabia (N = 1,205)

	Inpatient (N = 443)	Outpatient (N = 762)	Total (N = 1,205)	*p*-value
Schizophrenia	247 (55.8%)	220 (28.9%)	467 (38.8%)	< 0.001
Major depressive disorder	32 (7.2%)	223 (29.3%)	255 (21.2%)	< 0.001
Bipolar disorder	103 (23.3%)	88 (11.5%)	191 (15.9%)	< 0.001
Generalized anxiety disorder	4 (0.9%)	119 (15.6%)	123 (10.2%)	< 0.001
Substance-induced psychotic disorder	9 (2.0%)	32 (4.2%)	41 (3.4%)	0.045
Mental retardation	12 (2.7%)	20 (2.6%)	32 (2.7%)	0.930
Obsessive compulsive disorder	5 (1.1%)	25 (3.3%)	30 (2.5%)	0.021
Schizoaffective disorder	15 (3.4%)	9 (1.2%)	24 (2.0%)	0.008
Dementia	2 (0.5%)	15 (2.0%)	17 (1.4%)	0.031
Mixed personality disorder	6 (1.4%)	9 (1.2%)	15 (1.2%)	0.794
Panic disorder	0 (0.0%)	15 (2.0%)	15 (1.2%)	0.003
Social anxiety disorder	0 (0.0%)	14 (1.8%)	14 (1.2%)	0.004
Adjustment disorder	0 (0.0%)	11 (1.4%)	11 (0.9%)	0.009
Somatic symptom disorder	0 (0.0%)	10 (1.3%)	10 (0.8%)	0.017
Delusional disorder	7 (1.6%)	3 (0.4%)	10 (0.8%)	0.044
Psychotic disorder due to another medical condition	5 (1.1%)	5 (0.7%)	10 (0.8%)	0.512
Brief psychotic disorder	5 (1.1%)	4 (0.5%)	9 (0.7%)	0.302
Substance use disorder	5 (1.1%)	4 (0.5%)	9 (0.7%)	0.302
Dysthymic disorder	3 (0.7%)	4 (0.5%)	7 (0.6%)	1.000
Specific phobia	0 (0.0%)	4 (0.5%)	4 (0.3%)	0.303
Conversion disorder	0 (0.0%)	4 (0.5%)	4 (0.3%)	0.303
Attention deficit hyperactivity disorder	1 (0.2%)	3 (0.4%)	4 (0.3%)	1.000
Borderline personality disorder	2 (0.5%)	2 (0.3%)	4 (0.3%)	0.628
Primary insomnia	0 (0.0%)	2 (0.3%)	2 (0.2%)	0.535
Trichotillomania	0 (0.0%)	2 (0.3%)	2 (0.2%)	0.535
Post-traumatic stress disorder	1 (0.2%)	1 (0.1%)	2 (0.2%)	1.000
Depression due to another medical condition	0 (0.0%)	2 (0.3%)	2 (0.2%)	0.535
Acute stress disorder	1 (0.2%)	1 (0.1%)	2 (0.2%)	1.000
Paranoid personality disorder	1 (0.2%)	0 (0.0%)	1 (0.1%)	0.368
Dissociative disorder	0 (0.0%)	1 (0.1%)	1 (0.1%)	1.000
Antisocial personality disorder	1 (0.2%)	0 (0.0%)	1 (0.1%)	0.368
Enuresis disorder	0 (0.0%)	1 (0.1%)	1 (0.1%)	1.000
Anorexia nervosa	1 (0.2%)	0 (0.0%)	1 (0.1%)	0.368

Table 4. The prevalence of psychiatric diagnostic groups according to age, gender, and patient psychiatric settings in Saudi Arabia (N = 1,205)

	Age groups			*p*-value
	< 40	40-60	> 60	
Inpatient				
Primary psychotic disorders	155 (57.2%)	99 (64.3%)	13 (76.5%)	0.137
Primary bipolar disorders	68 (25.1%)	31 (20.1%)	0 (0.0%)	0.039
Primary depressive disorders	13 (4.8%)	14 (9.1%)	1 (5.9%)	0.217
Primary anxiety disorders	5 (1.8%)	2 (1.3%)	0 (0.0%)	---
Personality disorders	7 (2.6%)	0 (0.0%)	1 (5.9%)	---
Secondary disorders	7 (2.6%)	1 (0.6%)	0 (0.0%)	0.331
Multiple disorders	10 (3.7%)	5 (3.2%)	2 (11.8%)	---
Other disorders	6 (2.2%)	2 (1.3%)	0 (0.0%)	0.793
Outpatient				
Primary psychotic disorders	154 (34.8%)	72 (26.5%)	6 (13.6%)	0.003
Primary bipolar disorders	59 (13.3%)	26 (9.6%)	1 (2.3%)	0.044
Primary depressive disorders	71 (16.1%)	85 (31.3%)	14 (31.8%)	< 0.001
Primary anxiety disorders	73 (16.5%)	43 (15.8%)	6 (13.6%)	0.873
Personality disorders	9 (2.0%)	1 (0.4%)	0 (0.0%)	---
Secondary disorders	22 (5.0%)	11 (4.0%)	3 (6.8%)	0.682
Multiple disorders	27 (6.1%)	23 (8.5%)	13 (29.5%)	< 0.001
Other disorders	27 (6.1%)	11 (4.0%)	1 (2.3%)	0.323

Table 5. The prevalence of psychiatric diagnostic groups according to gender and patient psychiatric settings in Saudi Arabia (N = 1,205)

	Male (n = 252)	Female (n = 191)	*p*-value
Inpatient			
Primary psychotic disorders	181 (71.8%)	87 (45.5%)	< 0.001
Primary bipolar disorders	39 (15.5%)	60 (31.4%)	< 0.001
Primary depressive disorders	6 (2.4%)	22 (11.5%)	< 0.001
Primary anxiety disorders	3 (1.2%)	4 (2.1%)	0.704
Personality disorders	0 (0.0%)	8 (4.2%)	0.001
Secondary disorders	8 (3.2%)	0 (0.0%)	0.024
Multiple disorders	11 (4.4%)	6 (3.1%)	0.507
Other disorders	4 (1.6%)	4 (2.1%)	0.731
Outpatient			
Primary psychotic disorders	153 (40.4%)	79 (20.6%)	< 0.001
Primary bipolar disorders	31 (8.2%)	55 (14.4%)	0.007
Primary depressive disorders	56 (14.8%)	116 (30.3%)	< 0.001
Primary anxiety disorders	56 (14.8%)	68 (17.8%)	0.265
Personality disorders	8 (2.1%)	2 (0.5%)	0.063
Secondary disorders	28 (7.4%)	8 (2.1%)	0.001
Multiple disorders	31 (8.2%)	32 (8.4%)	0.930
Other disorders	16 (4.2%)	23 (6.0%)	0.264

Discussion

Our study suggests that more than half of the psychiatric patients receiving treatment in psychiatric settings in Saudi Arabia are unmarried although approximately three-quarters of the patients had at least one child. Furthermore, the majority of these psychiatric patients were unemployed (71.4%), perhaps because of having limited education (85.5%), which may also account for their low income (61.9%). These figures are much higher than the rates reported among the general population of Saudi Arabia, in which the current rate of illiteracy, unemployment and poverty are 7%, 11.7% and 12.7%, respectively[21]. The literature indicates that people with serious mental illnesses with a larger overall network and greater network satisfaction have better rates of recovery[22,23]. The U.S. National Comorbidity study observed that most psychiatric disorders decline with age and with higher socioeconomic status[24]. Although the association between poverty and common mental disorders is universal, it is not known whether poverty increases the prevalence of mental illness, whether poverty is a risk factor

for a negative outcome among mentally ill people, and/or whether poverty produces disability[1] and increased health care costs[25]. Because a large percentage of Saudi Arabian psychiatric patients may have a lower socioeconomic status, laddered healthcare policies should be implemented to address this issue, including the training of primary care workers to recognize and effectively treat common mental disorders and provide attentive follow-up treatment after discharge from psychiatric services[25,26].

In our study, we observed that the majority of patients had a single diagnosis, and fewer than 10% of patients had two or three diagnoses. As shown in Table 3, in both inpatient and outpatient settings, schizophrenia appears to be the most common diagnosis (38.8%), followed by major depressive disorder (21.2%). In addition, we observed that the most common psychiatric diagnoses among inpatients were schizophrenia (55.8%) and bipolar disorder (23.3%) whereas in outpatients, the most common psychiatric diagnoses were major depressive disorder (29.3%) and schizophrenia (28.9%). Another interesting finding is the low rate of anxiety disorders in our inpatient and outpatient sample, 1.6% and 16.3%, respectively.

The community prevalence of mental disorders in the Saudi Arabian population is unknown. However, worldwide, anxiety and depressive disorders are the two most common classes of mental disorders in the community, as high as 18% for anxiety disorders and 9% for mood disorders[27,28]. The prevalence of all psychotic disorders is approximately 3% (0.87% for schizophrenia and 0.24% for bipolar I disorder)[29]. Using the WHO Assessment Instrument for Mental Health Systems (MHS), data on the Saudi MHS were collected in 2009–2010 from several sources without meeting patients directly or reviewing their charts[20]. Among patients treated in mental health facilities, 40% were treated in mental hospitals, 50% in outpatient facilities (including clinics within general medical hospitals) and 10% in other facilities[20]. Within the Saudi MHS, the majority of patients treated in outpatient settings had neurotic (36%) or mood disorders (35%) whereas patients admitted to inpatient mental hospitals were more likely to suffer from schizophrenia (50%), substance use disorders (20%), and mood disorders (20%)[20]. Another prospective local study examining psychiatric admissions to a general hospital in the eastern region of SA from 1988-1998 observed that 19.5% of the patients had schizophrenia, 15.2% had bipolar disorders, 9.9% had depressive disorders and 8.6% had acute and transient psychotic disorders[30]. These findings reflect that not all people in the community suffering from psychiatric symptoms present at psychiatric hospitals/clinics, particularly within mental health hospitals. Moreover, people with psychiatric illnesses, particularly illnesses with mild to moderate severity, may seek advice from non-mental-health professionals, most likely because of stigma and cultural beliefs[31,32]. A study among the visitors to a number of faith healing (FH) settings in Riyadh, Saudi Arabia observed that a high proportion of the FH visitors had diagnosable mental illnesses that were not treated medically[17]. Depressive disorders were the most prevalent (34.9%), followed by anxiety disorders (18.7%), psychotic disorders (6.9%) and bipolar disorders (5%)[17]. In addition, there is a concern that psychiatric patients are punished rather than treated for bad behaviors resulting from their illnesses. In 2006, the US Bureau of Justice Statistics reported that 64% of jail inmates had had a recent mental health problem[33]. Even among developed countries like the US, despite an increase in the rate of psychiatric treatment over a decade from 1990-2003, most patients with a mental disorder did not receive treatment, regardless of the severity of the disorder[34].

The rate of substance-use disorder in our study was quite low (1.1%). Compared with our findings, an Indian study conducted in a tertiary care center showed that alcohol-use disorders account for 29% of substance-use disorders[35]. In Norway, approximately one-third of the admissions in an acute psychiatric ward had a substance-use disorder[36,37]. This discrepancy may be explained by the fact that patients with substance-use disorders in SA are, according to national policy, admitted to separate addiction facilities.

Notably, the prevalence of personality disorders in our study is low. Figure 1 indicated a prevalence of 1.3 in the outpatient setting and 1.8 in the inpatient setting. One explanation for this discrepancy is that the diagnosis of psychiatric disorders in this study depended on routine clinical interviews instead of semi-structured diagnostic interviews, rendering it more difficult to identify diagnostic comorbidities such as personality disorders[38]. Compared with our finding, one study conducted among psychiatric outpatients who were interviewed with the Structured Interview for DSM-IV showed that 31.4% of the patients had personality disorders. However, that number increased to 45.5% when patients with personality disorders not otherwise specified were included[39]. Another community study using the International Personality Disorder Examination (IPDE) screening questions in 13 countries concluded that the prevalence estimates were 6.1% for any personality disorder and 3.6% for Cluster A, 1.5% for Cluster B and 2.7% for Cluster C[40].

With regard to gender, our study indicated that primary psychotic disorders and secondary psychiatric disorders are significantly more frequent among men while primary bipolar disorders and depressive disorders were significantly more frequent among women in both settings. Comparable findings were reported in the U.S. National Comorbidity study, which observed that women had elevated rates of affective disorders and anxiety disorders whereas men had elevated rates of substance-use disorders and antisocial personality disorder[27]. Also, similar findings were reported in European studies[28,41] and a local primary care study[42]. Although the evidence of gender differences in the risk of schizophrenia is inconclusive, a meta-analysis observed the that men have a higher incidence and morbidity risk than women[43].

We also noticed in this study that certain mental illnesses were linked to specific ages in both inpatient and outpatient settings. Overall, among patients treated in psychiatric settings, psychotic and bipolar disorders were significantly more frequent among younger patients whereas depressive disorders were significantly more frequent among older patients; anxiety disorders were equal in all age groups. Local primary care studies linked depression and anxiety to younger ages[44,45]. A European study among general practice attendees showed that the peak age for major depression is young adulthood and the peak age for anxiety-spectrum disorders is midlife although the prevalence rates vary significantly among European nations[14]. Worldwide, half of all lifetime mental disorders in most studies begin by the mid-teens, and three-quarters begin by the mid-20s; severe disorders are typically preceded by less severe episodes that are rarely brought to clinical attention[46]. Although the median of age of onset is earlier for phobias and non-affective psychosis than for other anxiety and mood disorders, the later onsets are primarily secondary psychiatric conditions[46]. However, an early age of onset has been identified as being associated with a longer duration of untreated mental illness and poorer clinical and functional outcomes[47].

Notably, only 5.1% of the study participants where over the age of 60 although such age group compose nearly 9% of the Saudi population aged 18 years and older[21]. Current available data covers only depression among older adults in the KSA, which ranges from 18%[48] to 39%[49]. The low number of geriatric patients utilizing mental health care services may be attributable to their preference for general practitioners or other non-psychiatric doctors for their multiple and unexplained physical complaints[13,50]; in addition, many developing countries have observed a lack of specialized mental health services for older people[51]. Another reason why patients do not utilize the mental health professions is the cultural attribution of psychological suffering to the evil eye and magic, which causes patients to visit faith healers for help[17]. One study, whose findings were consistent with ours, showed that the aged rarely received care from mental health specialists[52]. The prevalence of multi-morbidity increased substantially with age, and the presence of a mental health disorder increased with the number of physical morbidities[53]. As a prototype of psychiatric illnesses in the elderly, depression remains underdetected and underdiagnosed although depression is a serious medical condition that not only affects mood but can lead to functional and cognitive decline[54].

The current study provides significant insights into the current patterns of psychiatric diagnoses among psychiatric patients treated in psychiatric settings throughout Saudi Arabia; however, the study has some limitations. One of these limitations is the cross-sectional design, which renders determining causality difficult. Moreover, because of the use of convenience sampling, our results should be generalized cautiously to all psychiatric patients in Saudi Arabia. Another potential limitation is that the diagnosis of psychiatric disorders in this study was based on routine clinical interviews and confirmed by the treating teams, primarily following longitudinal evaluation and follow up in the psychiatric setting. Although, the routine clinical interview conducted by clinicians continues to serve as the gold standard for psychiatric diagnosis in a clinical setting, however, the diagnostic comorbidity will be more likely to be identified accurately using a semi-structured diagnostic interview such as the Structured Clinical Interview for DSM-IV (SCID). Furthermore, in our study, the psychiatric diagnoses were confirmed by the treating team, primarily following longitudinal evaluation and follow up in the psychiatric setting.

In conclusion, this study delineated the patterns and correlational factors of psychiatric diagnoses among inpatient and outpatient psychiatric settings in Saudi Arabia. Further studies in this area are required to ascertain the community prevalence of mental illnesses in Saudi Arabia. Additionally, we must study various programs to improve accessibility to mental health services and expand treatment resources in primary, secondary and tertiary care services in Saudi Arabia.

Acknowledgments

This Project was funded by the Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia, Research Group no. RG–1435-087. Furthermore, the authors express their gratitude to Dr. Aiman El-Saed for his assistance in data analysis and to Fatima Jama for her assistance in data entry.

Conflicts of interest

None.

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Letter to the editor

Severe orthostatic hypotension after adding low-dose aripiprazole to clozapine

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Received: 12/31/2016 – **Accepted:** 5/10/2017
DOI: 10.1590/0101-60830000000125

Lin YS et al. / Arch Clin Psychiatry. 2017;44(3):84

Dear Editor,

Antipsychotics can cause orthostatic hypotension (OH) by blocking adrenergic receptors[1]. OH is easily under-recognized as it can be asymptomatic. In clinical practice, combination treatment of two or more antipsychotics is common; however, little attention has been paid to OH in this scenario. Here, we presented a patient who developed severe OH after adding aripiprazole 5 mg/d to clozapine 400 mg/d.

A 33-year-old man with a 15-year history of schizophrenia presented because of severe auditory hallucination and persecutory delusion. After admission, the dose of clozapine was gradually increased to 400 mg/day, and the psychotic symptoms were improved. Over the following 4 weeks, the patient still exhibited negative symptoms, including alogia, avolition, asociality, and poor self-care. Aripiprazole 5 mg/day was added, and the negative symptoms were improved. However, 2 weeks later, the patient fell down twice on a sudden rise from supine position. Physical and neurological examinations and the results of laboratory tests were negative. Notably, the lying-to-standing orthostatic test caused a remarkable change in blood pressure (BP). The patient showed 118/83 mmHg with pulse rate (PR) 90 beats per minute (bpm) in supine position and 70/36 mmHg with PR 122 bpm in standing position. Aripiprazole was discontinued, and the OH was relieved. After careful consideration of the risks and benefits, aripiprazole 5 mg/d was added again. However, OH recurred 2 weeks later. Therefore, aripiprazole was switched to escitalopram, and OH did not recur.

OH is defined as a drop in BP (> 20/10 mmHg) within in 3 minutes of standing. The OH is associated with aripiprazole because of the temporal relationship between its occurrence and the commencement of aripiprazole, its resolution upon aripirazole discontinuation, and its recurrence with aripiprazole rechallenge. An animal study suggested that both clozapine and aripiprazole could block α_1 adrenoceptors, while the potential to cause OH is higher in clozapine[2]. There are few data addressing OH under the combination therapy of aripiprazole and clozapine. A review article reported no pharmacokinetic interaction between aripiprazole and clozapine[3]. Considering the pharmacodynamics, aripiprazole and clozapine might act together to antagonize the α_1 receptors, thereby increasing the risk of OH. Moreover, 5-hydroxytryptamine 2A (5-HT_{2A}) antagonism could induce vasodilation[4], and central 5-HT_{1A} stimulation could produce hypotension and bradycardia[5]. Being a 5-HT_{2A} antagonist and a 5-HT_{1A} partial agonist, aripiprazole may increase the risk of OH.

In this case, the combination of aripiprazole and clozapine increased the risk of OH that was considered to be principally related to clozapine. However, the patient did not develop OH under high-dose clozapine treatment (400 mg/d). We suggest that the high-dose clozapine treatment have primed his vulnerability to OH. Therefore, even though the dose of add-on aripiprazole was low (5 mg/d), it increased the extent of α_1 antagonism, negatively affecting the vascular smooth muscle cells' postsynaptic α_1-adrenergic vasoconstriction.

Adverse effects occurring during the combination of two or more antipsychotic treatment is an under-recognized area. Our case reminds clinicians that several potential adverse effects may occur during antipsychotic combination treatment, even though the dose of add-on antipsychotic drug is relatively low.

Disclosure statement

The authors report no conflicts of interest.

Acknowledgement

None.

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