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VOLUME 48 • ISSUE 6 • NOV - DIC 2025

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Salud Mental, Año 48, No. 6, Noviembre-Diciembre 2025, es una publicación bimestral, editada por el Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz. Calzada México-Xochimilco No. 101, Col. San Lorenzo Huipulco, Alcaldía Tlalpan, C.P. 14370, Ciudad de México, Tel. 55 4160-5128. Página web: https://revistasaludmental.gob.mx, correo electrónico: revistasaludmental@gmail.com. Editor responsable: Dr. Héctor Pérez-Rincón García. Reservas de Derechos al Uso Exclusivo No. 04-1979-000000000-506-102 e ISSN: 0185-3325, otorgados por el Instituto Nacional del Derecho de Autor. Certificado de Licitud de Título y Contenido de la Comisión Calificadora de Publicaciones y Revistas Ilustradas de la Secretaria de Gobernación número 17472. Se terminó de imprimir en Editorial Cigome S.A. de C.V. Priv. de Oyamel S/N, Col. El Refugio, C.P. 50255, Toluca Estado de México. este número se terminó de imprimir en enero del 2026, con un tiraje de 200 ejemplares. Distribuido por José Leobardo Romero Ibarra, Paseo de los Sauces 117, Casa Blanca, Metepec, Estado de México.

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ISSN 0185-3325

salud mental

Volume 48 Issue 6 November-December 2025

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EDITORIAL
Volume 48, Issue 6, November-December 2025
doi: 10.17711/SM.0185-3325.2025.032

Cognitive Reserve: A Crucial Construct for Addressing Mental Health

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Citation:
Toledo-Fernández, A., & Villalobos-Gallegos, L. (2025). Cognitive Reserve: A Crucial Construct for Addressing Mental Health. *Salud Mental, 48*(6), 281-282. https://doi.org/10.17711/SM.0185-3325.2025.032

DOI: 10.17711/SM.0185-3325.2025.032

Mental health is also cognitive health. This statement may seem obvious, given that standard definitions of mental health refer to the capacity of an individual to use their abilities productively and adaptively (World Health Organization, 2004; Galderisi, 2017). This includes cognitive functions such as reasoning, attention, memory and executive control. However, the affective and interpersonal components of mental health tend to receive greater attention from both the general public and professionals, with most clinical research focusing on affective disorders (Moitra et al., 2023). Nevertheless, according to the most widely used form of psychotherapy, cognitive behavioral therapy (CBT), cognition is a key determinant of mental health even in its broadest definition: the absence of psychopathology.

One of the main focuses of clinical research in neuroscience is cognitive reserve (CR), expressed through the capacity of an individual to maintain their cognitive functioning in the context of brain pathology (Stern, 2021). CR attempts to explain why two individuals with similar brain lesions, as regards both extent and location, may nonetheless show different cognitive profiles, with one of them conserving more functionality than the other. This phenomenon raises two main questions: what neuropathologies does CR protect against and what are the determinants of CR?

Scientific research has explored genetics, with incipient findings concerning specific genes in elderly rodents (Yegla & Foster, 2022). It has examined nutrition, discovering that certain dietary regimes seem to protect against cognitive decline (Puri et al., 2023). But it has primarily analyzed engagement in cognitively stimulating activities (CSAs) such as education, work, leisure and socialization. Studies have observed a mild-to-moderate negative correlation between the severity of cognitive impairment and degree of engagement in CSAs across the lifespan (Stern, 2021). More recent research has observed a similar correlation with the severity of mental disorders (Porricelli et al., 2024). This has also been found in psychological traits that are common predictors of psychopathology, such as negative emotionality (Cuéllar-García et al., 2023; Karsazi et al., 2021). This cluster of findings answers the first question. CR not only protects against Alzheimer's (Nelson et al., 2021), traumatic brain injuries or strokes (Oliva et al., 2025), but also against mental disorders that are not merely neurological.

Although the rationale for this relationship is not yet understood, it is possible to put forward a few hypotheses. First, as the theory supporting CR suggests (Stern, 2021), engagement in CSAs may boost the efficiency of neural networks, including those involved in behavioral self-regulation, extending from the prefrontal cortex to crucial areas of the limbic system. Second, engagement in CSAs may provide cognitive or behavioral strategies (such as self-directed verbal instructions, self-monitoring of internal states, planning techniques, or modes of socialization) transferable to the self-regulation of psychopathological symptoms. These first hypotheses are in line with the current view of mental disorders as being not only psychosocial but also having neurocognitive roots (Haber & Robbins, 2022). Moreover, the relationship between CR and mental health could be explained by the behavioral effects created by an environment of CSAs creates, for it may provide goals for structuring and directing behavior, offer an incentive provide an incentive to adhere to these stimulating activities, and maintain social interactions within these

environments. This is true of schools and the workplace, commonly regarded as contexts for engagement in CSAs in the literature, and therefore as promoters of CR.

However, as promising as the research on CR may seem, there are substantial caveats. First, there is no single, universally accepted operationalization of CR. The use of several proxies is the common measuring procedure (Kremen et al., 2022), restricting the comparability of results between studies and populations. Current trends suggest the use of multidimensional batteries, including CR questionnaires and performance tests (Pinto et al., 2024). More recent studies are beginning to pay attention to the use of data analysis techniques for neuroimaging, such as graph theory for integrating several sources of neuroimage data (Pappalettera, et al., 2024), or using the residuals of the association between cognitive and brain integrity measures (Elman et al., 2022).

Second, since most of the evidence comes from observational studies, we have yet to see the magnitude of the effect of CR in prevention or treatment. One example would be the trial by de la Serna et al. (2023), which plans to promote CR in children with a substantial risk of schizophrenia and bipolar disorder. Third, much of the evidence on the use of CR with psychopathology has been conducted in populations with severe disorders, such as schizophrenia. This points to the need for research on more common mental health disorders like anxiety and depression.

Finally, there is limited published research on CR and mental disorders with Mexican or Latin American samples. Efforts in this regard are required to promote mental health in all its expressions, not merely in its affective dimension. Addressing CR could take the form of research trials for programs designed to encourage engagement in CSAs, not only in adults or elderly people but from an early age. The aim would be to mitigate the risk for mental disorders with cognitive tools for self-regulation. It could also be expressed through testing complementary psychotherapeutic procedures designed to foster attention, memory and executive control in cases with non-cognitive disorders such as anxiety and depression.

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ORIGINAL ARTICLE
Volume 48, Issue 6, November-December 2025
doi: 10.17711/SM.0185-3325.2025.033

Separate or Concomitant Use of Alcohol and Tobacco during Pregnancy: Prevalence and Associated Factors

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Received: 2 August 2024
Accepted: 20 November 2024

Citation:
Camargo Júnior., E. B., Freire dos Santos, K., Gonçalves Silva, G., de Fátima Fernandes, M. N., & da Silva Gherardi-Donato, E. C. (2025). Separate or Concomitant Use of Alcohol and Tobacco during Pregnancy: Prevalence and Associated Factors. *Salud Mental, 48*(6), 283-289. https://doi.org/10.17711/SM.0185-3325.2025.033

DOI: 10.17711/SM.0185-3325.2025.033

ABSTRACT

Introduction: Pregnancy is a crucial period for a child's physiological and psychological development. Alcohol and tobacco consumption during gestation is a public health concern due to the potential harm to maternal health, fetal development, and infant health. **Objective:** To identify the prevalence of separate and concomitant use of alcohol and tobacco during pregnancy and associated sociodemographic, obstetric, and clinical factors. **Method:** A quantitative cross-sectional study conducted with 253 postpartum women in a public maternity hospital in Brazil. Alcohol and tobacco use in the last trimester of pregnancy was assessed using the Alcohol Smoking and Substance Involvement Screening Test (ASSIST). Bivariate analyses and multivariate logistic regressions were performed. **Results:** The prevalence of alcohol use was 17.4%, tobacco use 7.9%, and combined use 4.7%. Alcohol use was associated with a history of abortion [Adjusted Odds Ratio (aOR) = 3.18] and higher family income. Tobacco use was associated with a higher number of children (aOR = 12.12 for four or more children). Combined use was associated with the absence of a partner (aOR = 4.11) and a previous history of depression (aOR = 3.63). **Discussion and conclusion:** The results highlight the need for implementing strategic programs for the prevention and control of alcohol and tobacco use during pregnancy, considering the identified risk factors. Raising awareness among healthcare professionals and creating targeted public policies are essential for promoting healthy pregnancy and ensuring maternal-child well-being.

Keywords: Alcohol consumption, tobacco use, pregnancy, prenatal care.

RESUMEN

Introducción: El embarazo es un período crucial para el desarrollo fisiológico y psicológico del niño. El consumo de alcohol y tabaco durante la gestación es una preocupación de salud pública debido a los posibles daños a la salud materna, al desarrollo fetal y a la salud infantil. Objetivo. Identificar la prevalencia del uso separado y concomitante de alcohol y tabaco durante la gestación y los factores sociodemográficos, obstétricos y clínicos asociados. **Objetivo:** Estudio transversal cuantitativo realizado con 253 puérperas en una maternidad pública en Brasil. El uso de alcohol y tabaco en el último trimestre del embarazo fue evaluado mediante el *Alcohol Smoking and Substance Involvement Screening Test* (ASSIST). Se realizaron análisis bivariados y regresiones logísticas multivariadas. **Método:** Estudio transversal cuantitativo realizado con 253 puérperas en una maternidad pública en Brasil. El uso de alcohol y tabaco en el último trimestre del embarazo fue evaluado mediante el Alcohol Smoking and Substance Involvement Screening Test (ASSIST). Se realizaron análisis bivariados y regresiones logísticas multivariadas. **Resultados:** La prevalencia del uso de alcohol fue del 17.4%, de tabaco del 7.9%, y del uso combinado del 4.7%. El uso de alcohol se asoció con antecedentes de aborto [Odds ratio ajustado/Razón de momios (aOR) = 3.18] y mayor ingreso familiar. El uso de tabaco se asoció con un mayor número de hijos (aOR = 12.12 para 4 o más hijos). El uso combinado se asoció con la ausencia de pareja (aOR = 4.11) y antecedentes de depresión (aOR = 3.63). **Discusión y conclusión:** Los resultados destacan la necesidad de implementar programas estratégicos para la prevención y el control del uso de alcohol y tabaco durante la gestación, considerando los factores de riesgo identificados. Es esencial la sensibilización de los profesionales de salud y la creación de políticas públicas orientadas a promover un embarazo saludable y garantizar el bienestar materno-infantil.

Palabras clave: Consumo de alcohol, uso de tabaco, embarazo, atención prenatal.

INTRODUCTION

Pregnancy is a crucial period for a child's physiological and psychological development. Maternal risk behaviors during this phase therefore have a significant impact on newborn health. Alcohol and tobacco consumption during pregnancy is a major public health concern because of its potential to harm maternal health, and fetal and embryonic development, and negatively impact child health (Scott & Sher, 2023).

Despite well-documented evidence of the teratogenic effects of alcohol and tobacco use during pregnancy, a sizable proportion of pregnant women continue to engage in these behaviors. Prevalence estimates of alcohol and tobacco use during pregnancy are broad and vary significantly by region. Globally, the prevalence of alcohol use during pregnancy is 9.8% (Popova et al., 2017), while tobacco use is 1.7%, amounting to 5.9% in the Americas (Lange et al., 2018). In Brazil, the prevalence of alcohol use during pregnancy ranges from 7.2% to 14% (Cabral et al., 2023; Dias et al., 2024; Pavesi et al., 2023). The prevalence of tobacco use during pregnancy ranges from 6.3% to 9.3% (Negrão et al., 2020; Pavesi et al., 2023). Given the significant prevalence and outcomes of the separate use of alcohol and tobacco during pregnancy, studies are required to examine the prevalence of the concomitant use of these substances and associated factors. However, studies evaluating the simultaneous use of alcohol and tobacco in pregnant women are scarce. Additionally, the available studies were conducted before the COVID-19 pandemic, which altered alcohol and tobacco use patterns in the population.

The scientific literature indicates that a complex set of factors are associated with alcohol and tobacco use during pregnancy, including mental health problems, obstetric variables, and sociodemographic and environmental characteristics (Dias et al., 2024; Kar et al., 2021). The analysis of socioeconomic contexts and access to health and obstetric services associated with substance use during pregnancy is essential given that this behavior constitutes a significant social problem. A study based on the analysis of medical records showed that factors such as inequality were associated with multiparous women and an insufficient number of prenatal consultations. In addition, smoking was correlated with lower education levels (Crisóstomo et al., 2022). Although some associations have been well established, other require further investigation. Research is needed to examine the factors linked to both individual and combined use of alcohol and tobacco during pregnancy, as this area remains insufficiently understood within scientific literature.

This study aimed to determine the prevalence of the separate and concomitant use of alcohol and tobacco during pregnancy and the associated sociodemographic, obstetric, and clinical factors.

METHOD

Study design

This is a cross-sectional, inferential study with a quantitative approach, based on the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) protocol.

Participants

The research was conducted at a public maternity hospital in the municipality of Rio Verde, in the southwest micro-region of the state of Goiás, in the west central region of Brazil. Participants were recruited using convenience sampling between February and April 2022. Postpartum women aged ≥ 18 years, whose pregnancies resulted in live births at the time of sample recruitment, conducted shortly after delivery and before hospital discharge, were included.

Because this was a study with convenience sampling from a finite population, a sample power calculation was performed. The sample power calculation for a bivariate logistic regression with 253 participants, a significance level of .05, an odds ratio of 1.5, and an event proportion of .3, yielded a sample power of approximately .864 (86.4%).

Measurement

The separate and combined use of alcohol and tobacco were evaluated as dependent variables in the present study. Substance use was assessed using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), validated for the Brazilian context (Henrique et al., 2004). Specific modules for alcohol and tobacco were used, and the defining question for use was "In the past three months, how often have you used the mentioned substance(s)?" Guidelines recommend that pregnant women abstain from consuming any alcohol or tobacco, as these are teratogenic substances and there is no consensus on safe consumption levels. Accordingly, responses other than "never" were categorized as substance use during pregnancy (Carson et al., 2010; World Health Organization [WHO], 2014; 2021).

The independent variables analyzed assessed the sociodemographic, obstetric, and clinical characteristics of participants. The questions covered age, skin color, educational attainment, marital status, family income, employment status, prenatal care, history of abortion, number of pregnancies, pregnancy complications, type of delivery, and start of prenatal care. Obstetric variables were evaluated by identifying the start and completion of prenatal care, number of pregnancies, pregnancy complications, type of delivery, number of live births, and

history of previous abortion. The primary clinical variable assessed was the self-reported history of depression diagnosis, determined by asking participants whether they had ever received a diagnosis of depression from a healthcare professional.

Procedure

Postpartum women were recruited before hospital discharge, during which time the research objectives were presented. Those who agreed to participate received a link to access the questionnaire through their cell phones. Data were collected between the second and fifth days postpartum, following the recommendations of the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

Statistical analyses

Data analyses were performed using the Statistical Package for the Social Sciences version 29. Chi-square or Fisher's exact tests were used to determine the association between the independent variables and substance use in bivariate analyses.

A multivariate logistic regression analysis was performed to assess the influence of independent variables on alcohol and tobacco use during pregnancy. Age was added to the regression models to control for confounding factors. Other variables included in the regression models were selected after significant association analysis in the bivariate analyses. The entry method was used to include independent variables in the models. The assumptions of multivariate logistic regression were verified using the Variance Inflation Factor (VIF) and Tolerance tests. Test results were acceptable, with VIF coefficients below 1.05 and tolerance below .98.

Ethical considerations

This study was conducted in accordance with the guidelines of the Declaration of Helsinki, particularly regarding informed consent. Additionally, ethical precepts established by Resolution 466/2012 of the Brazilian National Health Council were followed. All participants signed an Informed Consent Form (ICF) before beginning the study. The study was approved by the Research Ethics Committee (opinion number: 4.380.084).

RESULTS

The sample for this study included 253 postpartum women, mainly within the age range of 22 to 29 years (48.2%), and with brown skin (83%). The majority of participants were partnered (88.9%) and living with their partners (88.9%).

Table 1
Sociodemographic, obstetric, and clinical characteristics of postpartum women

Variable	*N*	*%*
Age		
≤ 21 years	66	26.1
22 – 29 years	122	48.2
≥ 30 years	65	25.7
Skin color		
White	43	17.0
Black	18	7.1
Brown	183	72.3
Other	9	3.6
Marital status		
Partnered	225	88.9
Unpartnered	28	11.1
Co-habiting with partner		
Yes	207	81.8
No	46	18.2
Education level		
No formal education	17	6.7
Primary/elementary	41	16.2
Secondary/high school	142	56.1
Higher education or above	53	20.9
Employment status		
Not engaged in paid employment	141	55.7
Engaged in paid employment	112	44.3
Family income*		
< 1 minimum wage	109	43.1
1-2 minimum wages	122	48.2
≥ 3 minimum wages	22	8.7
Prenatal care		
Yes	250	98.8
No	3	1.2
Start of prenatal care		
1st trimester	188	74.3
2nd trimester	40	15.8
3rd trimester	22	22
No prenatal care	3	1.2
Number of pregnancies		
Primiparous	177	70.0
Multiparous	76	30.0
Type of delivery		
Vaginal	100	39.5
Cesarean	153	60.5
Number of children		
1 child	108	42.7
2-3 children	119	47.0
4 or more	26	10.3
History of induced abortion		
Yes	34	13.4
No	219	86.6
Previous history of depression		
Yes	91	36.0
No	162	64.0

Note: n = sample size, * Minimum wage in Brazil in 2022 = R$ 1,212.00.

Regarding education, 56.1% had completed high school, 55.7% were unemployed, and 48.2% had a family income of between one and two minimum wages. Most patients had received prenatal care (98.8%) from the first trimester of pregnancy (74.3%). Most postpartum women were primiparous (70%) and did not experience complications during pregnancy (79.1%). Regarding the type of delivery, 60.5% had a cesarean section and 47% had two or three children.

Table 2
Relationship between alcohol and/or tobacco use and sociodemographic, obstetric, and clinical characteristics of postpartum women

Variable	*Alcohol n (%)*	*p**	*Tobacco n (%)*	*p**	*Alcohol and tobacco*	*p**
Total participants	*44 (17.4)*		*20 (7.9)*		*12 (4.7)*	
Age		.596		.782		.694
≤ 21 years	11 (25)		5 (25)		4 (33.3)	
22 – 29 years	24 (54.5)		11 (55)		6 (50)	
≥ 30 years	9 (20.5)		4 (20)		2 (16.7)	
Skin color		.524		.428		.544
White	6 (13.6)		2 (10)		2 (16.7)	
Black	5 (11.4)		3 (15)		2 (16,7)	
Brown	31 (70.5)		15 (75)		8 (66,7)	
Other	2 (4.5)		0 (0)		0 (0)	
Marital status		0,113		.055		.032
Partnered	36 (81.8)		15 (75)		8 (66.7)	
Unpartnered	8 (18.2)		5 (25)		4 (33.3)	
Co-habiting with partner		.085		.221		.239
Yes	32 (72.7)		14 (70)		8 (66.7)	
No	12 (27.3)		6 (30)		4 (33.3)	
Education level		.677		.317		1
No formal education	2 (4.5)		2 (10)		0 (0)	
Primary/Elementaryelementa	9 (20.5)		5 (25)		4 (33.3)	
Secondary/high school	26 (59.1)		8 (40)		5 (41.7)	
Higher education or above	7 (15.9)		5 (25)		3 (25)	
Employment status		.611		.314		.315
Not engaged in paid employment	23 (52.3)		9 (45)		5 (41.7)	
Engaged in paid employment	21 (47.7)		11 (55)		7 (58.3)	
Family income*		.012		1		.906
< 1 minimum wage	22 (50)		9 (45)		6 (50)	
1-2 minimum wages	14 (31.8)		10 (50)		5 (41.7)	
≥ 3 minimum wages	8 (18.2)		1 (5)		1 (8.3)	
Prenatal care		.438		.220		1
Yes	43 (97.7)		19 (95)		12 (100)	
No	1 (2.3)		1 (5)		0 (0)	
Start of prenatal care		.618		.178		.581
1st trimester	32 (72.7)		13 (65)		9 (75)	
2nd trimester	6 (13.6)		5 (25)		3 (25)	
3rd trimester	5 (11.4)		1 (5)		0 (0)	
No prenatal care	1 (2.3)		1 (5)		0 (0)	
Number of pregnancies		.519		.311		.756
Primiparous	29 (65.9)		12 (60)		8 (66.7)	
Multiparous	15 (34.1)		8 (40)		4 (33.3)	
Pregnancy complications		.366		1		.469
Yes	7 (15.9)		4 (20)		1 (8.3)	
No	37 (84.1)		16 (80)		11 (91.7)	
Type of delivery		.585		.666		.374
Vaginal	19 (43.2)		7 (35)		3 (25)	
Cesarean	25 (56.8)		13 (65)		9 (75)	
Number of children		.094		.022		.245
1 child	13 (29.5)		7 (35)		4 (33.3)	
2-3 children	24 (54.5)		7 (35)		5 (41.7)	
4 or more	7 (15.9)		6 (30)		3 (25)	
History of induced abortion		.013		.322		.061
Yes	11 (25)		4 (20)		4 (33.3)	
No	33 (75)		16 (80)		8 (66.7)	
Previous history of depression		.149		.065		.031
Yes	20 (45.5)		11 (55)		8 (66.7)	
No	24 (54.5)		9 (45)		4 (33.3)	

Note: *n* = sample size; * *p*-value from chi-square association analyses; † Minimum wage in Brazil in 2022 = R$ 1,212.00.

Regarding abortions, 13.4% reported a previous abortion, while 36% reported a depression diagnosis (Table 1).

The results showed a prevalence of alcohol use of 17.4% (95% CI 13 - 22.1), tobacco use of 7.9% (95% CI 4.7 - 11.5), and combined alcohol and tobacco use of 4.7% (95% CI 2.4 - 7.5) during pregnancy. Table 2 presents the chi-square association analyses regarding the use of these substances with the sociodemographic, obstetric, and clinical variables of the postpartum women. An association was found between alcohol use and family income (p = .012) and previous abortions (p = .013). There was an association between tobacco use and number of children (p = .022). Combined use of these substances was linked to marital status (p = .032) and prior depression history (p = .031) (Table 2).

In the multivariate analyses, alcohol use was significantly associated with a history of induced abortion after controlling for age. Women who reported a previous abortion were 3.18 times as likely to use alcohol during pregnancy (Adjusted Odds Ratio [aOR] = 3.18; 95% CI: 1.35 - 7.49; p = .008). Regarding family income, those with an income below one minimum wage (aOR = .35; 95% CI: .12 - .99; p = .050) or between one and two minimum wages (aOR = .19; 95% CI: .06 - .54; p = .002) had a lower probability of alcohol use than women with a family income of three minimum wages or more. Tobacco use was significantly associated with a woman's parity. Women who had four or more children were 12.12 times as likely to use tobacco than women with one child (aOR = 12.12; 95% CI: 2.44 - 60.07; p = .002). Unpartnered women were 4.11 times as likely to use both substances (aOR = 4.11; 95% CI: 1.09 - 15.46; p = .036). Moreover, those with a history of depression were 3.63 times as likely to combine alcohol and tobacco use (aOR = 3.63; 95% CI: 1.04 - 12.68; p = .043) (Table 3).

Table 3
Multivariate logistic regression analyses of variables associated with alcohol and/or tobacco use during pregnancy

Variable	*aOR (IC95%)**	*p*
Alcohol use		
Age	.98 (.92 – 1.04)	.600
History of abortion	3.18 (1.35 – 7.49)	.008
Family income		
Less than one minimum wage	.35 (.12 – .99)	.050
One to two minimum wages	.19 (.06 – .54)	.002
Tobacco use		
Age	.88 (.79 – .99)	.998
Number of children		
Two to three children	1.30 (.41 – 4.08)	.643
Four or more children	12.12 (2.44 – 60.07)	.002
Alcohol and Tobacco Use		
Age	.95 (.84 – 1.08)	.486
Without partner	4.11 (1.09 – 15.46)	.036
History of depression	3.63 (1.04 – 12.68)	.043

Note: * Adjusted odds ratio and 95% confidence interval adjusted for age.

DISCUSSION AND CONCLUSIONS

In the present study, the prevalence of alcohol, tobacco, and combined alcohol and tobacco use during pregnancy was 17.4%, 7.9%, and 4.7%, respectively. The results also demonstrated associations between alcohol use and a history of induced abortion and family income, tobacco use and number of children, and combined alcohol and tobacco use and marital status and history of depression.

Studies have shown that the prevalence of alcohol and tobacco use during pregnancy varies according to the context in which the woman is admitted, the data collection method, and the instruments used. A study conducted in southern Brazil among low-risk pregnant women, utilizing the same assessment instrument as the current research and employing face-to-face interviews at Family Health Units, reported a prevalence of 14% for alcohol consumption and 28.5% for tobacco use (Dias et al., 2024). In the state of Santa Catarina, a study conducted of postpartum women found a prevalence of 7.2% for alcohol use and 9.3% for tobacco use (Pavesi et al., 2023). The prevalence of alcohol use in the present study (17.4%) was higher than that found in previous studies (14% and 7.2%) and lower (7.9%) in regard to tobacco use (28.5% and 9.3%). The combined use of alcohol and tobacco has not been widely explored in recent publications. However, a study conducted between 2011 and 2012 observed a prevalence of 2.2% among pregnant women (Cabral et al., 2023). This value is lower than that found in the present study, which recorded a prevalence of 4.7% among the postpartum women evaluated.

The discrepancies among study estimates should be interpreted cautiously, due to the inconsistent terminology utilized for alcohol and tobacco use during pregnancy, as well as the absence of standardized recommendations for assessment instruments (Cabral et al., 2023; Chagas et al., 2021). However, it is worth noting that most studies define substance use as any amount of consumption reported during pregnancy (Cabral et al., 2023; Dias et al., 2024; Pavesi et al., 2023). Furthermore, the guidelines for monitoring pregnant women, established by health agencies, recommend abstaining from alcohol and tobacco use during pregnancy, given the adverse consequences of use, even in small quantities (Ministério da Saúde, 2022; WHO, 2013).

Alcohol and tobacco use during pregnancy is associated with individual/subjective issues, sociocultural and environmental contexts, and a lack of information on the adverse consequences and the absence of technical approaches to the subject during prenatal care (Martinelli et al., 2021). Health professionals should implement effective strategies for screening for alcohol and tobacco use during pregnancy, considering modifiable factors that can be addressed by the health system, as recommended by the WHO (2014). Screening should be performed to ensure the timely identification of substance use and to increase pregnant women's

access to specialized mental health services, preferably with valid instruments such as the WHO ASSIST (Henrique et al., 2004).

It is important to note that, in this study, the assessment of alcohol and/or tobacco use specifically referred to the last trimester of pregnancy and that the timing of exposure to these substances can be influenced by a range of factors. Studies indicate that alcohol and tobacco consumption tends to decrease as pregnancy progresses, and is more prevalent in the first trimester (Tigka et al., 2023; Pereira et al., 2022). This reduction throughout pregnancy may be associated with increased awareness among women regarding the potentially negative consequences of using these substances for fetal development. It is therefore essential for preventive and educational actions to be implemented at the beginning of prenatal care, with the goal of early screening and intervention to help maintain reduced alcohol and tobacco use throughout pregnancy.

After pregnant women have screened positive for alcohol and/or tobacco use during pregnancy, health professionals should conduct brief interventions, to encourage them to continue to abstain from using these substances (Minozzi et al., 2024). Health professionals should implement a brief intervention strategy using evidence-based health education, to inform pregnant women of the adverse consequences of alcohol and tobacco use for the mother-child dyad. This intervention should be delivered with warmth and empathy to establish a bond with the pregnant women and reduce the stigma they face (Chang, 2020).

The present study promotes the identification and understanding of the factors entailing a higher risk of alcohol and tobacco use, to contribute to decision-making in actions designed to prevent the use of these substances during pregnancy. Alcohol consumption was associated with a history of previous abortion and family income.

As in the present study, research conducted in Ethiopia identified a 4.07-fold increase in the likelihood of alcohol use among women with a previous abortion (Bete et al., 2023). The relationship between a history of induced abortion and alcohol use during pregnancy can be explained by the fact that women who have experienced this situation may have high levels of stress and anxiety. They may resort to alcohol use as a coping strategy (Koly et al., 2023). It is therefore necessary to use practices designed to minimize the impact of this situation through low-density actions for primary health care. These include mindfulness practices, which have yielded satisfactory results as a coping strategy for mental health problems (Gherardi-Donato et al., 2023).

In the present study, women with a higher family income were at a higher risk of alcohol use. A study conducted with pregnant women in Japan showed that a higher family income was associated with an increased risk of alcohol use during early pregnancy, but not during mid-pregnancy (Murakami et al., 2020). In contrast to the results of the present study, research conducted in Brazil reported higher alcohol consumption among pregnant women with lower socioeconomic status (Cabral et al., 2023). Further studies should be conducted to evaluate the influence of income as a social determinant of alcohol consumption among pregnant women.

Research participants with more children were more likely to use tobacco during pregnancy. This association may stem from underestimating the risks of tobacco use during later pregnancies, particularly when prenatal counseling is lacking and pre-pregnancy tobacco habits persist (Odendaal et al. 2020).

Furthermore, postpartum women who were unpartnered or had a history of depression had a higher likelihood of combined alcohol and tobacco use during pregnancy. These results are in line with a previously published study by Bete et al., 2023. The authors suggest that the lack of social support, often obtained through an affective relationship, could explain the association between being unpartnered and combining alcohol and tobacco use. Finally, the association found between previous depression and substance use in the present study is corroborated by recent research findings that substance use may increase during pregnancy among women with a history of depression (Chapman et al., 2024).

Routine screening for alcohol and tobacco risk factors should be part of prenatal care, especially by nursing staff in primary health units. Professionals should be trained to provide psychosocial interventions and, if necessary, refer pregnant women to the Psychosocial Care Network to access specialized mental health services such as the Psychosocial Care Center for Alcohol and Drugs.

Identifying pregnant women who are more likely to use alcohol and/or tobacco during pregnancy is crucial to guiding interventions. However, the results of this study have certain limitations. Key variables for identifying factors associated with substance use, such as pregnancy planning and a history of induced abortion, were not evaluated. Online data collection may introduce sampling bias, as it may fail to capture the experiences of individuals without internet access or digital devices. Moreover, self-reported alcohol and tobacco use during pregnancy may be underestimated because of social desirability bias and stigma. In this study, we used confidential online assessments to minimize social desirability bias and obtain accurate responses from participants.

Alcohol and tobacco use during pregnancy is a public health issue requiring urgent attention from the health system. Research indicates that factors such as a history of induced abortion, family income, number of children, marital status, and prior experiences with depression each uniquely affect the likelihood of substance use during pregnancy.

Given the substantial impact of these substances on maternal and fetal health, it is essential to implement

strategic, comprehensive programs designed to structure effective measures for the control and prevention of alcohol and tobacco consumption during the gestational period. Raising awareness among health professionals and creating targeted public policies are crucial steps towards promoting healthy pregnancies and ensuring the well-being of both mothers and babies.

Funding

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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salud mental

ORIGINAL ARTICLE
Volume 48, Issue 6, November-December 2025
doi: 10.17711/SM.0185-3325.2025.034

Family-based Association Study of 5-HTTLPR/*SLC6A4* and uVNTR/*MAOA* Polymorphisms in Patients with a History of Suicide Attempts

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Received: 27 May 2024
Accepted: 20 November 2024

Citation:
Sarmiento-Hernández, E., Fresán-Orellana, A., Camarena-Medellin, B., Sanabrais-Jiménez, M. A., Hernández-Muñoz, S., Aguilar-García, A., & Medina-Rodríguez, J. C. (2025). Family-based Association Study of 5-HTTLPR/*SLC6A4* and uVNTR/*MAOA* Polymorphisms in Patients with a History of Suicide Attempts. *Salud Mental, 48*(6), 291-296. https://doi.org/10.17711/SM.0185-3325.2025.034

DOI: 10.17711/SM.0185-3325.2025.034

ABSTRACT

Introduction: Biological factors, especially genetic ones, are associated with the development of suicidal behavior. A 1.7- to 10.6-fold risk of developing suicidal behavior has been observed in individuals with first- or second-degree relatives with suicidal behavior. It has been suggested that the serotonergic and dopaminergic systems are involved in suicide attempts, particularly the *SLC6A4* and *MAOA* genes. **Objective:** To analyze the allele transmission of 5-HTTLPR/*SLC6A4* and uVNTR/*MAOA* polymorphisms in families with suicide attempts. **Method:** Fifty families with proband with a history of suicide attempts were included. All participants were recruited at the Ramón de la Fuente Muniz National Institute of Psychiatry and evaluated using the International Neuropsychiatric Interview (M.I.N.I.). Allele transmission analysis of the 5-HTTLPR and uVNTR polymorphisms was performed using the Haploview program. **Results:** Analysis of allele transmission of the 5-HTTLPR/*SLC6A4* polymorphism showed greater transmission of the S allele in probands ($\chi^2 = 6.6$, $p = .0098$) with a previous suicide attempt and in those with two or more suicide attempts ($\chi^2 = 5.4$, $p = .019$). There was no observed preference in *uVNTR/MAOA* allele transmission. **Discussion and conclusion:** Our data support the hypothesis that the serotonin transporter is implicated in the development of suicide attempts in Mexican patients with mood disorders.

Keywords: Suicide attempt, 5-HTTLPR/*SLC6A4*, uVNTR/*MAOA*.

RESUMEN

Introducción: Los factores biológicos, principalmente los genéticos, se encuentran vinculados al desarrollo de la conducta suicida. Se ha observado un incremento de 1.7 a 10.6 veces el riesgo a desarrollar conducta suicida en individuos con antecedentes de familiares de primer o segundo grado con conducta suicida. Se sugiere que el sistemas serotoninérgico y dopaminérgico se encuentran implicados con el intento suicida, destacando los genes *SLC6A4* y *MAOA*. **Objetivo:** Analizar la transmisión de los alelos de los polimorfismos 5-HTTLPR/*SLC6A4* y uVNTR/*MAOA* en familias con intento suicida. **Método:** Se incluyeron cincuenta familias donde el probando tenía el antecedente de intento suicida. Todos los participantes fueron obtenidos en el Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz evaluados con la Entrevista Neuropsiquiátrica Internacional (M.I.N.I.). El análisis de transmisión de alelos de los polimorfismos 5-HTTLPR y uVNTR se realizó mediante el uso del programa Haploview. **Resultados:** El análisis del polimorfismo 5-HTTLPR/*SLC6A4* mostró una mayor transmisión del alelo S en los probandos con un intento suicida previo ($\chi^2 = 6.6$, $p = .0098$) y en aquellos con dos o más intentos suicidas ($\chi^2 = 5.4$, $p = .019$). No se observó la transmisión preferente de algún alelo del polimorfismo uVNTR/*MAOA* en la muestra analizada. **Discusión y conclusión:** Nuestros datos respaldan la hipotesis de que el transportador de serotonina se encuentra implicado con el desarrollo del intento suicida en pacientes mexicanos con trastornos del ánimo.

Palabras clave: Intento suicida, 5-HTTLPR/*SLC6A4*, uVNTR/*MAOA*.

INTRODUCTION

Suicide is a worldwide public health problem affecting all ages and genders, as noted by the WHO (Bachmann, 2018). It claims approximately 1.53 million lives annually, with attempts being ten to twenty times more prevalent. This is equivalent to an average mortality rate of one person every twenty seconds and an attempt every one to two seconds, reflecting its impact on global health (Bertolote & Fleishman, 2002). The incidence of suicide displays regional variations, reflecting differing mortality rates among continents. Mexico's annual suicide rate stands at five per 100,000 inhabitants, making it one of the countries with the lowest rates (Borges et al., 2010). Campillo & Dolci (2021) reported that suicide mortality rose by 175% between 1970 and 2007, culminating in 4,388 cases in 2007, with a rate of 4.12 per 100,000 individuals. This sharp rise warrants a closer look at the causes behind this concerning trend.

The association between suicide and psychiatric disorders is well-documented, with affective disorders, substance use, psychosis, eating disorders, and certain personality disorders being common contributors (Brådvik, 2018). Mood disorders, particularly depression, have been identified as the most frequent psychiatric conditions linked to completed suicides (Isometsä, 2014; Rihmer & Rihmer, 2019). Although psychopathology predicts suicide risk, most diagnosed individuals do not attempt suicide.

Twin and adoption studies have highlighted the genetic components involved in suicide. Other studies show that suicidal behavior is transmitted within families (Brent & Melhem, 2008; Turecki & Brent, 2016), underlining the need to consider genetics in suicide prevention strategies. Studies have examined the link between key enzyme genes, serotonin transporters, and suicidal behavior. The serotonin transporter gene *SLC6A4* has been strongly associated with suicide attempts (Gonda et al., 2011). The *SLC6A4* gene located on chromosome 17 (17q11.1-12), and a polymorphism in the promoter region, known as 5-HTTLPR, characterized by an insertion/deletion of a 44 base pair fragment, have been linked to suicidal behavior. This polymorphism has two alleles: the short form "S" (deletion) and the long variant "L" (insertion). The "SS" genotype and the "S" allele of the 5-HTTLPR polymorphism have been positively linked to completed suicides, suicide attempts, and a family history of suicidal behavior (Li & He, 2007). Nevertheless, there have been inconsistent findings across studies regarding these results (Turecki, 2014; Picouto & Braquehais, 2015). Another gene of interest encodes monoamine oxidase type A (*MAOA*), a crucial enzyme for neurotransmitter metabolism, including serotonin. Located on the short arm of chromosome Xp11.3, the *MAOA* gene also contains a variable number tandem repeat (uVNTR) polymorphism in the promoter region. It comprises thirty base pairs and expresses alleles with two, three, four, and five copies, each conferring different levels of transcriptional activity (Sabol et al., 1998).

Research in Mexico has established a genetic link to suicidal behavior, as demonstrated by the studies by Genis-Mendoza et al. (2017), González-Castro et al. (2019), Sarmiento-Hernández et al. (2019), Cabrera-Mendoza et al. (2020), and Sanabrais-Jiménez et al. (2022). Despite this progress, there is a dearth of family-based studies in this context. This study seeks to fill that gap by analyzing the transmission of alleles for the 5-HTTLPR/*SCL6A4* and uVNTR/*MAOA* polymorphisms in families where the proband has both a history of suicide attempts and a primary mood disorder diagnosis. We also aimed to compare demographic and clinical features between probands and their first-degree relatives.

METHOD

Participants

Participants were recruited through the outpatient, emergency, and hospitalization services at the INPRFM in Mexico City. Participants included adults over 18 with a lifetime history of suicide attempts, a primary mood disorder diagnosis according to DSM IV-TR (Segal, 2010), and at least one biological parent available during the study period. All participants completed the Mini International Neuropsychiatric Interview (M.I.N.I.) to confirm primary diagnoses and identify psychiatric comorbidities (Sheehan et al., 1998).

Assessment procedures

Demographic and clinical features were registered in an ad hoc sheet report. These included sex, age, current diagnosis (major depressive disorder, dysthymia, bipolar disorder), and age of illness onset. Other characteristics included current use of substances (nicotine, alcohol, marijuana, cocaine) and suicide attempt features (number of suicide attempts and method used in the last suicide attempt).

For genetic analysis, family-based association test (FBAT) methodology requires the genotyping of parents and probands to conduct the transmission analysis of variants. We therefore obtained a 5 ml sample of peripheral blood from the father, mother and proband for family trios and from the parent and proband for dyads.

Genetic analysis

Genomic DNA from all participants (parents and probands) was isolated from peripheral blood lymphocytes

using a high-salt method. The endpoint PCR analysis of the 5-HTTLPR/*SLC6A4* polymorphism was performed in a total volume of 15 μl, containing 1.8 mM of MgCl2, 200 mM each of dATP, dCTP, and dTTP, 100 mM each of dGTP and 7-deaza-dGTP, 0.96 units of AmpliTaq Gold polymerase (AmpliTaq Gold [Product], Perkin–Elmer, Norwalk, CT, USA), 1.3 μl of primers (5-GGC GTT GCC GCT CTG AAT TGC and 5-GAG GGA CTG AGC TGG ACA ACC CAC) and 150 ng of genomic DNA. The amplification conditions consisted of an initial denaturation step of ten minutes at 95°C; forty-five cycles consisting of thirty seconds at 95°C, thirty seconds at 61°C, and one minute at 72°C, followed by a final step of seven minutes at 72°C. PCR products were separated on 2% high-melting-point agarose gels and visualized under UV after ethidium bromide staining (Camarena et al., 2001). Analysis of the uVNTR/*MAOA* polymorphism was performed in keeping with the conditions described by Sabol et al. (1998). The amplification product was run on 3% MetaPhor gels and visualized under UV light after staining with ethidium bromide.

Statistical analysis

Categorical variables were described using frequencies and percentages, while means and standard deviations were used to summarize continuous variables.

Chi-Square (χ^2) tests and Student's t-tests were used to compare patients with a history of suicide attempts with their parents. The level of significance was set at $p < .05$. All analyses were performed using the R Studio statistical program version 1.0.136 (R Core Team, 2018).

Hardy-Weinberg equilibrium analysis was conducted with the HWE software (available at https://wpcalc.com/en/equilibrium-hardy-weinberg/). Allele transmission of the 5-HTTLPR/*SLC6A4* and uVNTR/*MAOA* polymorphisms was analyzed with the set of family-based association tests using the Haploview program, version 4.1 (Barrett et al. 2005).

Ethical considerations

This study was approved by the Ethics and Research Committees of the Ramón de la Fuente Muñiz National Institute of Psychiatry (INPRFM). All participants gave voluntary, informed consent after the study's objectives and procedures had been explained. None of the participants received any form of compensation for their participation in the study. Family members diagnosed with psychiatric conditions during the interview were informed of their diagnosis and recommended to arrange a clinical consultation at the outpatient services of the INPRFM for further evaluation and treatment.

RESULTS

Demographic and clinical characteristics

A total of fifty families were included, 94% of which (n = 47) were trios (proband, mother, and father), while the remaining 6% were dyads consisting of the patient and one parent. The average number of suicide attempts among probands was two (SD = 1). The demographic and clinical characteristics of probands, mothers, and fathers are given in Table 1. A higher number of probands had a diagnosis of major depressive disorder than the group of parents. (Table 1). In addition, mothers had a lower frequency of comorbidity with the use of nicotine, alcohol, and cocaine than probands and fathers.

Table 1
Demographic and clinical characteristics of families

	Probands $n = 50$	*Mothers* $n = 48$	*Fathers* $n = 49$	*Statistic*
Demographic features				
Age, mean (Mean, *SD*)	24.3 (6.1)	49.4 (7.8)	53.2 (10.3)	
Sex, *n* (%)				
Women	40 (80)			
Men	10 (20)			
Clinical features				
Main diagnosis, *n* (%)				
Major depressive disorder	38 (76)	12 (25)	2 (4)	$\chi^2 = 59.3$, $p < .001$
Dysthymia	11 (22)	0	0	
Bipolar disorder	1 (2)	0	0	
Age of illness onset (Mean, *SD*)	20.3 (5.4)	37.1 (14.4)	27.5 (10.6)	$F = 22.3$, $p < .001$
Substance use, *n* (%)				
Nicotine	22 (44)	6 (12)	28 (57)	$\chi^2 = 21.6$, $p < .001$
Alcohol	20 (40)	1 (2)	34 (69)	$\chi^2 = 47.1$, $p < .001$
Marijuana	5 (10)	0	2 (4)	$\chi^2 = 5.4$, $p = .06$
Cocaine	5 (10)	0	1 (2)	$\chi^2 = 7.0$, $p = .02$
Suicide attempt features				
Number of suicide attempts, *n* (%)				
One	18 (36)	9 (18)	3 (6)	
Two	20 (40)	1 (2)	0	
Three or more	12 (24)	0	0	
Suicide method in the last attempt, *n* (%)				
Medication ingestion	33 (66)	10 (100)	3 (100)	
Firearms use	11 (22)	0	0	
Hanging	6 (12)	0	0	

Table 2
Analysis of allele transmission of polymorphisms in the SLC6A4 and MAOA genes in families with suicide attempts

Polymorphism	Allele Transmitted	Transmission	Non-transmission	χ^2	p
Families with one suicide attempt					
5-HTTLPR/*SLC6A4*	S	40	7	6.6	.0098*
uVNTR/*MAOA*	1	10	9	.05	.81
Families with two or more suicide attempts					
5-HTTLPR/*SLC6A4*	S	25	11	5.4	.019*

Allele transmission analysis

Genotype distribution conformed to Hardy-Weinberg equilibrium ($p > .05$). Table 2 showed the allele transmission analyses for the 5-HTTLPR/*SLC6A4* and uVNTR/*MAOA* polymorphisms in the fifty families studied. For the 5-HTTLPR/*SLC6A4* polymorphism, there was a preferential transmission of the S allele in the general sample ($\chi^2 = 6.6$, $p = .0098$). In the allele transmission analysis of the *MAOA* gene, no preferential allele transmission was observed ($\chi^2 = .053$, $p = .8185$).

DISCUSSION AND CONCLUSION

The demographic and clinical characteristics of the study participants are consistent with those reported in previous research. Suicide attempts have been found to occur more frequently among women than men (Bachmann, 2018), predominantly affecting individuals aged between 15 and 29 (Aguilar-Velázquez et al., 2017; Wu et al., 2020). In terms of clinical characteristics, research has consistently shown that mood disorders increase suicide risk, identifying them as a critical risk factor within the realm of psychopathology (Jamison, 2000; Tondo et al., 2020). The inclusion criteria for this study were therefore designed to encompass patients diagnosed with a mood disorder with a lifetime history of suicide attempts.

Disorders related to the use of alcohol and other substances have been identified as significant risk factors not only for suicidal behavior, but also for the presence of psychopathology (Lee et al., 2019; Lynch et al., 2020). Our study was no exception, as most of the population studied reported substance use, with nicotine and alcohol use being more frequent. No differences were found in suicidal methods compared to other studies analyzing this variable. More violent and lethal methods such as hanging are used in completed suicides, while non-violent methods such as drug ingestion are usually the method of choice in suicide attempts (Kposowa & McElvain, 2006; Tsirigotis, et al, 2011).

Regarding the allele transmission analysis of the uVNTR polymorphism of the *MAOA* gene in families with suicide attempts, no transmission of any alleles was observed in the complete sample. Our study is therefore consistent with the only other report analyzing the association between the *MAOA* gene and suicide attempts in families (De Luca et al., 2005).

In addition, our study showed a higher transmission of the S allele in families with suicide attempts, as well as in those with two or more suicide attempts. Zalsman et al. (2001) conducted a family-based association study of 5-HTTLPR/*SLC6A4* without finding significant differences. It is important to note that both studies were conducted in families where all probands presented at least one suicide attempt. However, our study only analyzed probands with a primary diagnosis of a mood disorder, while the other study included patients with other psychiatric disorders. Our data suggest that the transmission of the S allele could be specifically implicated in patients with suicide attempts and a primary diagnosis of a mood disorder.

Although gamily-based association studies constitute a significant method for exploring the genetic foundations of complex behaviors like suicide, they are not the only approach for examining the links between candidate genes and familial suicide history. Joiner et al. (2002) focused on the 5-HTTLPR/*SLC6A4* polymorphism in forty-seven volunteers, assessing their family history of suicidal behavior. Their findings indicated that carriers of the SS genotype reported a greater incidence of suicide completion and multiple suicide attempts among first-degree relatives than carriers of SL and LL genotypes. Our findings therefore align with and support previous family studies in the literature, suggesting the involvement of the S allele of the 5-HTTLPR/*SLC6A4* polymorphism in the genetic etiology of suicide attempts.

Some studies have reported an association between the S allele of the 5-HTTLPR/*SLC6A4* polymorphism, and the presence of violent suicide attempts in patients with affective disorders (Fanelli & Serretti, 2019; Sivaramakrishnan et al, 2023). In addition, it has been observed that carriers of the S allele presented two or three times less expression of the *SLC6A4* gene than carriers of the L allele (Lesch et al., 1996). Moreover, some studies have shown that being a carrier of the low-expression allele of 5-HTTLPR/*SLC6A4* is associated with elevated levels of aggression and impulsivity (Waltes, et al, 2016). Our findings could suggest that higher transmission of the S allele of the 5-HTTLPR in *SLC6A4* gene, which implies lower expression of the gene, could be associated with aggression and impulsivity, acting as triggers for the suicide attempt.

Limitations

Our study has certain limitations. The first was the small

sample size, which restricts the generalizability of our results. The latter should therefore be interpreted with caution, and regarded as preliminary until they are replicated in a larger sample. The second is that only the *SLC6A4* and *MAOA* genes were analyzed. Suicidal behavior is a complex phenomenon involving multiple genes across neurobiological systems, including polyamines, GABAergic, neuroinflammatory pathways, lipid metabolism, and the hypothalamic-pituitary-adrenal axis (Lutz et al., 2017).

There is a higher observed prevalence of "S" allele transmission within families with a documented history of suicide attempts. This reinforces the theory that the 5-HTTLPR polymorphism in the serotonin transporter gene plays a significant role in the manifestation of suicidal behaviors among individuals with mood disorders, as well as their immediate family members. This finding underscores the genetic underpinnings of suicidal tendencies, highlighting the importance of considering familial genetic patterns when assessing suicide risk, to provide a more nuanced understanding of its etiology in the context of mood disorders.

Funding

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

None.

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salud mental

ORIGINAL ARTICLE
Volume 48, Issue 6, November-December 2025
doi: 10.17711/SM.0185-3325.2025.007

Assessment of Sleep Health and Physical Activity in Young Adults During the Pandemic

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Received: 22 March 2024
Accepted: 21 November 2024

Citation:
Saygılı Düzova, Ü., Hatice Serap, K., Emine Kaplan, S., Sevim Süeda, A. (2025). Assessment of Sleep Health and Physical Activity in Young Adults During the Pandemic. *Salud Mental*, *48*(6), 297-305. https://doi.org/10.17711/SM.0185-3325.2025.007

DOI: 10.17711/SM.0185-3325.2025.007

ABSTRACT

Introduction. Restrictions, social isolation measures, increased stress, and changing daily routines during the COVID-19 pandemic led to a significant decrease in young adults' physical activity levels and sleep quality. **Objective.** The aim of this study is to examine the relationship between the physical activity levels and sleep quality of young people studying at a university during the COVID-19 pandemic. **Method.** This descriptive, correlational study was conducted with 670 young adults studying healthcare. Data was collected using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) and Pittsburgh Sleep Quality Index (PSQI) and student information form. **Results.** 73.1% of the students reported insufficient sleep and 12.7% reported no physical activity. It was determined that 92.5% of the students whose average IPAQ-SF score was 2107.64 ± 54.70 MET-min/week and total PSQI score average was 7.51±2.92, increased their internet use and 94% used smartphones. A moderate negative relationship was found between the overall mean PSQI score and sleep duration, and between habitual sleep efficiency and the overall mean PSQI score. **Discussion and Conclusion.** The COVID-19 pandemic negatively affected students' physical activity and sleep quality, highlighting the need for targeted interventions to improve this situation.

Keywords: Physical Activity, Sleep Quality, Young Adults, COVID-19 Pandemic.

RESUMEN

Introducción. Las restricciones, las medidas de aislamiento social, el aumento del estrés y el cambio de rutinas diarias durante la pandemia de COVID-19 han provocado una disminución significativa en los niveles de actividad física y la calidad del sueño de los adultos jóvenes. **Objetivo.** El objetivo de este estudio fue examinar la relación entre los niveles de actividad física y la calidad del sueño de jóvenes que estudiaron en una universidad durante el período de la pandemia de COVID-19. **Método.** Este estudio descriptivo y correlativo se llevó a cabo con 670 jóvenes adultos que estudiaban atención médica. Se recopilaron datos utilizando el cuestionario internacional de actividad física (IPAQ-SF) e índice de calidad del sueño de Pittsburgh (PSQI) y el formulario de información de los estudiantes. **Resultados.** El 73,1% de los estudiantes refirió sueño insuficiente y el 12,7% no realizó actividad física. Se determinó que el 92,5% de los estudiantes, cuyo puntaje promedio en el IPAQ-SF fue 2107,64 ± 54,70 MET-min/semana y el puntaje promedio total en el PSQI fue 7,51 ± 2,92, incrementaron su uso de ınternet y el 94% utilizó teléfonos inteligentes. Se encontró una relación negativa moderada entre la puntuación media total del PSQI y la duración del sueño, y entre la eficiencia habitual del sueño y la puntuación media general del PSQI. **Discusión y conclusión.** La pandemia de COVID-19 ha afectado negativamente la actividad física y la calidad del sueño de los estudiantes, revelando la necesidad de intervenciones específicas para mejorar esta situación.

Palabras clave: actividad física, calidad del sueño, jóvenes adultos, pandemia de COVID-19.

INTRODUCTION

Coronavirus disease (COVID-19) forced people and groups worldwide to be more responsible after the World Health Organization (WHO) declared it a pandemic. Unprecedented restrictions were imposed to prevent transmission of the disease throughout communities and control the number of cases. In addition, a number of socially isolating policies were implemented, including the closure of gyms, nursing homes, schools, and universities as well as restrictions on mobility in the most severely affected areas (Romero-Blanco et al., 2020). In addition to measures such as lockdown, weekend curfews, and the closure of social areas such as restaurants, cafeterias, and gyms, business and education models changed, and working from home and online education were implemented (Birmingham et al., 2021) This process, which dramatically affected daily life, negatively impacted both physical and mental health (Timurtaş et al., 2022). The main COVID-19 effects on mental health include stress, worry, fear, depressive symptoms, and sleep disturbance (Rana et al., 2020; Restubog et al., 2020; Shigemura et al., 2020; Xiao et al., 2020).

Among the general population, sleep problems are relatively common and significantly linked to morbidity and mortality (Grandner et al., 2017). It is estimated that over 60% of university students experience poor sleep quality on a regular basis (Lund et al., 2010). During the pandemic, people were reported to be extremely stressed, anxious, and afraid after seeing videos, reading news stories, and watching TV shows on COVID-19. This made it difficult for them to fall asleep and altered their sleep habits (Savitsky et al., 2020). It has also been observed that intensive smart phone and Internet use has adversely affected the circadian rhythm, causing insomnia and other sleep disorders. One study found that changing sleep patterns in health education students leads to poor performance, behavioral modifications, and dietary changes (Tahir et al., 2021). According to several studies, students under stress are more likely to experience health issues, depression, and sleep disorders, negatively affecting their academic performance and quality of life (Köktürk et al., 2021; Sharififard et al., 2020; Shigemura et al., 2020; Silva, et al., 2020; Timurtaş et al., 2022).

Physical activity plays a pivotal role in health. Several studies have confirmed that physical activity levels affect mood and well-being (Kosendiak et al., 2022; Lin et al., 2020; Zhang et al., 2020). Among healthy people, physical activity and exercise have been linked to better sleep quality and fewer sleep disruptions. Work-related behaviors, lifestyles, and leisure activities have changed as a result of the pandemic. During the COVID-19 lockdowns, people began spending more time at home, contributing to a sedentary lifestyle and increasing the time spent sitting. During this period, a significant decrease in physical activity levels was observed in students. The closure of swimming pools, gyms, and fitness centers limited students' access to physical activity, causing them to become almost completely sedentary (Kosendiak et al., 2022).

The research questions to be addressed within the scope of the study are as follows:

1. What is the level of physical activity in young adults?
2. What is the sleep quality level in young adults?
3. What factors affect how well young people sleep and how much they exercise?
4. Is there a link between how active young people are and how well they sleep?

METHOD

Study design

The study has a descriptive, correlational, cross-sectional design. It was planned and reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), a checklist for registering descriptive studies.

Participants

This study was conducted at the Vocational School of Health Services of a university in the Central Anatolia Region of Turkey between April and July 2022. This institution offers a two-year, four-semester associate degree, completed with a total of 120 European Credit Transfer System (ECTS) credits. The target universe of the study comprises first- and second-year students (n = 1800) studying in the departments of Operating Room Services, Medical Imaging, Medical Laboratory Techniques, First and Emergency Aid, Anesthesia, Eldercare, Physiotherapy, Dialysis, Audiometry, and Child Development, enrolled at this institution during the 2021-2022 academic year. According to Cohen's sample size calculation formula for known target populations, the minimum number of participants was calculated as 485, with a 99% confidence interval and a 5% margin of error (α = .05 table value 1.96) (Daniel & Cross, 2018). The sample was obtained using the random sampling method. Invitations to participate in the study were sent to randomly selected students from each department from the official university e-mail address, and students were also invited to participate through class announcements. A participation rate of approximately 37.2% was achieved with 670 students who agreed to participate in the study.

Inclusion criteria

- Being currently enrolled as an active student at the university.
- Being between the ages of 18 and 25.
- Voluntarily agreeing to participate in the study and provide informed consent.

- Having good overall health at the time of enrollment in the study, with no known chronic diseases, serious health conditions or acute medical problems.

Exclusion criteria

- Declining to participate in the study.
- Presence of a severe health condition (chronic diseases such as diabetes, cardiovascular diseases, cancer, or neurological disorders) that could significantly affect participation in the study or interfere with the study.
- Having a physical or mental health issue, including acute illnesses, mental health disorders (such as depression or anxiety), or personal issues that could affect the ability to comply with the study requirements, such as attending study sessions or completing surveys.
- Pregnancy or any other condition that may involve specific medical risks or restrictions during the study period.

Data collection and instruments

During the study period, data were collected using the Introductory Information Form, Pittsburgh Sleep Quality Index (PSQI), and International Physical Activity Questionnaire- Short Form (IPAQ-SF).

Introductory information form

This form, prepared in line with the literature, comprises questions regarding the sociodemographic characteristics of the students participating in the study. The form comprises 15 questions including factors such as participants' age, area of study, year of study, family structure, perceived income status, the place where they spend most of their lives, current place of residence, smoking status, alcohol use, increase in smoking, alcohol use, internet and smartphone use during the pandemic period, and presence of chronic diseases (Köktürk et al., 2021; Romero-Blanco et al., 2020; Silva et al., 2020).

PSQI

PSQI is a self-rate questionnaire providing information on sleep quality and the type and severity of sleep disturbances over a one-month period. The 18 items in the index make it possible to assess the parameters affecting sleep quality, sleep duration, sleep latency, and the frequency and severity of sleep-related problems. Items are grouped into seven components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). Each item in the scale is rated with a score between 0 (no disturbance) and 3 (severe disturbance). The sum of the scores for the seven components yields the total PSQI score. The score for each component ranges from 0 to 3, with the total PSQI score ranging from 0 to 21. A total score of 5 or less indicates good sleep quality. The Turkish validity and reliability study of the scale was conducted by Agargün et al., and the Cronbach's alpha was reported as .80 (Agargun, 1996; Buysse et al., 1989).

IPAQ-SF

The IPAQ-SF was used to assess participants' physical activity levels. This self-reported questionnaire consists of seven items exploring three different types of physical activities: walking, moderate-intensity activities, and vigorous-intensity activities over the past seven days. The duration and frequency of each activity are assessed within three intensity ranges. The energy expenditure for each type of activity is measured using multiples of metabolic equivalents (METs). Total activity is expressed as MET-minutes, calculated by multiplying the MET score by the number of minutes performed. To determine the walking score, the duration of walking in minutes is multiplied by 3.3 METs. The moderate-intensity activity score is obtained by multiplying the duration of moderate-intensity activity in minutes by four METs, while the vigorous-intensity activity score is calculated by multiplying the duration of vigorous-intensity activity in minutes by eight METs. A total of 3000 MET-minutes per week or less indicates that participants are considered physically inactive (Craig et al., 2003).

Data collection

After the necessary official permissions had been secured, students were informed of the purpose of the study from the university's official e-mail address, with those choosing to participate signing informed consent was. Exclusion and inclusion criteria were clearly stated in the informed consent form, and students who did not give consent were excluded from the study. To minimize physical contact due to the COVID-19 pandemic, data were collected through an online survey. The survey allowed participants to provide information on topics such as their health habits, COVID-19 knowledge, precautions taken, and the effects of the pandemic on their mental health.

Statistical analysis

The data were examined using SPSS Statistics 22.0, with six hundred and seventy students taking part in the survey. Table 1 shows the frequency and percentage distributions of demographic data. The Pearson Chi-Square test was used to examine the relationships between the variables. The Kolmogrov-Smirnov Test of Normality was performed to determine whether the data showed normal distribution and whether the test would be parametric or non-parametric. The Levene test was used to examine the homogeneity of variances. The parametric test was conducted for the

Table 1
Sociodemographic characteristics of participants

Features	*X ± SD*	
Age	*20.67 ± 2.34*	
	N	*%*
Gender		
Female	539	80.4
Male	131	19.6
Year of study		
Freshman	247	36.9
Sophomore	423	63.1
Department of study		
Operating room services	65	9.7
Medical imaging evening school	34	5.1
Medical laboratory techniques	176	26.3
First and emergency aid	56	8.4
Anesthesia	56	8.4
Medical imaging techniques	73	10.9
Eldercare	37	5.5
Physiotherapy	58	8.7
Dialysis	42	6.3
Audiometry	20	3.0
Child development	43	7.9
Family type		
Nuclear family	545	81.3
Extended family	125	18.7
Perceived level of family income		
Income more than expenses	66	9.9
Income equal to expenses	401	59.9
Income less than expenses	203	30.3
Place where participants spent most of their lives		
Village	77	11.5
Town	144	21.5
City	449	67.0
Current place of residence		
With family	411	61.3
With a roommate	30	4.5
In a dorm	229	34.2
Presence of a chronic disease		
Yes	41	6.1
No	629	93.9
Smoking		
Yes	139	20.7
No	531	79.3
Increase in smoking during the pandemic		
Yes	83	12.4
No	587	87.6
Alcohol use		
Yes	40	6.0
No	630	94.0
Increase in alcohol use during the pandemic		
Yes	21	3.1
No	649	96.9
Increase in internet use during the pandemic		
Yes	620	92.5
No	50	7.5
Increase in smart phone use during the pandemic		
Yes	630	94.0
No	40	6.0
Total	670	100.0

variables that met assumptions, and the non-parametric test was used for those that did not. An independent, two-sample t-test was used to assess the difference between the two groups. The Tukey Test or the Mann Whitney U Test was used in post-hoc tests to compare the groups with differences. A significant value of .05 was used. Comparative analyses used one-way ANOVA and Pearson correlation. In the Pearson correlation, the absolute values of r were classified as follows: 0-.19 indicates a very weak correlation, .2-.39 indicates a moderate correlation, .40-.59 indicates a moderate correlation, .6-.79 indicates a strong correlation, and .8-1 indicates a very strong correlation. Data was considered statistically significant at $p < .05$.

Ethical considerations

For all studies conducted during the COVID-19 period, the necessary permissions were obtained from the Turkish Ministry of Health. Permission was also obtained from the institution where the scientific research was conducted. The Selçuk University Faculty of Medicine received approval from the non-invasive ethics committee (IRB: 2022/07). All the procedures in this research were carried out in accordance with The Declaration of Helsinki, with informed consent being obtained from all students.

RESULTS

Sociodemographic characteristics of participants

Eighty-four percent of the students in the study were female, with an average age of 20.67 ± 2.34. Most participants (26.3%) were studying medical imaging and medical laboratory techniques; 63.1% were second year students, and 61.3 lived with their families. A total of 81.3% of the participants had nuclear families; 59.9% had an income equal to their expenses; 93.9% did not have a chronic disease; 20.7% reported that they smoked, and 94.0% stated that they did not use alcohol. In addition, most students reported an increase in their Internet and smart phone use during the pandemic (92.5% and 94%, respectively) (Table 1).

PSQI Components and Mean Global PSQI scores, mean IPAQ-SF score, and mean MET scores of participants

The Mean Global PSQI score of students was 7.51 ± 2.92. An examination of the mean scores for PSQI components revealed that 26.9% of students had a mean score above five in the following components: subjective sleep quality (1.32 ± .60), sleep latency (1.94 ± .70), sleep duration (.63 ± .84), habitual sleep efficiency (1.06 ± 1.19), sleep disturbances (2.60 ± 1.53), use of sleeping medication (.16 ± .64),

and daytime dysfunction (1.48 ± 1.07). After analyzing participants' physical activity levels, we found that 12.7% were not physically active, 26.7% had low levels of physical activity, and 60.5% had sufficient activity levels. The mean IPAQ-SF score of participants was 2107.64 ± 54.70 MET-min/week. The sitting MET score was 653.97 ± 515.70, the walking MET score was 1140.20 ± 1002.90, the moderate-intensity activity MET score was 164.95 ± 286.48, and the vigorous-intensity activity MET score was 148.65 ± 660.56 (Table 2).

Relationship between overall and component mean PSQI scores and physical activity levels of participants

The relationship between PSQI components and each participants's mean overall score and their degree of physical activity was examined. No appreciable difference was observed in the quality of sleep between students who were physically active and those who were not (Table 3).

Correlation between the mean PSQI component score, PSQI and overall MET score of participants

The overall PSQI-score and overall MET score showed a weak, non-significant correlation (r = -.024, p = .531). A somewhat positive correlation was found between sleep duration and habitual sleep efficiency. We found that sleep length increased with habitual sleep efficiency. A moderate positive correlation was identified between the overall PSQI score and the components of sleep latency and daytime dysfunction, indicating that as the overall PSQI score increased, so did sleep latency and daytime dysfunction levels. In addition, a moderate negative correlation was observed between the overall PSQI score and sleep duration, suggesting that higher PSQI scores were associated with shorter sleep duration. It was found that sleep duration decreased as the overall PSQI score increased. Moreover, a

Table 2
PSQI Component and overall mean PSQI scores, mean IPAQ-SF scores, and mean MET scores

	N	%
Good sleep quality	180	26.9
Poor sleep quality	490	73.1
Physically inactive	85	12.7
Low physical activity level	179	26.7
Sufficient physical activity level	406	60.5
Total	670	100.0
	Ort. ± SS.	Min-max
Subjective sleep quality	1.32 ± 0.60	0-2
Sleep latency	1.94 ± 0.70	0-3
Sleep duration	0.63 ± 0.84	0-3
Habitual sleep efficiency	1.06 ± 1.19	0-3
Sleep disturbances	2.60 ± 1.53	0-6
Use of sleeping medication	0.16 ± 0.64	0-3
Daytime dysfunction	1.48 ± 1.07	0-3
Overall PSQI	7.51 ± 2.92	1-18
IPAQ-SF	2107.64 ± 54.70	0-10104
Sitting MET	653.97 ± 515.70	0-1575
Walking MET	1140.20 ± 1002.90	0-2772
Moderate-intensity MET	164.95 ± 286.48	0-1440
Vigorous-intensity MET	148.65 ± 660.56	0-6000

Table 3
Relationship between mean overall and component PSQI scores and physical activity level

		N	*X* ± *SD*	
Subjective sleep quality	Inactive	85	1.38 ± .57	*F* = 2.447
				p = .087
	Minimal	179	1.24 ± .60	
	Very active	406	1.34 ± .61	
Sleep latency	Inactive	85	1.98 ± .71	*F* = 2.309
				p = .735
	Minimal	179	1.91 ± .69	
	Very active	406	1.94 ± .70	
Sleep duration	Inactive	85	.52 ± .82	*F* = .898
				p = .408
	Minimal	179	.60 ± .83	
	Very active	406	.65 ± .85	
Habitual sleep efficiency	Inactive	85	1.05 ± 1.23	*F* = .128
				p = .880
	Minimal	179	1.02 ± 1.21	
	Very active	406	1.07 ± 1.17	
Sleep disturbances	Inactive	85	.90 ± .29	*F* = .636
				p = .530
	Minimal	179	.91 ± .27	
	Very active	406	.88 ± .31	
Use of sleeping medication	Inactive	85	.15 ± .58	F = .051
				p = .951
	Minimal	179	.17 ± .67	
	Very active	406	.16 ± .64	
Daytime dysfunction	Inactive	84	1.50 ± 1.06	*F* = .134
				p = .874
	Minimal	179	1.45 ± 1.06	
	Very active	406	1.50 ± 1.07	
Overall PSQI	Inactive	84	1.77 ± .42	*F* = .748
				p = .474
	Minimal	179	1.70 ± .45	
	Very active	406	1.73 ± .44	

Table 4
Correlation between mean PSQI component score, mean overall PSQI score, and overall MET score

Overall MET		*Overall MET*	*Subjective sleep quality*	*Sleep latency*	*Sleep duration*	*Habitual sleep efficiency*	*Sleep disturbances*	*Use of sleeping medication*	*Daytime dysfunction*
Subjective sleep quality	*r*	.023							
	p	.553							
Sleep latency	r	-.041	.267						
	p	.290	.000						
Sleep duration	*r*	.071	.105	.065					
	p	.068	.007	.091					
Habitual sleep efficiency	*r*	.015	.265	.099	.548				
	p	.698	.000	.010	.000				
Sleep disturbances	*r*	-.052	.116	.162	-.026	-.003			
	p	.177	.003	.000	.506	.943			
Use of sleeping medication	*r*	.038	.083	.074	.094	.070	.042		
	p	.331	.032	.057	.015	.071	.277		
Daytime dysfunction	*r*	.002	.348	.181	.072	.080	.168	.161	
	p	.963	.000	.000	.061	.039	.000	.000	
Overall PSQI	*r*	.024	.348	.455	-.594	.689	.229	.374	.587
	p	.531	.000	.000	.000	.000	.000	.000	.000

Note: r = Pearson correlation, **p* < .05, ***p* < .001.

significant correlation was observed between habitual sleep efficiency and the overall PSQI score. As the overall PSQI score increased, so did habitual sleep efficiency. Although the associations with other variables were statistically significant, they were found to be weak, low, or very low in strength (Table 4).

DISCUSSION AND CONCLUSION

This study examined the sleep quality and physical activity levels of young adults during the COVID-19 pandemic and evaluated the relationship between these two variables.

Sleep quality of young adults

In our study, the mean PSQI score of participants was 7.51 ± 2.92, with 73.1% being found to have poor sleep quality. An examination of sleep quality showed that sleep disturbances (2.60 ± 1.53) and sleep latency (1.94 ± .70) had the highest mean scores. This rate is higher than the mean sleep quality scores reported in previous studies in Turkey, in which the PSQI was used as a data collection tool: 6.15 ± 1.90 (Aysan et al., 2014), 7.89 ± 2.36 (Kucukgoncu et al., 2010), 6.90 ± 2.4 (Saygılı et al., 2011), and 6.28 ± 3.05 (Şenol et al., 2012). Given that the rates of students with poor sleep quality reported in the literature generally vary between 50% and 60%, the 73.1% rate in our study clearly demonstrates how conditions during the pandemic negatively affected sleep quality. It has been reported that COVID-19 negatively affected individuals' sleep quality by 7.88 ± 3.43 (Xiao et al., 2020). The study conducted by Ramos Socarras et al., (2021) on 583 adolescents and young adults in Canada revealed that the COVID-19 pandemic negatively affected sleep patterns, delaying the onset of sleep, and leading to an increase in waking up early at night and in the morning, and the frequency of nightmares (Ramos Socarras et al., 2021). In the study conducted by Pinto et al., (2020) in Portugal, 69.6% of participants reported at least one sleep difficulty, with frequent waking up being identified as the most common problem (Pinto et al., 2020). A study conducted by Oliveira Souza et al., (2023) found that 40% of middle-aged adults experienced sleep quality deterioration during the pandemic, with 30% of participants experiencing sleep disorders due to social isolation (Oliveira Souza et al., 2023). These studies show that the anxiety and stress caused by the pandemic significantly reduced sleep quality by increasing the difficulty of individuals in initiating and maintaining sleep. However, sleep problems can also trigger other problems. In a study evaluating the sleep problems of young adults, irregular sleep habits, insufficient sleep duration, and poor sleep quality were identified as common problems. It also reported that young adults use substances such as alcohol and non-prescription drugs to maintain their sleep patterns and use stimulants to stay awake (Işık et al., 2015; Cheng et al., 2012). It was observed that these sleep problems affected students' daily life activities and safety, and in some cases, they fell asleep while driving and caused accidents. It was observed that poor sleep quality not only caused health problems in participants, but also poor academic performance, distraction, and lack of motivation. It has been reported in the literature that poor sleep quality causes problems such as falling asleep in class, low grade point averages, and general sluggishness in daily life (Aysan et al., 2014). These findings show that young adults tend to use risky strategies for sleep management and that this situation has reached levels that can jeopardize their health and safety (Köktürk et al., 2021).

Smartphone, internet, and smoking habits of young adults

Certain routines and habits of individuals changed during the pandemic. This study found that alcohol and cigarette use increased among young adults. In addition, 92.5% of participants reported an increase in internet use and 94% in smartphone use. A similar increase in these habits in young adults was also reported in the literature during this

period (Rabia & Fazlıoğulları, 2021; Capdevila-Gaudens et al., 2021; Cardoso et al., 2022). Tahir et al., (2021)found a link between internet addiction and insufficient sleep. The same study revealed that internet addiction accounts for 13.2% of the variance in poor sleep quality and is a significant predictor of poor sleep quality. In particular, it has been observed that increased screen time suppresses melatonin secretion, making it difficult to fall asleep and reducing sleep quality (Tahir et al., 2021). A systematic review and meta-analysis examining the prevalence and risk factors of mental health problems among medical students during the COVID-19 pandemic revealed that individuals in this group were more prone to health problems linked to conditions during the pandemic. The same study showed that the increase in smartphone and internet use, in particular, had negative effects on health by increasing the risks of problematic use and addiction among young people. These effects were more pronounced and jeopardized the quality of life in groups under academic and professional pressure, such as medical students (Peng et al., 2023). Our study also emphasizes this increase in screen time during the pandemic, highlighting its indirect effects on sleep quality.

Physical activity of young adults

In this study, the physical activity levels of the students were evaluated using IPAQ-SF. It was found that 60.5% of participants had sufficient physical activity levels, 26.7% showed low-level physical activity, and 12.7% were completely physically inactive. The average MET score was found to be 2107.64 ± 54.70 MET-min/week. In addition, the MET sitting time score was 653.97 ± 515.70, the MET walking score was 1140.20 ± 1002.90, the moderate-intensity MET score was 164.95 ± 286.48, and the high-intensity MET score was 148.65 ± 660.56. These findings show that the physical activity levels of the participants were largely based on low- and moderate-intensity activities. The lockdown and social isolation measures implemented during the pandemic significantly affected physical activity levels. Our study observed that physical activity was largely concentrated in low-intensity activities (such as walking). According to the literature, this situation was related to the restriction of outdoor activities, forcing people to engage in indoor activities requiring less movement during the pandemic. In particular, the fact that high-intensity physical activities were quite low (148.65 ± 660.56%) may reflect the restrictive effect of the pandemic on physical activity. It has been reported in the literature that high-intensity physical activities have a more pronounced effect on sleep quality (Erdogan & Revan, 2019). This effect may not have been seen in our study since the majority of participants engaged in low-intensity activities. Other factors related to the pandemic, such as increased screen time and internet addiction, may offset the positive effects of physical activity on sleep (Tahir et al., 2021).

In conclusion, this study examined the sleep quality and physical activity levels of young adults during the COVID-19 pandemic, revealing the complex effects of conditions during the pandemic on these two major health indicators. A significant proportion of participants (73.1%) had poor sleep quality, associated with the uncertainty, stress, and changing life habits caused by the pandemic. In addition, it was found that low- and moderate-intensity physical activity accounted for most of the physical activity and although physical activity levels were generally found to be sufficient, this did not show a significant relationship with sleep quality. This situation indicates that increased screen time, psychological stress, and social isolation during the pandemic may offset the positive effect of physical activity on sleep. The significant increase in internet (92.5%) and smartphone (94.0%) use during the pandemic is a key factor indirectly affecting sleep quality. This finding is consistent with the literature showing that excessive use of digital devices is associated with circadian rhythm disorders and difficulty falling asleep. In addition, problems observed in sleep components such as sleep latency, sleep duration, and daytime dysfunction reveal how poor sleep quality negatively affects young adults' daily lives and academic or occupational performance. These findings clearly demonstrate that both the physical and mental health of young adults should be supported in crisis situations such as the pandemic. Health authorities and educational institutions can provide online exercise programs to encourage young adults to engage in regular physical activity, awareness campaigns to develop healthy sleep habits, and guidance for limiting screen time. In addition, encouraging high-intensity physical activities and strengthening young adults' stress coping mechanisms are critical to improving their overall health and well-being. Although this study provides relevant information on understanding the health behaviors of young adults under pandemic conditions, causal relationships cannot be established due to their cross-sectional design. Future studies could examine the relationships between physical activity, sleep quality, and other psychosocial factors more comprehensively. In addition, the long-term effects of digital addiction and post-pandemic lifestyle changes on sleep and physical activity should also be explored. These studies could provide a significant foundation for developing health policies and supporting the health of young adults.

Acknowledgements

The authors would like to thank all the students who took part in this study.

Conflict of interest

The authors have no conflict of interest to declare.

Funding

None.

Declarations

Ethics committee approval was obtained before this study (date: March 2022, decision no: 2022/07).
Consent to Participate All participants gave their written informed consent before participating in the study in accordance with the principles of the Declaration of Helsinki.

Author contributions

USD and EKS conceptualized the study, SA and BB organized the data collection process, HSK conducted the data analysis and drafted the methodology section. All the authors wrote the conclusion section together and contributed to the revision of the final version of the article.

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salud mental

ORIGINAL ARTICLE
Volume 48, Issue 6, November-December 2025
doi: 10.17711/SM.0185-3325.2025.035

Aripiprazole versus Brexpiprazole for People with Schizophrenia: A Systematic Review

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Received: 18 Abril 2024
Accepted: 20 February 2025

Citation:
Flores Medina, Y., Rosel Vales, M., Escamilla Orozco, R. I., Saracco-Alvarez, R., Guerrero Medrano, A. F., Celada Borja, C. A., Tiburcio Sainz, M., & Martínez-Vélez, N. A. (2025). Aripiprazole versus Brexpiprazole for People with Schizophrenia: A Systematic Review. *Salud Mental, 48*(6), 307-316. https://doi.org/10.17711/SM.0185-3325.2025.035

DOI: 10.17711/SM.0185-3325.2025.035

ABSTRACT

Introduction: Schizophrenia is a chronic, complex, and multifactorial psychiatric disorder characterized by various clinical manifestations. The first line of treatment for this condition is antipsychotics. Second-generation antipsychotics use partial agonist mechanisms of D2 receptors that regulate dopaminergic tone, presumably reducing the incidence of extrapyramidal symptoms. Two second-generation molecules that have shown adequate efficacy for the treatment of positive symptoms in schizophrenia are aripiprazole and brexpiprazole and there are reviews comparing their effectiveness and safety in treatments of up to four weeks. **Objective:** To evaluate the efficacy and tolerability of aripiprazole compared with brexpiprazole in people diagnosed with schizophrenia or schizophrenia-like psychosis in medium- and long-term treatments. **Method:** The search was conducted by a specialist from the Cochrane schizophrenia group on March 9, 2023, in the MEERKAT registry, for (*Aripiprazole* and *Brexpiprazole*). **Results:** A total of 166 registers were identified from the electronic searches. Fifteen were eliminated due to duplication. The titles and abstracts of 151 records were examined, and four full texts were retrieved and assessed for eligibility according to inclusion and exclusion criteria. During this process, three studies were excluded, and finally only one study met the criteria for inclusion in this review. **Discussion and conclusion:** A single study was found to show data on efficacy, safety, and tolerability in patients with medium-term treatments. Since the evidence identified contains significant biases, it is not possible to establish a recommendation favoring the prescription of one of the antipsychotics in the study over the other.

Keywords: Brexpiprazole, aripripazole, schizophrenia, systematic review.

RESUMEN

Introducción: La esquizofrenia es un trastorno psiquiátrico crónico, complejo y multifactorial con diferentes manifestaciones clínicas. La primera línea de tratamiento para esta condición son los antipsicóticos, los de segunda generación utilizan mecanismos de acción con agonismo parcial de los receptores D2 que regulan el tono dopaminérgico, presumiblemente reduciendo la incidencia de síntomas extrapiramidales. Dos moléculas de segunda generación que han mostrado adecuada eficacia para el tratamiento de los síntomas positivos en esquizofrenia son el aripiprazol y el brexpiprazol y existen revisiones que comparan su efectividad y seguridad en tratamientos de hasta 4 semanas. **Objetivo:** Evaluar la eficacia y tolerabilidad del aripiprazol en comparación con el brexpiprazol en personas diagnosticadas con esquizofrenia o psicosis similar a la esquizofrenia en tratamientos de mediano y largo plazo. **Método:** La búsqueda se realizó en el registro MEERKAT, (*Aripiprazol* y *Brexpiprazol*) por un especialista del grupo Cochrane de esquizofrenia el 9 de marzo de 2023. **Resultados:** Se identificaron 166 registros a partir de las búsquedas electrónicas. Se eliminaron 15 por duplicación. Se examinaron los títulos y resúmenes de 151 registros, se recuperaron cuatro textos completos, finalmente solo un estudio cumplió los criterios para ser incluido en esta revisión. **Discusión y conclusión:** Un solo estudio muestra datos sobre la eficacia, seguridad y tolerabilidad en pacientes con tratamientos de mediano plazo. La evidencia identificada muestra sesgos importantes, por lo que no es posible establecer una recomendación que favorezca la prescripción de uno de los antipsicóticos del estudio sobre el otro.

Palabras clave: Brexpiprazol, aripripazol, esquizofrenia, revisión sistemática.

INTRODUCTION

Schizophrenia is a chronic, complex, multifactorial psychiatric disorder with clinical manifestations that include positive symptoms such as delusions, hallucinations, disorganized thinking and disorganized behavior, and negative symptoms such as anhedonia, social withdrawal, flat affect, alogia, and apathy (Millier et al., 2014). This condition also encompasses neurocognitive failures associated with occupational and social outcomes. (Mihaljević-Peleš et al., 2019). Schizophrenia has a lifetime prevalence of 1% and an incidence of 15 cases per 100,000 population, with onset usually occurring in early adolescence (Hasan et al., 2020). The ratio of women to men with schizophrenia is 1:1.3 (Sommer et al., 2020).

Antipsychotic drugs are the mainstay of treatment for schizophrenia, their mechanism of action being to regulate dopaminergic neurotransmission. Most first-generation antipsychotics work by blocking dopamine D2 receptors to varying degrees. Second-generation or atypical antipsychotic drugs employ additional mechanisms to regulate dopaminergic function, such as partial antagonism of dopamine receptors and antagonism. They also use partial antagonism of serotonin receptors to improve psychotic symptoms while reducing the incidence of extrapyramidal symptoms (McCutcheon et al., 2020; Owen et al., 2016). Among second-generation antipsychotic drugs, partial agonists–aripiprazole, brexpiprazole, and cariprazine–constitute a subclass, as their mechanism of action involves the partial agonism of D2 receptors. Partial agonism regulates dopamine tone, which has been hypothesized to reduce the incidence of adverse effects and the risk of dopamine supersensitivity psychosis (Frankel & Schwartz, 2017).

Aripiprazole, the first partial agonist, was first released in 2002. It decreases D2 transmission without full receptor blockade. In the absence of dopamine, it increases D2-mediated transmission (Kikuchi et al., 2021). The receptor-binding affinities (Ki, nmol/L) of aripiprazole are D2 = .34, D3 = .8, serotonin 5-HT1A = 1.7, 5-HT2A = 3.4, 5-HT2C = 96, 5-HT7 = 39, alpha1 = 52, histamine H1 = 61, and muscarinic acetylcholine M_1 = 6800 (Kikuchi et al., 2021).

Brexpiprazole, first introduced in 2015, was designed to improve tolerability, mainly by reducing the risk of side effects reported with aripiprazole: akathisia, restlessness, and sleep disturbances (Kikuchi et al., 2021). The receptor-binding affinities (Ki, nmol/L) of brexpiprazole are D2 = .30, D3 = 1.1, 5-HT1A = .12, 5-HT2A = .47, 5-HT2C = 34, 5-HT7 = 3.7, alpha1 = 3.8, H1 = 19, and M1 ≥ 1000 (Kikuchi et al., 2021).

Important differences exist between brexpiprazole and aripiprazole treatments. The clinical profile of brexpiprazole shows lower intrinsic activity on the dopamine agonist spectrum than aripiprazole, which has fewer effects such as activation, agitation, and akathisia, enabling better overall tolerability (Stahl, 2016).

Brexpiprazole has a similar effect to aripiprazole in reducing psychotic symptoms and similar rates of metabolic adverse effects (Ward & Citrome, 2019). Both drugs are associated with a reduced incidence of all-cause discontinuation compared to placebo (Kishi et al., 2020). Aripiprazole acts through 5HT2A antagonism, 5HT1A agonism, and alpha 1B antagonism to mitigate extrapyramidal side effects, but brexpiprazole has greater potency at each of the three receptors (Stahl, 2016). The higher affinity for 5-HT1A could reflect the greater effectiveness of brexpiprazole in the treatment of depressive symptoms (Citrome et al., 2016a). Moreover, the lower antihistaminergic properties of brexpiprazole may reduce somnolence and sedation (Stahl, 2016). Compared to aripiprazole, brexpiprazole has fewer sedative and activating adverse effects (Ward & Citrome, 2019) and may demonstrate greater efficacy in improving positive and cognitive symptoms (Citrome et al., 2016a). A pooled analysis of schizophrenia trials reported a number needed to treat (NNT) of eight for aripiprazole vs. placebo, and an NNT of seven for brexpiprazole vs. placebo. Response was defined as a 30% or more decrease in the total Positive and Negative Syndrome Scale (PANSS) score or a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2 (very much improved or much improved; Citrome, 2015). Although antipsychotic medication can help reduce positive symptoms, the negative syndrome is more difficult to treat, with mixed results in clinical trials (Correll & Schooler, 2020).

Despite the literature highlighting the benefits of brexpiprazole compared to aripiprazole, studies such as Huhn et al., (2019) found that treatment with aripiprazole resulted in more effective symptom reduction (general, positive, negative and depressive symptoms) and better tolerability (all-cause discontinuation risk ratio (RR) .80, 95% confidence interval (CI) .73 to .86) compared with brexpiprazole (RR .89, 95% CI .80 to .98). Other outcomes included akathisia, where brexpiprazole ranked slightly better than aripiprazole (RR 1.35 with brexpiprazole vs RR 1.95 with aripiprazole), and prolactin elevation, where aripiprazole ranked better than brexpiprazole. These data indicate that the superiority of brexpiprazole over other molecules is not confirmed (Huhn et al., 2019).

Aripiprazole has proven useful in the treatment of psychotic symptoms, as well as in the treatment of adverse effects and comorbidities. Some research has indicated that brexpiprazole may have greater efficacy than aripiprazole and a similar or better tolerability profile. It is therefore important to examine the available evidence to compare these two medications, as both are widely accessible yet have varying costs.

There are multiple protocols but only seven Cochrane Reviews of aripiprazole in people with schizophrenia

(Belgamwar & El-Sayeh, 2011; Bhattacharjee & El-Sayeh, 2008; Brown et al., 2013; El-Sayeh & Morganti, 2006; Hirsch & Pringsheim, 2016; Khanna et al., 2014; Ostinelli et al., 2018) and no reviews for brexpiprazole, only two protocols (Bazrafshan et al., 2017; Ralovska et al., 2023).

Some studies have compared the efficacy, safety and tolerability of aripiprazole versus brexpiprazole in individuals with fewer than four weeks of treatment (Kishi et al., 2020). Our review will focus on medium- (six weeks to six months) and long-term treatment (over six months) and will obtain additional information on outcomes such as quality of life, behavior, cognitive functioning, and service use. To our knowledge, no other meta-analyses have included these measures, which is why this review could contribute to increasing information on the effects of aripiprazole versus brexpiprazole. The present review aimed to assess the efficacy and tolerability of aripiprazole compared to brexpiprazole in people diagnosed with schizophrenia or schizophrenia-like psychosis.

METHOD

Eligibility criteria

Studies: We included randomized controlled trials (RCTs) in the search, as well as studies reported as full-text articles.

Participants: Adults (over 18 years of age) of both sexes with diagnostic criteria for schizophrenia or related disorders, including schizoaffective disorder. Since we were interested in the phases of the illness that could be treated with antipsychotic drugs, we excluded the prodromal phase and included people with first-episode schizophrenia, and early and persistent illness in the search.

To ensure that the results were as relevant as possible to the current care of people with schizophrenia, studies focusing on those with specific problems (such as negative symptoms, adverse reactions, or treatment-resistant illness) were included in the search.

Table 1
Sources and search strategies

Source	*Search strategy*
1. CENTRAL (The Cochrane Library) http://crso.cochrane.org/SearchSimple.php The date of the search is March 9, 2023 and the records are updated to January 31, 2023 in MeerKat v1.0.	#1 MeSH descriptor: [Clinical Trials as Topic] explode all trees #2 MeSH descriptor: [Randomized Controlled Trial] explode all trees #3 MeSH descriptor: [Double-Blind Method] explode all trees #4 MeSH descriptor: [Single-Blind Method] explode all trees #5 MeSH descriptor: [Cross-Over Studies] explode all trees #6 (randomized controlled trial):pt (Word variations have been searched) #7 (controlled clinical trial):pt (Word variations have been searched) #8 (clinical trial):pt (Word variations have been searched) #9 ((clinic$ NEAR/2 trial)):ti,ab,kw (Word variations have been searched) #10 ((random$ NEAR/5 control$ NEAR/5 trial$)):ti,ab,kw (Word variations have been searched) #11 ((crossover or cross-over)):ti,ab,kw (Word variations have been searched) #12 (((singl$ or double$ or trebl$ or tripl$) NEAR (blind$ or mask$))):ti,ab,kw (Word variations have been searched) #13 (randomi$):ti,ab,kw (Word variations have been searched) #14 (random$ NEAR/5 (assign$ or allocat$ or assort$ or reciev$)) #15 {or #1-#14} #16 MeSH descriptor: [Schizophrenia] explode all trees #17 MeSH descriptor: [Paranoid Disorders] explode all trees #18 (schizo$):ti,ab,kw (Word variations have been searched) #19 (hebephreni$):ti,ab,kw (Word variations have been searched) #20 (oligophreni$):ti,ab,kw (Word variations have been searched) #21 (psychotic$):ti,ab,kw (Word variations have been searched) #22 (psychosis):ti,ab,kw (Word variations have been searched) #23 (psychoses):ti,ab,kw (Word variations have been searched) #24 (((chronic$ or sever$) NEAR/2 mental$ NEAR/2 (ill$ or disorder$))):ti,ab,kw (Word variations have been searched) #25 MeSH descriptor: [Dyskinesia, Drug-Induced] explode all trees #26 MeSH descriptor: [Psychomotor Agitation] explode all trees #27 MeSH descriptor: [Neuroleptic Malignant Syndrome] explode all trees #28 MeSH descriptor: [Diagnosis, Dual (Psychiatry)] explode all trees #29 ((tardiv$ NEAR dyskine$)):ti,ab,kw (Word variations have been searched) #30 (akathisi$):ti,ab,kw (Word variations have been searched) #31 (acathisi$):ti,ab,kw (Word variations have been searched) #32 ((neuroleptic$ and (malignant NEAR/2 syndrome))):ti,ab,kw (Word variations have been searched) #33 ((neuroleptic$ and (movement and disorder$))):ti,ab,kw (Word variations have been searched) #34 (parkinsoni$):ti,ab,kw (Word variations have been searched) #35 (neuroleptic-induc$):ti,ab,kw (Word variations have been searched) #36 {or #29-#35} #37 ((parkinson's NEAR/1 disease)):ti,ab,kw (Word variations have been searched) #38 #36 NOT #37 #39 {or #16-#28} #40 #38 OR #39 #41 #15 AND #40 #42 #41 in Trials #43 Aripiprazole #44 Brexpiprazole #45 #42 AND #43 AND #44

Table 1
Sources and search strategies (continued)

Source	*Search strategy*
2. EMBASE (date of search: 9 March 2023)	1. (schizo$ or psychotic$ or psychosis or psychoses).mp. 2. ((chronic$ or severe$ or persistent$) adj (mental$ or psychological$) adj (disorder$ or ill$)).mp. 3. exp schizophrenia/ 4. exp psychosis/ 5. mental patient/ 6. (tardiv$ adj dyskine$).mp. 7. neuroleptic agent/ 8. (neuroleptic$ and (malignant adj2 syndrome)).mp. 9. tardive dyskinesia/ 10. akathisia/ 11. exp neuroleptic malignant syndrome/ 12. (neuroleptic$ and movement and disorder$).mp. 13. parkinsoni$.mp. 14. parkinson's.mp. 15. or/1-14 16. 15 not parkinson's.ti. 17. (clin$ adj2 trial).mp. 18. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. 19. (random$ adj5 (assign$ or allocat$)).mp. 20. randomi$.mp. 21. crossover.mp. 22. exp randomized-controlled-trial/ 23. exp double-blind-procedure/ 24. exp crossover-procedure/ 25. exp single-blind-procedure/ 26. exp randomization/ 27. or/17-26 28. and/16,27 29. aripiprazole/ 30. brexpiprazole/ 31. 28 and 29 and 30

Note: October 9, 2023 e Included ongoing studies.

Interventions: 1) Aripiprazole is available in oral and long-acting injectable (LAI) depot formulations. The dose range of the oral formulation was between 10 mg/day and 30 mg/day. The doses considered for therapeutic use were up to 400 mg/month for the LAI (long-acting injectable) formulation. 2) Brexpiprazole is accessible as an oral formulation. For this review, doses ranging from 2 mg/day to 4 mg/day (the established therapeutic doses) were contemplated.

Search methods for identifying studies

The search was conducted by the Cochrane schizophrenia group information specialist on March 9, 2023. The MEERKAT registry was searched in March 2023 using (*Aripiprazole* AND *Brexpiprazole*). Since few references were retrieved in this system, a search was performed in the EMBASE and Cochrane CENTRAL trial databases.

The Information Specialist compiled this register from systematic searches of the following major resources: Cochrane Central Register of Controlled Trials (CENTRAL) and Embase. As explained on the Schizophrenia Group website (schizophrenia.cochrane.org/register-trials), the register also included hand searching and conference proceedings. It did not place any limitations on language, date, document type, or publication status. The search strategies used can be seen in Table 1. The reference lists of all included studies were checked for other relevant studies. We attempted to contact the first author of the relevant unpublished studies, but received no response, so we did not include them in this review. (For the complete protocol of this systematic review see Martínez-Vélez et al., 2023).

Procedure

The search records were imported into the Covidence software (www.covidence.org). During the first stage of screening, two of the authors (YF and MR) independently screened study titles and abstracts to rule out those that were clearly ineligible and another author (RS) acted as referee. Two other reviewers (YF and AG) independently obtained and reviewed full reports of all potentially eligible records. Where disagreements could not be resolved by discussion, the lead author of the review team (NM) was consulted.

Two researchers (YF, AG) performed data extraction using the Covidence extraction template. Extraction was performed independently, considering the relevant results of the included study.

The following variables were extracted: Study identification (source of sponsorship, country, setting, author(s)' name(s), institution(s), email(s), and address(es)), Methods (study design and group), and Population (inclusion and exclusion criteria). For outcomes, we utilized the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and Composite Cognitive Test Battery reported as least square at Week 6 of treatment. We also used the Simpson-Angus Extrapyramidal Side Effects Scales, Clinical Global Impression-Improvement (CGI-I), Abnormal Involuntary Movements Scale, Barnes Akathisia

Rating Scale (BARS), Change in Body Weight, and Body Mass Index. We collected mean and standard deviation changes from baseline at Week 6 for cholesterol, HDL, LDL, triglycerides, glucose, and prolactin.

Forms: Covidence (www.covidence.org) was used, and data were entered and subsequently exported to the Review Manager Web (RevMan Web 2023). RevMan Web.

Assessment of Risk of Bias in Included Studies: Two reviewers (YF, AG) independently assessed the risk of bias in the included trial using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions presented in Appendix 3 (Higgins et al., 2023). This is based on evidence of associations between possible overestimation of effect and level of risk of bias or as reported by domains. For this review, this included sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. When evaluators disagreed, the final rating was considered by consensus, with all decisions being documented.

Assumptions about participants who dropped out or were lost to follow-up. The included study did not analyze participants who completed the study. For assumptions about participants who dropped out or were lost to follow-up, the last observation carried forward (LOCF) method was chosen for the only study included in this review.

Since there was only one study, it was not possible to conduct a graphic or statistical evaluation of reporting biases.

We used the GRADE approach to assess the certainty of the evidence (Schünemann et al., 2023); and the GRADEpro GDT (2015) to export data from our review and create one summary of findings table. This table provided outcome- specific information concerning the overall certainty of evidence from the study included the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important for patient care and decision-making.

RESULTS

A single study with the established features was identified. The main analysis therefore concerned the only study included after all the steps described in the flow diagram (PRISMA) (Figure 1). We found 166 records from electronic searches, fifteen of which were eliminated because they were duplicated, meaning that the titles and abstracts of 151 records were examined. Of these, only four full texts were retrieved, and their eligibility was assessed according to the inclusion and exclusion criteria described in the protocol (type of study, population and intervention). During this process, three studies were excluded, and finally, only one study met the criteria for inclusion in this review.

Included studies

The characteristics of the included study are presented (Citrome et al., 2016a)

Design: This was an exploratory, open-label, multicenter, flexible-dose study of adult patients conducted between February 27, 2014 and July 25, 2014 at nineteen sites across the United States. Patients were randomly assigned 2:1 to receive brexpiprazole or aripiprazole.

Participants: A total of ninety-seven patients were randomized, with sixty-four patients receiving brexpiprazole and thirty-three receiving aripiprazole. A total of sixty-one (62.9%) patients completed the study, forty (62.5%) in the brexpiprazole group and twenty-one (63.6%) in the aripiprazole group.

Inclusion criteria: Adult patients aged 18–65 with a Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR) diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders.

Exclusion criteria: Patients were excluded if they were presenting with a first episode of schizophrenia, or had been hospitalized for more than twenty-one days for the current acute episode. They were also excluded if they had a current DSM-IV-TR Axis 1 diagnosis other than schizophrenia, or

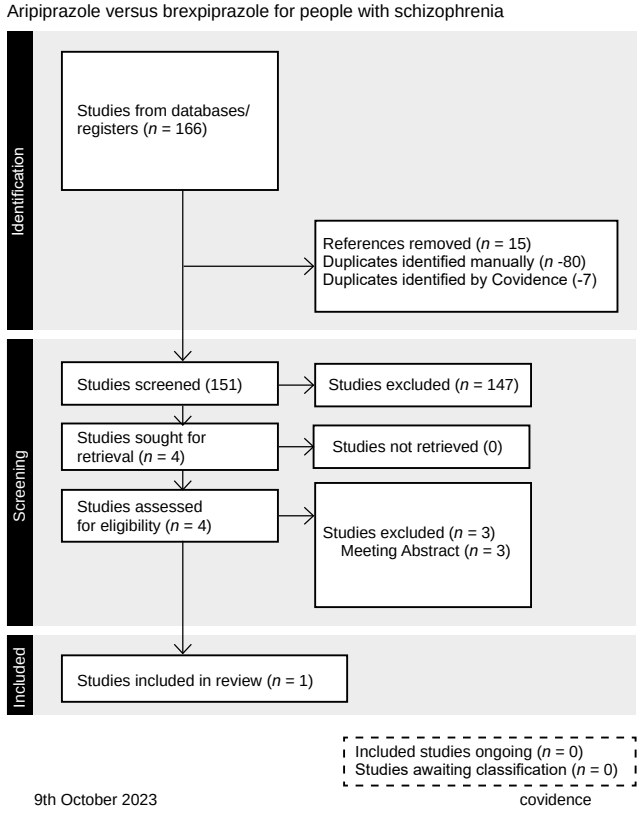

Figure 1. Flow diagram of the review process (PRISMA).

showed an improvement of 20% or more in the total PANSS score between screening and baseline assessments.

Interventions

Brexpiprazole: Treatment for six weeks up to 4 mg/day, once daily dose, tablets, oral or brexpiprazole for six weeks up to 20 mg/day, once daily dose, tablets, orally, Brexpiprazole (1–4 mg/ day) starting at 1 mg/day and titrating to a target dosage of 3 mg/day at the end of week 1 for brexpiprazole. Dosage adjustments occurred in stepwise increments or decrements of 1 mg for brexpiprazole. Dosage increases were only allowed at scheduled visits, whereas decreases could have occurred at any time during the trial following the Week 1 visit. Adjustments were made according to the clinical judgment of the investigator.

Aripiprazole: Treatment for six weeks up to 4 mg/day, once daily dose, tablets, oral or Aripiprazole for six weeks up to 20 mg/day, once daily dose, tablets, orally. Aripiprazole (10–20 mg/day), starting at 10 mg/day and titrating to a target dosage of 15 mg/day at the end of week 1 for aripiprazole. Dosage adjustments occurred in stepwise increments or decrements of 5 mg for aripiprazole. Dosage increases were only allowed at scheduled visits, whereas decreases could have occurred at any time during the trial following the Week 1 visit. Adjustments were made based on the clinical judgment of the investigator.

Outcomes: Included change from baseline to Week 6 in the Positive and Negative Syndrome Scale total score, Barratt Impulsiveness Scale-11 score, and Cogstate computerized cognitive test battery scores. Patients treated with brexpiprazole (n = 64) or aripiprazole (n = 33) showed reductions in symptoms of schizophrenia as assessed by the Positive and Negative Syndrome Scale total score (−22.9 and −19.4, respectively). A modest reduction in impulsivity was observed with brexpiprazole, but not aripiprazole (mean change in the Barratt Impulsiveness Scale-11 total score: − 2.7 and .1, respectively). No change in Cogstate scores was observed for either drug.

Excluded studies

The three studies excluded were meeting abstracts. Efforts to find further data on these studies in other publication formats were unsuccessful (Citrome et al., 2015a; Citrome et al., 2015b; Citrome et al., 2016b).

Risk of bias in included studies

Allocation: Low risk of bias. Patients were randomized 2:1 to receive brexpiprazole or aripiprazole. Randomization was performed using the interactive voice response system or the interactive web response system (Figure 2).

Blinding: This was an open-label trial.

Incomplete outcome data: High risk of bias, although the authors indicated that there was a loss of data and provided the number of patients who reached the end of the trial. The data for the analysis included a full sample with imputed data, without a sensitivity analyses.

The review authors checked the clinical trial register to reduce selective reporting.

Other potential sources of bias: Sequence Generation. Unclear risk of bias. Patients were enrolled and randomized (2:1) to target doses of 3 mg/day, open-label brexpiprazole 3 mg/day, or aripiprazole. Unequal allocation can be scientifically advantageous and consistent with ethical study design. First, it may have substantial advantages in early phase trials, when the aim of investigation is to explore treatment dimensions. A second circumstance where uneven allocation may be justified is when study treatments are extremely costly. The need for additional safety information may also justify unequal allocation. Researchers often justify the use of unequal allocation in 2-armed confirmatory trials by appealing to patient demand or recruitment facility. However, the authors did not provide a rationale for this type of randomization.

Primary outcomes

The PANSS scale rating and Cognitive Test Battery composite score were not eligible as primary outcomes for inclusion because only the least squares changes were reported (Table 2).

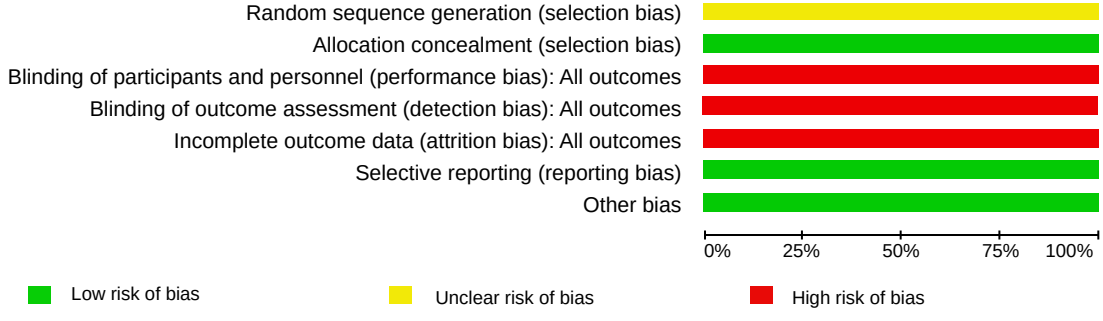

Figure 2. Risk of bias.

Table 2
Aripiprazole compared to brexpiprazole for people with schizophrenia

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Certainty of the evidence (GRADE)
	Risk with brexpiprazole	Risk with aripiprazole			
AIMS Scale	The mean AIMS Scale change was **0**	MD **.1 lower** (.27 lower to .07 higher)	-	97 (1 RCT)	⨁⨁◯◯ Low[a,b,c,d]
Specific Levels of Functioning Scale change to 6 weeks	The mean specific Levels of Functioning Scalechange to six weeks was **7.7**	MD **2.2 higher** (3.09 lower to 7.49 higher)	-	97 (1 RCT)	⨁⨁◯◯ Low[a,b,c,d]
CGI-I	The mean CGI-I change was **-1.6**	MD **.2 lower** (.61 lower to .21 higher)	-	97 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e]
Change in body weight	The mean change in body weight was **4.3**	MD **.5 higher** (1.65 lower to 2.65 higher)	-	97 (1 RCT)	⨁⨁◯◯ Low[b,c,d]
Body mass index change from baseline	The mean body mass index change from baseline was **1.4**	MD **.2 higher** (.47 lower to .87 higher)	-	97 (1 RCT)	⨁⨁◯◯ Low[b,c,d]
Barrat Impulsiveness Scale change from baseline	The mean Barrat Impulsiveness Scale change from baseline was **-2.7**	MD **2.8 lower** (6.2 lower to .6 higher)	-	97 (1 RCT)	⨁◯◯◯ Very low[b,c,d,f]

Note: * The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% *CI*). *CI:* confidence interval; *MD:* mean difference
[a] Unclear risk of selection bias;
[b] Open-label study;
[c] Incomplete outcome data;
[d] Publication bias is highly suspected;
[e] Non-specific improvement evaluation;
[f] Both population and intervention responses are not directly related to impulsivity.
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

No significant differences were found between the CGI-I scores of brexpiprazole compared to aripiprazole (MD -.20, 95% CI -.61 to .21; very low-certainty evidence). We found that aripiprazole may result in only a slight, non-significant difference in SLOF scores (MD 2.20, 95% CI -3.09 to 7.49; low-certainty evidence).

Concerning the presentation of extrapyramidal side effects, no differences were detected on the AIMS scale (MD -.10, 95% CI -.27 to .07; low-certainty evidence). No differences in body weight (MD .50, 95% IC-1.65 to 2.65; low-certainty evidence) or body mass index changes (MD .20, 95% CI -.47 to .87; low-certainty evidence) were detected regarding metabolic effects either.

Secondary outcomes

A small difference was observed in the Barrat impulsivity scale change, which could be marginally relevant, suggesting that brexpiprazole could be better for reducing impulsivity (MD -2.80, 95% IC -6.20, .60, low-certainty evidence).

DISCUSSION AND CONCLUSION

We found only one study eligible for inclusion in this review. This was a 2-arm parallel-group in open-label trial with brexpiprazole 3mg/day or aripiprazole 15mg/day for six weeks in patients with schizophrenia.

We considered the evidence for all outcomes to be of low or very low certainty using the GRADE criteria for the scales used by the authors of the selected study. We found a low level of evidence for the following results: AIMS scale, Specific Levels of Functioning Scale Change to six weeks. We found a similarly low level of evidence for change in body weight, change in body mass index from baseline, and very low evidence with the CGI-I scale and Barrat Impulsiveness scale change from baseline.

The main difficulties in identifying the evidence on the interventions involve the biases found in the study including sequence generation, blinding of participants, blinding of outcome assessors, and incomplete outcomes. Biases with a lower risk of occurrence are selection bias, and reporting bias. Performance bias, detection bias, and attrition bias have a high risk of bias, and unclear risk of bias sequence generation The first two (selection bias and information bias) and the second two (selection bias and information bias) were low risk. Patients with a composite score greater than -.5 at baseline were randomized equally to each treatment group. Randomization was performed using the Voice/Web Response System, which can be accessed via telephone or the Internet, and the authors reported data for the prespecified outcomes. This bias was minimized by

reviewing the clinical trial registry to minimize selective reporting.

The risk of bias was increased because it was an open-label study and the allocation, although randomized, was not blinded, which decreases the statistical power of the results. On the other hand, the authors indicated that there was a loss of data and provided the number of patients who reached the end of the trial. However, in their analysis of the data, they included the full sample with imputed data, without sensitivity analysis or excluding the missing data from the final analysis.

The risk of bias in the sequence generation was unclear because patients were enrolled and randomized (2:1) to target doses of brexpiprazole 3 mg/day or aripiprazole in the open-label study.

Sequence Generation. Unclear risk of bias. Patients were enrolled and randomized (2:1) to target doses of open-label brexpiprazole 3 mg/day or aripiprazole. Unequal allocation can be scientifically advantageous. First, it may have substantial advantages in early phase trials where the goal of the research is to explore treatment dimensions. A second circumstance in which unequal allocation may be justified is when the study treatments are particularly costly Hey & Kimmelman (2014). However, the authors did not justify this type of randomization.

According to the results of the included study, the improvement in the total PANSS scale between the two interventions was comparable and significant at six weeks of treatment, without establishing the superiority of one drug over the other. Interestingly, a systematic review and meta-analysis network Kishi et al., (2020) found a very similar response rate between aripiprazole and brexpiprazole, which were superior to placebo. Another systemic review Huhn el at. (2019), compared the efficacy and tolerability of thirty-two antipsychotics (including aripiprazole and brexpiprazole) orally for the acute treatment of subjects with multi-episode schizophrenia. It found improvement in total symptoms and positive symptoms for both when compared to placebo. Likewise, Aripiprazole was among the five antipsychotics that reported improvement in quality of life, while brexpiprazole achieved a favorable change in psychosocial functioning.

For our revision, no differences were observed in the cognitive functioning with any of the antipsychotics. Mean changes in abnormal movement assessment scales were not clinically relevant for any of the interventions, nor were changes in prolactin or metabolic parameters. For our revision, no differences were observed in the cognitive functioning with any of the antipsychotics. Mean changes in abnormal movement assessment scales were not clinically relevant for any interventions, nor were changes in prolactin or metabolic parameters. Similarly, Kishi et al., (2020) reported a low incidence of adverse effects leading to discontinuation (akathisia, extrapyramidal symptoms), compared to placebo. However, their study reported a higher incidence of weight gain with both antipsychotics. Another review Huhn el at. (2019) also highlights brexpiprazole for its positive response rate and aripiprazole for the lower incidence of antiparkinson drug usage to treat extrapyramidal effects.

Regarding the economic advantages of both antipsychotics, aripiprazole and brexpiprazole, several factors should be considered. These include cost, their existence within the basic tables of health institutions and hospitals and the overall economic impact on the care of side effects and treatment adherence. It is also necessary to examine the role some may have in the effect on the symptomatic dimensions of schizophrenia responsible for long-term disability that interfere with psychosocial functioning (negative symptoms and cognitive symptoms).

Aripiprazole is usually available as a generic drug, which generally significantly reduces its cost compared to patent drugs. As it has been available for a longer period, knowledge of both specialists (experience in use) and aripiprazole may be more widely available.

Brexpiprazole is a newer drug with no generic options as yet, significantly increasing its cost. If it demonstrates a better tolerability profile, this could translate into reduced side effect care costs, better treatment adherence and less need for additional medication (correctors). If it translates into a better overall or specific response to the positive, negative, affective, and cognitive symptoms of schizophrenia, it could improve patients' functioning and quality of life, including less need for additional medication (correctors). If it translates into a better overall or specific response to the positive, negative, affective, and cognitive symptoms of schizophrenia, it could improve patients' functioning and quality of life. This would include fewer relapses and cost savings in hospitalizations and scheduled office or emergency department visits.

The result of this review has several significant limitations as it is limited to a single study that is not even a controlled clinical trial. It also has important biases, as described in the discussion. It is therefore not possible to establish a recommendation for the prescription of one of the antipsychotics in the study over the other.

There remains ample room for further research on this topic, as results and evidence from ongoing studies can be incorporated, particularly in this group of drugs that have been proposed in the literature as a third generation of antipsychotics due to their unique pharmacological profile.

More research is required to highlight the differences between both drugs that appear to be similar, to justify the high cost of one over the other, particularly in developing countries.

Several research topics may be explored, both when comparing aripiprazole with other second-generation antipsychotics and in broader contexts. Brexpiprazole and

aripiprazole have been proposed as prototype third-generation drugs. It would be worth exploring this line and determining whether they really deserve to be characterized as such, due to their different mechanism of action.

Funding

None.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

The Editorial Base of Cochrane Schizophrenia is situated across the University of Melbourne (Australia), Technical University of Munich (Germany), and University of Nottingham (UK). It produces and maintains standard text for use in the methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

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ORIGINAL ARTICLE
Volume 48, Issue 6, November-December 2025
doi: 10.17711/SM.0185-3325.2025.036

Differences between Mexican Men and Women in the Phenomenon of Transphobia

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Received: 4 June 2024
Accepted: 13 November 2024

Citation:
Domínguez, T., Fresán, A., & Robles-García, R. (2025). Differences between Mexican Men and Women in the Phenomenon of Transphobia. *Salud Mental, 48*(6), 317-322. https://doi.org/10.17711/SM.0185-3325.2025.036

DOI: 10.17711/SM.0185-3325.2025.036

ABSTRACT

Introduction: Transphobia and social discrimination cause several psychosocial, health, and mental health problems in transgender people globally. Mexico is the second most dangerous country in the world for transgender since it has the highest rate of transphobic hate crimes. Despite the severity of the problem, studies on transphobia in Mexico remain scarce. **Objective:** In view of the predominance of the hetero-patriarchal and *machista* culture in Mexican society, this study seeks to explore differences between men and women as regards transphobia in Mexican adults living in Mexico. **Method:** Five hundred and one participants answered the Genderism and Transphobia Scale-Revised-Short Form (GTS-R-SF) through an anonymous online survey. **Results:** Findings showed that men exhibit more trans-prejudice and are less accepting of gender-nonconforming people than women. **Discussion and conclusion:** Strategies should be developed and implemented for the general population —especially men— to help reduce stigma and trans-prejudice. It is also necessary to increase the acceptance of gender diversity to guarantee social inclusion and provide greater protection for transgender people from discrimination and social rejection.

Keywords: Gender-nonconforming people, transgender, transphobia, genderism, gender equality, discrimination.

RESUMEN

Introducción: La transfobia y la discriminación social provocan diversos problemas psicosociales, de salud y de salud mental en las personas transgénero a nivel mundial. México es el segundo país más peligroso del mundo para las/los transgénero ya que tiene la tasa más alta de crímenes de odio transfóbico. A pesar de la gravedad del problema, los estudios sobre transfobia en México siguen siendo escasos. **Objetivo:** Considerando el actual predominio de la cultura heteropatriarcal y machista en la sociedad mexicana, este estudio tiene como objetivo explorar las diferencias entre hombres y mujeres sobre el fenómeno de la transfobia en adultos mexicanos. **Método:** 501 participantes respondieron la Escala de Genderismo y Transfobia-Revisada-Versión breve (GTS-R-SF) a través de una encuesta anónima en línea. **Resultados:** Los resultados mostraron que los hombres exhiben más prejuicios trans y aceptan menos a las personas no conformes con su género que las mujeres. **Discusión y conclusión:** Se recomienda desarrollar e implementar estrategias dirigidas a la población en general y, en particular, a los hombres, enfocadas a reducir el estigma y los prejuicios trans, así como a mejorar la aceptación de la diversidad de género para garantizar la inclusión social y proporcionar una mayor protección a las personas transgénero de la discriminación y el rechazo social.

Palabras clave: Género no conforme, transgénero, transfobia, genderismo, equidad de género, discriminación.

INTRODUCTION

Transgender is a term used for gender diverse individuals, whose assigned sex/gender at birth differs from their current gender identity, gender expression, or behavior (American Psychological Association, 2015). It encompasses a wide range of people such as transsexuals (those seeking to change their sex to the gender with which they identify, using hormone and/or surgical treatment). It also includes trans or gender non-conforming people (those who adapt their body to the gender with which they identify with slight medical intervention [hormone therapy]). In addition, it comprises cross-dressers (those who change their gender temporarily using external signs such as clothing and make-up; Carrera-Fernández et al., 2014).

Most studies on attitudes toward transgender people have shown that this group is still far from being fully accepted by society (Carrera-Fernández et al., 2014). Its members are often victims of multiple types of violence across several areas of life due to stigma and society's intolerance of gender non-conformity (Bockting, 2014; Bradford et al., 2013; Cruz, 2014; D'Augelli et al., 2003; Robles et al., 2016; Grossman & D'Augelli, 2006; Grossman et al., 2011; Henning-Stout & James, 2000; Kosenko et al., 2013; Lombardi et al., 2002; Robles et al., 2016; Stotzer, 2009).

According to the literature, anti-trans prejudice and hate against trans people includes three key constructs: transphobia, genderism, and gender-bashing (Hill, 2003; Hill & Willoughby, 2005). Transphobia comprises negative beliefs and attitudes about transgender people, expressed through violence (physical, sexual, or verbal), harassment, discrimination, and prejudice toward this group (Herbst et al., 2007). Like homophobia and homonegativity, transphobia is based on emotional disgust, irrational fear, hatred, or intolerance toward individuals who do not conform to society's gender/sex expectations (Hill & Willoughby, 2005). However, thransphobia differs from homophobia as it focus on broader issues such as gender roles and gender identities (Nagoshi et al., 2008).

Genderism is a broad negative cultural ideology perpetuating negative judgments and reinforcing the negative evaluation of gender non-conformity or incongruence between sex and gender. Genderists believe that those who do not conform to socio-cultural expectations of gender are pathological. Genderism is a type of social oppression that can be forced on individuals and often leads to internalized psychological shame. Gender-bashing refers to fear expressed in acts of violence, assault, and/or harassment towards people who do not conform to gender norms or sociocultural expectations. Genderism is therefore the overarching negative cultural ideology, transphobia is emotional disgust and fear, while gender-bashing is fear expressed through acts of violence (Hill, 2003; Hill & Willoughby, 2005).

Transphobia is a social problem that systematically and unfairly exposes transgender people to exclusion, repression, and other forms of personal, institutional, and social harassment (Galupo et al., 2014; Joel et al., 2014; Whitfield et al., 2019). All these forms of discriminatory social actions are so widespread that transgenderism has become a pathological condition that is stigmatized and sanctioned (Alonso-Martínez et al., 2021; Haley et al., 2019; Hatzenbuehler, 2009; Páez et al., 2015). This, in turn, causes psychosocial, health, and mental health problems in transgender people globally (Lo & Horton, 2016), particularly in low- and middle-income contexts (Bazargan & Galvan, 2012; Bockting, 2014; Bradford et al., 2013; Cruz, 2014; Kenagy, 2005; Lombardi et al., 2002; Martínez-Guzmán & Johnson, 2021; Melendez & Pinto, 2007). According to Transgender Europe and the International Report of the Transgender Murder Monitoring Project (Bautista et al., 2018), Mexico is the second most dangerous country in the world after Brazil for transgender since it has the highest rate of transphobic hate crime and impunity (Grant, 2021).

The multiple forms of violence affecting transgender people, particularly transgender women, are rooted in both structural and sociocultural factors associated with the hetero-patriarchal system and the cultural norm of *machismo* permeating Mexican society. These factors define rigid gender roles, reflect heteronormative expectations of male behavior, contribute to the reproduction of male domination, and maintain social structures that justify the exercise of gender violence. They begin in the family and extend to multiple social contexts (Constant, 2017; Verduzco et al., 2011; Steffens et al., 2014; da Espinosa et al., 2020).

Despite the severity of the problem, studies on transphobia in Mexico remain scarce. Further research is required to explore the intolerance and prejudice that give rise to the transphobia phenomenon in the Mexican population, to expand our understanding of the causes of violent attitudes toward gender non-conforming. It is also necessary obtain evidence to develop awareness campaigns, strategies, and interventions to improve transgender acceptance, eliminate the prejudice that leads to violent attitudes and promote inclusive environments for the transgender population.

The aim of the present study was therefore to analyze sex differences in transphobic attitudes toward transgender people. Based on previous studies (Carrera-Fernández et al., 2014; Chen & Anderson et al., 2017; Costa & Davies, 2012; Nagoshi et al., 2008), and given the predominance of the hetero-patriarchal and *machista* phenomenon in Mexican society, we expected men to have more transphobic attitudes than women.

METHOD

Study design and participants

This is a cross-sectional, internet-based study.

Subjects

The present study included adult Mexican participants from the general population residing in Mexico, recruited by a convenience sample approach. Inclusion criteria were being between 18 and 75 years of age and having an electronic device to answer the survey.

Procedure

The sample was recruited from November 2019 to March 2020. Participants were mexican adults who were invited by social networks (Facebook & WhatApp) to complete an anonymous online survey designed using Qualtrics®, containing the Genderism and Transphobia Scale-Revised-Short Form (GTS-R-SF, Tebbe et al., 2014). The aims and procedures were explained at the beginning of the survey, and participants who voluntarily agreed to participate gave their informed consent before answering the survey. Participants did not receive any incentive or remuneration for their participation in the study.

Measurement

After providing their informed consent, participants first answered questions on socio-demographic variables (such as age, sex, educational achievement, marital status, and current working activities) and subsequently completed the GTS-R-SF.

The GTS-R-SF is a self-administered scale with 13 items, each rated on a 7-point Likert scale ranging from 1 (strongly agree) to 7 (strongly disagree). In keeping with the study by Hill & Willoughby (2005), all items are reverse scored except for item 2 ("*If a friend wanted to have his penis removed to become a woman, I would openly support him*"). Higher total scores indicate greater anti-trans prejudice. This scale covers two main domains: genderism/transphobia (eight items) and gender-bashing (five item) (Tebbe et al., 2014). The genderism/transphobia dimension assesses negative cognitions about gender non-conformity and negative emotional reactions toward trans individuals reflected in negative anti-trans statements.The gender-bashing dimension assesses the propensity for behavioral violence toward trans people (Hill & Willoughby, 2005).

The Spanish version of the GTS-R-SF was used in the present study (Domínguez & Fresán, 2022). For this version, the original scale of Tebbe et al. (2014) was translated into Spanish based on recommendations by American Research Teams (US Census Bureau, 2010). It was reviewed by two independent health professional experts in the care and treatment of transgender people and a pilot study was undertaken to ensure that all items were clear and comprehensible to people in the community (n = 40). Finally, internal reliability for the present sample was determined using the Composite Reliability Index (CRI) (genderism/transphobia CRI = .91, gender bashing CRI = .72, total CRI = .85).

Statistical analysis

Frequencies and percentages for categorical variables and means, standard deviations (SD), and ranges were used for descriptive purposes. The 21.0 version of the SPSS statistical software was used for all analyses. Demographic features and the GTS-R-SF dimensions and total scores were compared using contingency table chi-squared tests (χ^2) and independent samples t-tests. The effect size was calculated for the significant results obtained in the chi-squared tests (Cramer's V) and the independent samples t-tests (Cohen d), with values being interpreted as small (.1 – .3), medium (.4 – .7), and large (> .8). All analyses used SPSS version 21.0, with significance set at $p < .05$.

Ethical considerations

All study procedures and materials were performed in keeping with the principles of the Declaration of Helsinki and approved by the Ethics and Research Committees of the Ramón de la Fuente Muñiz National Institute of Psychiatry in Mexico City (reference number: CONBIO-ETICA-09-CEI-01020170316).

RESULTS

A total of 501 Mexican adults (> 18 years old) drawn from the general population and currently living in Mexico participated in the study. Approximately two-thirds of the 501 participants were women (67.9%, n = 340). The mean age of the sample was 36.0 years (SD = 12.0, range 18-73), and over two-thirds were engaged in paid employment (67.7%, n = 339). All participants were from urban areas in twenty-five out of the thirty-two states in Mexico, although most were from Mexico City (63.5%, n = 318). The remaining demographic features are displayed in Table 1. No differences emerged between men and women in terms of so-

Table 1
Demographic features and comparison of GTS-R-SF by sex

	Total *n = 501*	*Men* *n = 161*	*Women* *n = 340*	*Statistic*
Demographic features				
Age (mean, SD)	35.9 12.0	35.5 12.2	36.1 11.9	*t* (499)= -.5, *p* = .60
Marital status (*n*, %)				
Single	212 42.3	74 46.0	138 40.6	
Partnered	241 48.1	77 47.8	164 48.2	χ^2 = 3.9, *df* 3, *p* = .26
Divorced/ separated	46 9.2	10 6.2	36 10.	
Widowed	2 0.4		2 0.6	
Education (*n*, %)				
Primary or secondary	90 18.0	30 18.6	60 17.6	
Undergraduate	196 39.1	66 41.0	130 38.2	χ^2 = .6 *df* 2, *p* = .73
Graduate	215 42.9	65 40.4	150 44.1	
Occupation (*n*, %)				
Unemployed	11 2.2	3 1.9	8 2.4	
Homemaker	32 6.4	1 0.6	31 9.1	χ^2 = 14.2, *df* 4, *p* = .007
Student	107 21.4	33 20.5	74 21.8	
Retiree or pensioner	12 2.4	4 2.5	8 2.4	Cramer's *V* = .16
Employee	339 67.7	120 74.5	219 64.4	
GTS-R-SF (mean, SD)				
Genderism/ Transphobia	13.1 7.4	14.2 8.0	12.5 7.0	*t* (499) = 2.4; *p* = .01 *d* = .22
Gender-bashing	6.9 2.9	7.6 3.7	6.6 2.5	*t* (499)= 3.4; *p* = .001 *d* = .31
Total GTS-R-SF score	20.1 8.9	21.9 9.8	19.2 8.3	*t* (499)= 3.1; *p* = .002 *d* = .29

ciodemographic features, except for occupation, where a higher proportion of women were engaged in household activities and more men in paid employment.

Findings from the comparison of GTS-R-SF dimensions between men and women showed that male participants exhibited significantly higher scores than women in both the genderism and transphobia and gender bashing dimensions as well as the total GTS-R-SF score (Table 1).

DISCUSSION AND CONCLUSIONS

Consistent with studies from other countries, findings on differences by sex in GTS-R-SF showed that men exhibit more trans-prejudice and are less accepting of gender-nonconforming people than women (Antoszewski et al., 2007; Carrera-Fernández et al., 2014; Chen & Anderson, 2017; Costa & Davies, 2012; Hill & Willoughby, 2005; Landen & Innala, 2000; Nagoshi et al., 2008; Winter et al., 2007, 2008). This phenomenon is rooted in both structural and sociocultural factors linked to the hetero-patriarchal system and the *machismo* culture predominant in Mexican society. It reflects heteronormative expectations of male behavior, contributes to the promotion of the superiority and domination of men over women, defines rigid gender roles, and maintains social structures justifying the exercise of gender violence in multiple social contexts (Constant, 2017; Verduzco et al., 2011; Steffens et al., 2014; Espinosa et al., 2020). Our findings contrast with those of Gorrotxategi et al., 2020), conducted on Spanish university students of social education (mean age of 20 years), who reported higher mean scores in the dimensions of the GTS-R-SF scale in both men (transphobia/genderism = 38.9 vs 14.2, and gender bashingg = 36.5 vs 7.6) and women (transphobia/genderism = 41.3 vs. 12.5, and gender bashing = 41.4 vs. 6.6). In the GTS-R-SF validation study, the mean scores of the transphobia/genderism and gender bashing dimensions were under four points (Tebbe et al., 2014). This shows that trans-prejudices are higher in our sample, possibly reflecting the cultural heteronormative expectations of Mexican culture. These studies included university students (*n* = 64; Gorrotxategi et al., 2020) and undergraduate students (*n* = 314; Tebbe et al., 2014) aged 18 to 35, which differs from the mean age of our participants (age range 18-75 years). One possible explanation for these differences is the current change in the interpretation of gender and sexuality observed in younger generations (Gorrotxategi et al., 2020). Extreme anti-trans prejudices (like those assessed with the GTS-R-SF) are less common and even opposed to the values of these new generations. However, this should be further studied in similar samples.

Some authors have also argued that the high prevalence of transphobia among men is influenced by traditional male identity based on misogyny and homophobia. Men's prejudice and discrimination toward transgender people appear to be used as a means of reaffirming and preserving their masculinity and heterosexuality (Carrera-Fernández et al., 2014; Kimmel, 1994). Moreover, findings support the fact that men strive more than women to adhere to gender rules and are likely to feel more threatened than women by transgender people. This is due to the conservative beliefs of the cis-normative system and the irrational fear and hatred of

those who do not fit the dominant gender categories and challenge traditional social and familial norms and roles (Burnes et al., 2010; Alonso-Martínez et al., 2021; Vandello et al., 2008).

Transphobia is a social problem that systematically and unfairly exposes transgender people to exclusion, repression, and other forms of personal, institutional, and social harassment (Galupo et al., 2014; Joel et al., 2014; Whitfield et al., 2019). These discriminatory actions are so widespread that transgender has become a pathological condition that is stigmatized and sanctioned, leading to destructive behaviors and discriminatory actions that threaten their human rights (Alonso-Martínez et al., 2021; Haley et al., 2019; Hatzenbuehler, 2009; Páez et al., 2015). These experiences of rejection and violence cause significant personal suffering that can negatively impact transgender physical and mental health, making it necessary to develop and implement awareness campaigns, anti-discrimination policies, and legislative actions. This will reduce transphobia and guarantee social inclusion in all sectors based on human rights and social justice, expand the rights of transgender people and provide greater protection from discrimination and social rejection (Stieglitz, 2010).

The current research has certain limitations that should be considered when interpreting results. First, our sample had high educational attainment and were from urban areas of the country, which is not representative of the Mexican population, characterized by low educational attainment and diverse cultural backgrounds when rural populations are included. Future studies should examine our results in other Mexican settings with larger, more diverse samples to compare research findings across cultures. This would also make it possible to identify groups that would benefit from interventions focused on the transformation of social attitudes into the acceptance of gender diversity and the reduction of anti-trans prejudice (Páez et al., 2015; Clark & Hughto et al., 2019).

Funding

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

The authors would like to thank those who participated in the study.

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GUÍA PARA LOS AUTORES

La revista Salud Mental publica artículos originales sobre psiquiatría, psicología, neurociencias y disciplinas afines de acuerdo con los siguientes formatos:

1. **Editoriales**
   Se escriben por invitación del Director-Editor de la revista. Deben expresar opiniones autorizadas sobre temas específicos de interés para la comunidad científica y para el área de la salud mental. Su objetivo es estimular el debate y promover nuevas líneas de investigación. *Extensión máxima: 1000 palabras*.
2. **Artículos originales (sección revisada por pares)**
   Presentan resultados de investigaciones no publicados en otras revistas. Pueden desarrollarse a partir de las siguientes metodologías:
   - **Metodología cuantitativa:** Incluye resultados primarios y secundarios de estudios transversales, ensayos clínicos, casos y controles, cohortes y estudios cuasi experimentales. *Extensión máxima: 3500 palabras*.
     De acuerdo con el tipo de estudio, los manuscritos deben cumplir con las guías:
     • Los ensayos clínicos aleatorizados deben adecuarse a las guías *CONSORT* (http://www.consort-statement.org).
     • Los estudios con diseños no experimentales, a las guías *TREND* (http://www.trend-statement.org).
     • Los estudios transversales, de cohorte, y de casos y controles, a la guía *STROBE* (http://www.strobe-statement.org).
   - **Metodología cualitativa:** Incluye reportes de grupos focales, entrevistas a profundidad, redes semánticas y análisis de contenido. *Extensión máxima: 5000 palabras*.
     Deben cumplir con la guía *COREQ* (https://doi.org/10.1093/intqhc/mzm042).
3. **Artículos de revisión (sección revisada por pares)**
   - **Revisiones sistemáticas:** Preferentemente deben incluir un metaanálisis. *Extensión máxima: 4000 palabras*.
4. **Casos clínicos (sección revisada por pares)**
   Incluye reportes de efectos de un método diagnóstico o terapéutico que sea útil o relevante en el ámbito médico, académico o científico. *Extensión máxima: 2000 palabras.*
   Deben cumplir con la guía *CASE REPORT* (https://www.care-statement.org/checklist)

Nota: El conteo de palabras para cada una de estas secciones excluye el título, los resúmenes y las palabras clave, así como los apartados de financiamiento, conflictos de interés y agradecimientos; tampoco se consideran las palabras incluidas en tablas, figuras y referencias.

IDIOMAS

Salud Mental recibe y publica únicamente manuscritos en inglés.

ASPECTOS ÉTICOS EN LA PUBLICACIÓN

Vea los Lineamientos éticos en el sitio web de Salud Mental (revistasaludmental.gob.mx/index.php/salud_mental/ethicalguidelines).

AUTORÍA

El número de autores dependerá del tipo de manuscrito enviado. Para artículos originales y artículos de revisión el número máximo de autores será de ocho. Solo cuando se trate de estudios multicéntricos el número máximo de autores será de doce, siempre y cuando se justifique de acuerdo con el alcance del estudio.

En caso de autoría colectiva, se incluirá el nombre de los redactores o responsables del trabajo seguido de «*y el grupo...*» cuando todos los miembros del grupo se consideren coautores del trabajo. Si se desea incluir el nombre del grupo, aunque no todos sus miembros sean considerados coautores, se mencionarán a los autores responsables seguido de «*en nombre del grupo...*» o «*por el grupo...*». En cualquier caso, los nombres e instituciones de los miembros del grupo se incluirán en un anexo al final del manuscrito.

LINEAMIENTOS EDITORIALES

Es muy importante que los autores consideren los siguientes puntos antes de enviar sus manuscritos:

1. Los manuscritos deben redactarse de forma clara y concisa, sin errores de ortografía ni de sintaxis.
2. El texto debe estar escrito en formato Word, en fuente Times New Roman de 12 puntos, a doble espacio, con márgenes de 2.5 cm. y en tamaño carta.
3. Las páginas se numeran consecutivamente, empezando por la página del título y con el número escrito en la esquina superior derecha.
4. La primera página (donde se encuentra el título) debe contener los siguientes apartados en el orden que aquí se menciona:
   - **Título del trabajo en español y en inglés.** El título debe ser descriptivo e indicar los resultados principales del estudio. *Extensión máxima: 25 palabras*
   - **Título corto en español y en inglés.** *Extensión máxima: 6 palabras*.
   - **Nombre completo del autor y de los coautores.** Los autores deberán colocarse en listado; luego, en superíndice, deberá colocarse un número arábigo que indique la institución de adscripción.
   - **Número ORCID de los autores.** Es requisito que cada uno de los autores cuente con su número de identificación ORCID, el cual se puede conseguir en https://orcid.org/register
   - **Adscripción de los autores.** Se debe indicar con números arábigos y en superíndice. Las adscripciones se colocan inmediatamente después de los nombres de los autores (no como notas en pie de página). Es necesario que la adscripción especifique: departamento, área, institución, ciudad y país de cada autor. No es necesario indicar la dirección postal. Las instituciones deben escribirse en su idioma original, sin traducción. Si los autores añaden siglas, éstas deben pertenecer al nombre oficial. No se deben escribir cargos ni grados de los autores (doctor, residente, investigador, etc.).

     Ejemplo:

     Juan José García-Urbina,[1]

     Héctor Valentín Esquivias Zavala[2]

     [1] Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, México.
     [2] Departamento de Publicaciones, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, México.

- Al final de la primera página, en el apartado ***"Correspondencia"***, se proporcionarán los datos de contacto del autor corresponsal (dirección postal completa, teléfono, correo electrónico). Es con quien Salud Mental se comunicará durante todo el proceso editorial.

  Ejemplo:

  Correspondencia:
  Juan José García-Urbina
  Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz.
  Calz. México-Xochimilco 101, San Lorenzo Huipulco, Tlalpan, 14370, Ciudad de-México, México.
  Tel: 55 4152-3624
  E-mail: jurb@imp.edu.mx

5. La segunda página debe contener los resúmenes del trabajo presentado en inglés y español. *Extensión máxima: 250 palabras.*
   - ***Artículos originales y Revisiones sistemáticas.*** Los resúmenes deben estar conformados por: Introducción, Objetivo, Método, Resultados y Discusión y conclusión.
   - ***Casos Clínicos.*** Los resúmenes deben estar conformados por: Introducción, Objetivo, Principales hallazgos, Intervenciones y resultados y Discusión y conclusión.
   - ***Palabras clave.*** Al final de cada resumen se incluirá un mínimo de cuatro y un máximo de seis palabras clave, separadas por comas y en minúsculas. Las palabras clave deben ser las mismas en inglés y en español. Éstas suelen emplearse para la indexación de los artículos, por lo cual tres de ellas deben encontrarse en el MeSH (*Medical Subject Headings*) que se puede consultar en: http://www.nlm.nih.gov/mesh/MBrowser.html.
6. A partir de la tercera página comienza el cuerpo del manuscrito, el cual deberá conservar la estructura señalada en el resumen.
   - ***Introducción (o Antecedentes en el caso de las Revisiones narrativas).*** El último párrafo de este apartado debe incluir de forma clara los objetivos del trabajo y, si se cree necesario, las hipótesis.
   - ***Método.*** Es preciso que cuente con las siguientes secciones:
     • Diseño del estudio
     • Participantes/descripción de la muestra
     • Sedes
     • Mediciones
     • Procedimientos
     • Análisis estadísticos
     • Lineamientos éticos.

   Nota: En caso de los artículos de revisión y casos clínicos, estas secciones pueden ser modificadas de acuerdo con la guía PRISMA (revisiones sistemáticas o la guía CASE REPORT (casos clínicos).

   - **Resultados.** Se presentarán en una secuencia lógica dentro del texto. Pueden apoyarse con tablas, gráficas y figuras.
   - **Discusión y conclusión.** En esta sección se destacarán los aspectos nuevos e importantes del estudio y las conclusiones que derivan del mismo, así como las posibles implicaciones de sus hallazgos y sus limitaciones.
7. Después del apartado de Discusión y conclusión, es preciso agregar las declaraciones de los autores en el siguiente orden:
   - ***Financiamiento.*** En este apartado se debe declarar si el estudio o la preparación del manuscrito recibió algún tipo de financiamiento, indicando el nombre de la entidad que proporcionó los fondos.

     Ejemplo:

     Este estudio fue financiado en parte por el CONSEJO NACIONAL DE CIENCIA Y TECNOLOGÍA. (No. XXXXXXX).

     Si no se recibió ningún apoyo financiero, los autores deben declararlo también.

     Ejemplo:

     Ninguno.

   - ***Conflicto de intereses.*** En esta sección, los autores deberán declarar si tienen conflictos de intereses relacionados con su actividad científica. Tener un conflicto de interés no supone necesariamente un impedimento para la publicación del manuscrito. Si no existe conflicto de interés se debe insertar la siguiente frase: *"Los autores declaran no tener algún conflicto de intereses"*.
   - ***Agradecimientos.*** Cuando se considere necesario, se mencionarán después de las declaraciones anteriores los agradecimientos a personas, centros o entidades que hayan colaborado o apoyado en la investigación.
8. **Referencias.** Las referencias se colocan después de las declaraciones del autor (Financiamiento, Conflicto de intereses y Agradecimientos), y ***deben seguir exclusivamente las normas de publicación de la American Psychological Association (APA), en su última edición*** (https://normas-apa.org).
9. **Tablas y figuras.** Salud Mental establece un máximo de cinco elementos gráficos en total. ***El estándar solicitado para la elaboración de tablas y figuras es el de la American Psychological Association (APA), última edición*** (https://normas-apa.org)***.*** Éstas se colocarán al finaldel manuscrito después de las referencias:
   - Las tablas deben contener título y, en la parte inferior, una nota con el desglose de las siglas.
   - Las figuras deben enviarse en un formato de alta resolución (mínimo 300 dpi).
   - Los títulos de las tablas y los pies de las figuras deben ser claros, breves y llevar siempre el número correspondiente que los identifique. Dentro del texto, el autor debe indicar entre paréntesis y con mayúsculas en qué parte del texto sugiere insertar los elementos gráficos.

     Ejemplo:

     Se cambiaron las definiciones de algunos patrones conductuales (Tabla 3) de manera que fueran más comprensibles en el idioma español y se redefinieron las categorías que agrupan dichos patrones con base en la literatura especializada. (INSERTAR AQUÍ TABLA 3)

ARCHIVOS COMPLEMENTARIOS

1. ***Carta de autorización de uso de la obra.*** Debe estar firmada por todos los autores y enviarse en formato PDF que se puede descargar en https://revistasaludmental.gob.mx/public/Carta-autorizacion-para-publicacion.pdf.
2. ***Carta de presentación.*** El autor debe exponer las fortalezas de su aportación científica, resaltando el alcance, la originalidad y la importancia de su contribución

al campo de la salud mental. *Es de carácter obligatorio mencionar a tres revisores nacionales o internacionales en el campo de conocimiento del manuscrito sometido, favor de indicar el nombre completo y correo electrónico de cada uno de los revisores.* Debe cargarse en formato PDF.

ÉNFASIS Y PUNTUACIÓN

1. Es importante que los manuscritos eviten en general las notas a pie de página, aunque se pueden considerar si son claramente necesarias.
2. Las cursivas deben utilizarse para:
   - Destacar palabras extranjeras.
   - Enfatizar expresiones populares.
   - Mencionar títulos de libros, documentos ya publicados y publicaciones periódicas.
3. Las cursivas pueden emplearse para:
   - Resaltar términos significativos o importantes cuando se mencionan por primera vez.
   - Destacar una palabra u oración dentro de una cita.
4. Las comillas dobles deben usarse solamente para:
   - Citar párrafos de otros autores dentro del texto.
   - Citar textualmente fragmentos del discurso de los sujetos de estudio.
5. Evite el uso de paréntesis doble, es decir, un paréntesis dentro de otro. En su lugar utilice corchetes.
6. Puede emplearse guiones largos para indicar oraciones parentéticas.
7. Deben utilizarse de forma correcta todos los signos de puntuación. Por ejemplo, si emplea signos de interrogación en un texto en español, deben colocarse los de apertura y cierre correspondientes; se procede de igual manera con las comillas.

FÓRMULAS MATEMÁTICAS Y ESTADÍSTICAS

Para presentar los resultados se deben considerar las siguientes indicaciones:

1. Escribir con letra las cifras de cero a nueve y con números las cifras de 10 en adelante.
2. Utilizar números cuando se trate de fechas, muestras, etcétera.
3. Incluir en los datos estadísticos los intervalos de confianza.
4. Los símbolos estadísticos se escriben en cursivas (por ejemplo, *M, SD, n, p)*.
5. Expresar la probabilidad exacta con dos o tres decimales (por ejemplo, p = .04; p = .002) sin el cero adelante del punto decimal. En caso de ser menor a .001 indicarlo con un < .001.
6. Dejar un espacio antes y después de cada signo (a + b = c en lugar de a+b=c).
7. Emplear puntos en lugar de comas para indicar decimales.

VERIFIQUE LO SIGUIENTE ANTES DE SOMETER SU MANUSCRITO

Antes de enviar su manuscrito, cerciórese de adjuntar la documentación solicitada. A los autores, se les devolverá aquellos envíos que no cumplan con los lineamientos editoriales.

1. Manuscrito en formato en WORD.
2. Carta de presentación en formato PDF.
3. Carta de autorización de uso de obra en formato PDF.

GUIDELINES FOR AUTHORS

Salud Mental publishes original articles on psychiatry, psychology, neurosciences and other related fields in the following formats:

1. **Editorials**
   Written at invitation of the Director Editor, editorials express authoritative opinions on specific topics of interest to the scientific community and the area of mental health. They are designed to foster debate and promote new lines of research. *Maximum extension: 1000 words*.

2. **Original articles (peer-reviewed section)**
   These articles present research results unpublished in other journals, and can be written using the following methodologies:

   - *Quantitative methodology.* This methodology includes primary and secondary results from cross-sectional studies, clinical trials, cases and controls, cohorts, and quasi-experimental studies. *Maximum extension: 3500 words*.

     Depending on the type of study, manuscripts should adhere to the following guidelines:

     - Randomized clinical trials should adhere to the *CONSORT guidelines* (http://www.consort-statement.org).
     - Studies with non-experimental designs should adhere to the *TREND guidelines* (http://www.trend-statement.org).
     - Cross-sectional, cohort, and case-control studies should adhere to the *STROBE guidelines* (http://www.strobe-statement.org).

   - *Qualitative methodology.* This methodology includes focus group reports, in-depth interviews, semantic networks, and content analysis. *Maximum extension: 5000 words*.

     Articles using this type of methodology should comply with the *COREQ guidelines* (https://doi.org/10.1093/intqhc/mzm042).

3. **Review articles (peer-reviewed section)**
   - **Systematic reviews.** These reviews should preferably include a meta-analysis. *Maximum extension: 4000 words*.

4. **Case reports**
   They include reports on the effects of a diagnostic or therapeutic method that is useful or relevant in the medical, academic, or scientific field. *Maximum length: 2000 words.*
   These should comply with the *CASE REPORT guidelines* (https://www.care-statement.org/checklist).

Note. The word count for each of these sections excludes the title, abstracts, and keywords, as well as the funding, conflicts of interest and acknowledgments sections. Words included in tables, figures and references are not considered either.

LANGUAGES

Salud Mental receives and publishes only manuscripts in English.

ETHICAL ASPECTS IN PUBLISHING

See Ethical Guidelines for the journal at https://revistasaludmental.gob.mx/index.php/salud_mental/ethicalguidelines

AUTHORSHIP

The number of authors will depend on the type of manuscript submitted. The maximum number of authors for original or review articles is eight. Only in the case of multicenter studies will the maximum number of authors be increased to twelve, provided this is justified by the scope of the study.

In the event of collective authorship, the name of the editors or those responsible for the article will be included followed by “and the group...” when all members of the group consider themselves co-authors of the work. If the name of the group is to be included, even if not all its members are considered co-authors, the authors responsible will be mentioned followed by “on behalf of the ...group or “by the...group.” In any case, the names and institutions to which members of the group are affiliated should be included in an appendix at the end of the manuscript.

EDITORIAL GUIDELINES

It is of the utmost importance for authors to consider the following before sending their manuscript:

1. Manuscripts should be written clearly and concisely, with no spelling or grammatical errors.
2. The text should be written in Word format, Times New Roman font, size 12, with double-spacing and 2.5 cm margins on letter size sheets.
3. Pages should be numbered consecutively, beginning with the title page, with the number written in the upper right corner.
4. The first page (showing the title) should contain the following sections in the order mentioned here:
   - *Title of article in Spanish and English*. The title should be descriptive and indicate the main results of the study. *Maximum extension: 25 words.*
   - *Short title in Spanish and English*. *Maximum extension: 6 words.*
   - *Full name of author and co-authors*. The authors must be listed and then an Arabic number must be placed in superscript, indicating the institution to which they are affiliated.
   - *Author ORCID number.* It is a requirement that all authors have their ORCID identification number, which can be obtained at https://orcid.org/register
   - *Author affiliation*. This should be indicated with Arabic numerals and in superscript. Affiliations should be placed immediately after authors’ names (not as footnotes). Affiliations should specify the department, area, institution, city, and country of each author. It is not necessary to indicate the postal address. Institutions must be written in their original language, without translation. If the authors add acronyms, these must be included in the official name. No positions or degrees of the authors (such as doctor, resident, or researcher) should be written.

   . For example:

   Juan José García-Urbina,[1] Héctor Valentín Esquivias Zavala[2]

   [1] Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, México.
   [2] Departamento de Publicaciones, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, México.

- The **"Correspondence"** section should be placed at the end of the first page, indicating the corresponding author with their postal address, phone and email address. This will be the only author Salud Mental will contact during the process.

  For example:

  Correspondence:
  Juan José García-Urbina
  Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz.
  Calz. México-Xochimilco 101, San Lorenzo Huipulco, Tlalpan, 14370, Ciudad de México, México.
  Phone: 55 4152-3624
  E-mail: jurb@imp.edu.mx

5. The second page should contain abstracts of the article in English and Spanish. Each abstract should contain a maximum of 250 words.

   - **Abstracts of original articles and systematic reviews** should comprise the following: Introduction, Objective, Method, Results, and Discussion and Conclusion.
   - **Abstracts of Clinical Cases** should comprise Introduction, Objective, Main findings, Interventions, Results, and Discussion and Conclusion.
   - **Keywords.** At the end of each abstract, a minimum of four and a maximum of six keywords should be included, separated by commas and in lower case. Keywords must be the same in English and Spanish. These are used for indexing articles, which is why three of them must be found in the *MeSH (Medical Subject Headings)* (http://www.nlm.nih.gov/mesh/MBrowser.html).

6. The body of the manuscript begins on the third page, which should follow the structure indicated in the abstract:

   - **Introduction (or Background for Narrative Reviews)**. The last paragraph of this section should clearly include the objectives of the review and, if necessary, the hypotheses.
   - **Method.** This should contain the following sections:
     - Study design
     - Subjects/sample description
     - Sites
     - Measurements
     - Procedure
     - Statistical analysis
     - Ethical considerations

       In the case of review articles and clinical cases, these sections may be modified in keeping with the PRISMA guideline (systematic reviews) or the CASE REPORT guideline (clinical cases).
   - **Results.** These should be presented in a logical sequence within the text. They can be supported with tables, graphs, and figures.
   - **Discussion and Conclusion**. This section will highlight new and relevant aspects of the study and the conclusions derived from it, as well as the possible implications of its findings and its limitations.

7. After the Discussion and Conclusion section, author statements should be added in the following order:

   - **Funding**. In this section, authors should declare whether the study or the preparation of the manuscript received any type of funding, indicating the name of the entity that provided the funds.

     For example:

     This study was partially funded by CONSEJO NACIONAL DE CIENCIA Y TECNOLOGÍA (No. XXXXXXX).

     If no financial support was received, authors must state it was well.

     For example:

     None.
   - **Conflict of interest.** In this section, authors must declare whether they have conflicts of interest related to their scientific activity. Having a conflict of interest will not necessarily prevent publication of the manuscript. If there is no conflict of interest, the following phrase must be inserted: "The authors declare that they have no conflicts of interest."
   - **Acknowledgments**. If deemed necessary, acknowledgment of the people, centers or entities that have collaborated or supported the research will be mentioned after the previous statements.

8. **References.** Are placed after the authors' declarations (Funding, Conflicts of interest, and Acknowledgements), and must adhere to the ***Publication Guidelines of the American Psychological Association (APA), last edition*** (https://normas-apa.org).

9. **Tables and figures.** *Salud Mental* establishes a maximum total of five graphic elements. The standard requested for tables and figures adheres to the ***Guidelines of the American Psychological Association (APA), last edition*** (https://normas-apa.org). These will be placed in the same document as the manuscript after the references.

   - Tables must contain a title and a note with an explanation of the acronyms used at the bottom.
   - Figures must be submitted in a high resolution format (minimum image size 300 dpi).
   - Titles of the tables and figure captions must be clear, brief, and always have an identifying number. Within the text, the author must indicate in parentheses and capital letters where the graphic elements should be inserted.

     For example:

     The definition of some behavioral patterns was changed (Table 3) so that they were more comprehensible in Spanish and the categories that group such patterns were redefined based on specialized literature. (INSERT TABLE 3 HERE)

COMPLEMENTARY FILES

1. **Authorization letter for Publication**. This should be signed by all the authors and submitted in PDF format. Download the form at https://revistasaludmental.gob.mx/public/Authorization-letter-for-publication.pdf.
2. **Cover letter**. The author should describe the strengths of their scientific contribution, highlighting the scope, originality, and importance of their contribution to the field of mental health. *It is mandatory to mention three national or international reviewers in the field of knowledge of the submitted manuscript, please indicate the full name and email address of each of the reviewers.* This must be uploaded in PDF.

EMPHASIS AND PUNCTUATION

1. Manuscripts should generally avoid footnotes, although they may be considered if essential.
2. Italics should be used to:
   - Highlight foreign words
   - Emphasize popular expressions
   - Mention titles of books, published documents and periodicals
3. Italics can be used to:
   - Highlight significant or important terms when they are first mentioned
   - Highlight a word or sentence within a quote
4. Double quotes should only be used for:
   - Citing paragraphs from other authors within the text
   - Quoting verbatim fragments of the study subjects' words
5. Avoid using double parentheses, in other words, one parenthesis inside another, and use square brackets instead.
6. Long dashes can be used to indicate parenthetical sentences.
7. All punctuation marks must be used correctly. For example, if question marks are used in a Spanish text, the corresponding opening and closing signs must be included together with quotation marks.

MATHEMATICAL AND STATISTICAL FORMULAE

The following points must be considered when results are presented:

1. Write figures from zero to nine in letters and use numbers for figures from 10 onwards.
2. Use numbers with dates and samples, etc.
3. Include confidence intervals in statistical data.
4. Statistical symbols are written in italics (M, SD).
5. Express exact probability to two or three decimal places (for example, $p = 0.04$; $p = 0.002$), *with no zero in front of the decimal point.* If it is less than .001, it should be written as follows < 0.001.
6. Leave a space before and after each sign (a + b = c instead of a+b=c).
7. Use periods instead of commas to indicate decimals.

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