THE
EUROPEAN
JOURNAL
OF **PSYCHIATRY**

SHORT COMMUNICATION

Gender differences in the therapeutic response to lifestyle improvement-based interventions for treatment-resistant depression

Alejandra Aguilar-Latorre[a,b,c,1,*], Margalida Gili[b,d,e,1], Capilla Navarro-Guzmán[d], Aurora Garcia[e], Aina M. Yáñez[b,e,f,g], Mauro Garcia-Toro[b,e,g,h]

[a] Institute for Health Research Aragón (IIS Aragón), Zaragoza, Spain

[b] Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS), Carlos III Health Institute, Madrid, Spain

[c] Department of Psychology and Sociology, University of Zaragoza, Huesca, Spain

[d] Department of Psychology, University of the Balearic Islands, Palma, Balearic Islands, Spain

[e] University Institute of Health Science Research (IUNICS), University of the Balearic Islands, Palma, Spain

[f] Department of Nursing and Physiotherapy, University of the Balearic Islands, Palma, Balearic Islands, Spain

[g] Health Research Institute of the Balearic Islands (IdISBa), Palma, Spain

[h] Department of Medicine, University of the Balearic Islands, Palma, Spain

Abstract   Treatment-resistant depression (TRD) poses a significant societal challenge, with gender-specific treatment gaps. In a clinical trial targeting TRD, we introduced lifestyle-based interventions. Analyzing data from 24 men and 70 women with TRD, the current study aimed to assess gender-related efficacy differences. Descriptive and univariate analyses unveiled variations in sociodemographic and clinical factors. Utilizing repeated measures ANOVA while controlling for baseline values and age, results indicated a notable gender disparity. Specifically, women exhibited a significantly poorer progression of depressive symptoms. This underscores the need for tailored interventions addressing gender-specific nuances in TRD treatment.
© 2024 The Authors. Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Psiquiatría y Salud Mental. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Depression has become one of the leading causes of disease-induced disability in our society.[1] Despite the existence of

  * Corresponding author at: Faculty of Human Sciences and Education of Huesca, University of Zaragoza, C/ Valentín Carderera, 4, 22003 Huesca, Spain.
  E-mail address: aaguilar@unizar.es (A. Aguilar-Latorre).
  [1] These two authors contributed equally to this work.

effective therapeutic strategies, both biological and psychosocial, they fall short in providing satisfactory resolution for all cases. Consequently, treatment-resistant depression (TRD) cases remain prevalent.[1] Hence, it is crucial to explore alternative approaches for the treatment of TRD. Preliminary evidence suggests that psychosocial programs centered around promoting lifestyle improvements hold great promise in this regard[2]. However, further comprehensive studies are warranted to ascertain their efficacy,

particularly in understanding their gender-specific effectiveness for both men and women.[3] Therefore, analyzing gender disparities in the psychosocial treatment of TRD remains an ongoing challenge, aimed at confirming whether the gender equality in the therapeutic response is equal to that witnessed in non-resistant cases.[4]

At the beginning of 2020, we started a clinical trial to enhance first-line treatments by assessing the efficacy of three lifestyle-based adjuvant interventions in participants with TRD.[5] For this reason, the present study aims to analyse potential variations in therapeutic response based on the gender of the participants.

Methods

Design

This study is a secondary data analysis of a three-arm pragmatic parallel randomized controlled clinical trial (RCT). The main goal of the RCT was to compare the effectiveness of the three adjuvant strategies combined with usual treatment [a) Minimal Lifestyle Intervention (MLI); b) Mindfulness-Based Cognitive Therapy (MBCT); and c) Lifestyle Modification Program (LMP)] in reducing depressive symptoms at a 12-month follow-up. Each intervention was applied over an 8-week period. Information was gathered at baseline (T0) and then at the intervals of 2 months (T1), 6 months (T2), and 12 months (T3). The protocol and results were published elsewhere.[5,6] The trial was registered in ClinicalTrials.gov (NCT04428099; 11-06-2020). The current paper addresses the secondary aim of examining the influence of gender on the therapeutic response.

Interventions

Minimal lifestyle intervention
The MLI group received individual online messages with lifestyle change suggestions in addition to their usual treatment. These recommendations aimed to improve depressive symptoms by promoting actions such as maintaining a consistent sleep schedule, engaging in regular physical activity, spending time outdoors, adopting a healthy diet, and enhancing social support.[7] Treatment as usual (TAU) for all three interventions included antidepressant medication and/or psychotherapy based on individual preferences.

Mindfulness-based cognitive therapy
The MBCT group, in addition to TAU, received the original eight-week MBCT protocol for depression developed by Segal, Williams, and Teasdale.[8] This adapted online format consisted of weekly group-based sessions lasting three hours each, spanning over eight weeks. These sessions addressed various topics including the causes, symptoms, and course of depression; treatment approaches for depression; attention and mindfulness techniques.[8]

Lifestyle modification program
The LMP group, in addition to TAU, participated in eight weeks of weekly group-based sessions lasting three hours each. These sessions covered various topics including the causes, symptoms, and course of depression; treatment

approaches for depression; the significance of physical exercise for overall well-being; strategies to stay motivated in incorporating physical exercise into daily routines; the importance of nutrition, social support, and maintaining healthy sleep patterns; and the role of negative rumination and techniques to identify and address this pattern. Practical recommendations were provided on how to integrate these suggestions into long-term habits.[5,9,10]

Participants

People who were at least 18 years old and who were currently experiencing major depressive disorder were invited to participate. The inclusion and exclusion criteria are published in the protocol[5].

Procedure

Mental health workers contacted and recruited patients diagnosed with Treatment-Resistant Depression (TRD) from the Balearic Islands through phone calls and social media channels. Once a participant met the eligibility criteria and received information about the study, informed consent for participation was obtained either in person at the Health Research Institute of the Balearic Islands (IdISBa) or through a web platform.

Due to the COVID-19 pandemic's restrictions, the three interventions were delivered online.

Measurements

Sociodemographic information was collected using an ad-hoc questionnaire at baseline (age, sex (female or male), education (none, primary, secondary, or university), occupation (working or not working), marital status (with or without a partner), and having children (yes or no)). Also, clinical characteristics were collected. Specifically, if they had any first-degree relatives (parents/children/siblings) that have/had depression, and the number and type (none, Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRI), other antidepressants or anxiolytic) of antidepressants taken at baseline and at the twelve-month follow-up.

The primary outcome was self-reported depressive symptoms using the Beck Depression Inventory-II in Spanish.[11] This 21-item questionnaire asked respondents to rate the severity of their depressive symptoms on a scale from 0 to 3. The results are combined to produce a total score that can range from 0 to 63. Greater depression symptom severity is associated with higher scores. At baseline, the internal consistency of the BDI-II in our sample was good, with a Cronbach's alpha of 0.85.

Statistical analyses

Descriptive analysis (frequencies and percentages for categorical variables; means and standard deviation for continuous variables), and univariate analysis (one-way ANOVA and Fisher's exact probability test) were used to examine between-group differences in sociodemographic and clinical data between the two genders. General Linear Modelling (specifically, repeated measures ANOVA) was performed to

compare the effect of gender (man, woman) on the therapeutic response (measured by BDI-II). The repeated measures ANOVA was adjusted by age and intervention group. The significance level was set at 0.05 using two-sided tests. The analyses followed a complete case approach using IBM SPSS Statistics software (version 25.0).

Results

A total of 94 patients were randomized at one of three arms and were assessed at baseline. Table 1 summarizes the main demographic and clinical characteristics of our sample, comparing the two genders. Most participants were middle-aged women, who had completed secondary or university education, were not working and had no partner. No differences were found between both genders in terms of baseline demographic characteristics and clinical variables. However, it is worth noting that women exhibited a higher prevalence of first-degree relatives (parents/children/siblings) with a history of depression.

As shown in Fig. 1, significant between-group differences were observed for depressive symptoms after controlling for the intervention group and age. Mauchly's test indicated that sphericity could be assumed, $\chi^2(5) = 8.76$, $p = 0.119$. The results show that there was a significant effect of gender on depressive symptoms [$F(3, 47) = 5.780$, $p = 0.002$; $\eta^2 = 0.270$]. These results suggested that being a woman was significantly related to a worse therapeutic response. This association implies a large effect size.

Table 1 Demographic and clinical characteristics of the participants according to gender.

Variables	Men (*n* = 24)	Women (*n* = 70)	*p*
Age, *M* (*SD*)	46.71 (14.64)	48.64 (12.54)	0.534
Education			
None/Primary, n (%)	3 (12.5)	16 (22.9)	0.382
Secondary/University, n (%)	21 (87.5)	54 (77.1)	
Living			
Alone	6 (25)	14 (20)	0.578
With company	18(5)	56 (80)	
Occupation			
Working, n (%)	5 (20.8)	20 (28.6)	0.594
Not working, n (%)	19 (79.2)	48 (68.6)	
Marital status			
With a partner, n (%)	5 (20.8)	23 (32.9)	0.308
Without a partner, n (%)	19 (79.2)	46 (65.7)	
Having children, *yes n (%)*	14 (58.3)	42 (60)	1.000
First-degree relatives (parents/children/ siblings) that have/had depression, *yes n (%)*	10 (41.7)	49 (70)	**0.016**
N° of antidepressants taken at T0, *M* (*SD*)	1.96 (1.04)	1.97 (1.25)	0.963
Kind of antidepressants taken at T0, *n (%)*			
None	3 (12.5)	10 (14.3)	0.321
SSRI	4 (16.7)	18 (25.7)	
SNRI	8 (33.3)	13 (18.6)	
Other antidepressants	9 (37.5)	22 (31.4)	
Anxiolytic	—	7 (10.0)	
N° of antidepressants taken at T3, *M* (*SD*)	1.75 (1.07)	2.21 (1.28)	0.115
Kind of antidepressants taken at T3, *n (%)*			
None	1 (7.1)	8 (19.5)	0.324
SSRI	1 (7.1)	8 (19.5)	
SNRI	5 (20.8)	9 (22.0)	
Other antidepressants	7 (29.2)	12 (29.3)	
Anxiolytic	—	4 (9.8)	
BDI-II, *M* (*SD*)			
T0	35 (11.20)	35.25 (11.02)	0.925
T1	19.81 (14.34)	20.73 (11.85)	0.778
T2	16.41 (11.68)	20.47 (14.49)	0.302
T3	12.64 (11.09)	23.18 (15.59)	0.023
T1-T0	−13.62 (11.80)	−13.63 (11.87)	0.996
T2-T0	−15.41 (14.05)	−14.16 (13.94)	0.754
T3-T0	−20.35 (13.94)	−11.04 (14.05)	**0.035**

Note. p: p-value for the one-way ANOVA or Fisher's exact test. Bold values denote statistical significance at the *p* < 0.05 level. BDI-II, Beck II Self-Applied Depression Inventory; T0, Baseline assessment; T1, Post-intervention assessment; T2, Six-month follow-up; T3, Twelve-month follow-up; SSRI, Selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.
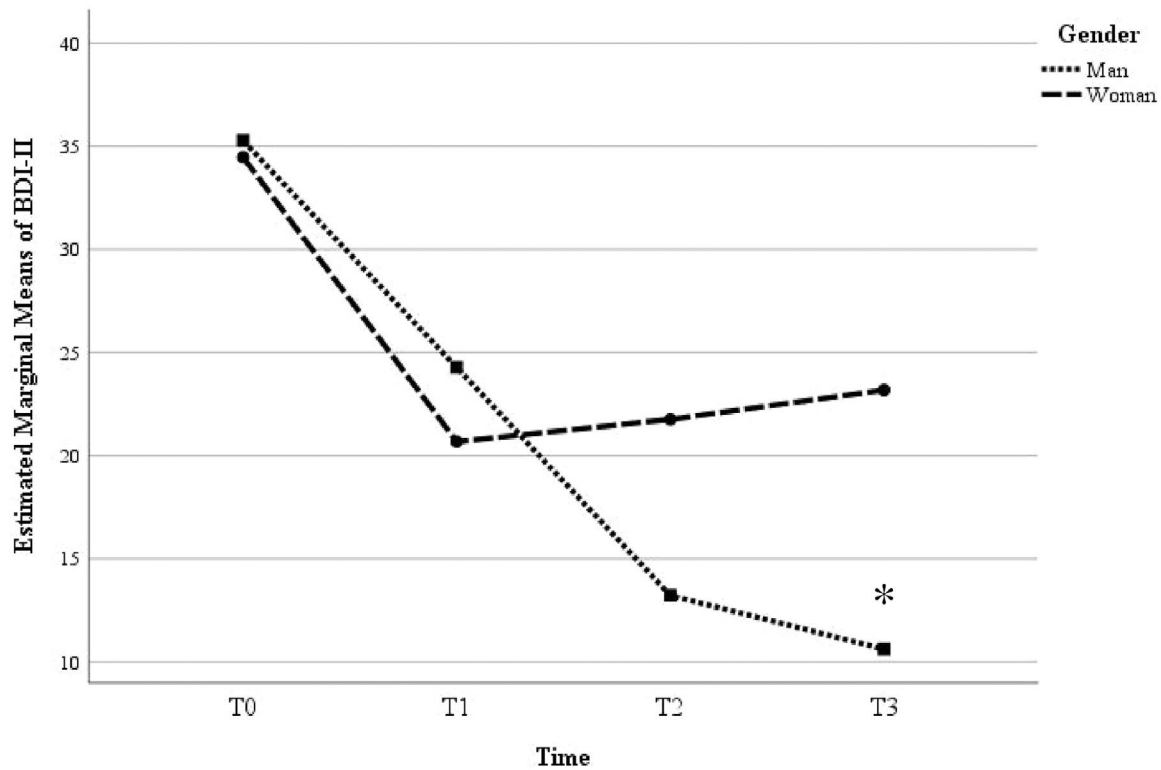
Fig. 1 Estimated Marginal Means of BDI-II.

Note. * $p < 0.05$ between men and women. Statistics used: Repeated measures ANOVA adjusted by age and intervention group.

Discussion

The objective of this study was to examine gender-specific differences in the therapeutic response to three adjunct interventions aimed at reducing depressive symptoms during the early phase of the COVID-19 pandemic. Initially, no disparities were observed between men and women in terms of therapeutic outcomes during the initial two months of implementing the interventions. However, during the follow-up assessments at 6 and 12 months, men exhibited a continued improvement in therapeutic response, while women did not show a similar trend (Fig. 1). Noteworthy is the notable difference in the reduction of psychological support, a consequence of the study's design. This discrepancy in support may partly account for the observed gender disparity, although other factors such as differential adherence to program recommendations by men cannot be disregarded. Unfortunately, we were unable to monitor participant compliance during this period, preventing us from testing this hypothesis. It is crucial to explore why sustained and substantial psychological support was essential for fostering therapeutic response in women but not in men. On the one hand, one possible explanation may be attributed to the inherent discriminatory gender roles that women often bear, resulting in greater burdens and family responsibilities, among other factors.[12] Thus, it is coherent to think that the greater vulnerability of women to depression generated by their discriminatory psychosocial role needs to be

compensated with greater psychological support to attain a comparable antidepressant response to that of men. Moreover, it is reasonable to posit that the unfavorable social circumstances experienced by women may have posed challenges in adhering to the therapeutic program's recommendations aimed at enhancing their lifestyles. On the other hand, it's plausible that biological dissimilarities existed between men and women in this specific sample, attributable to varying proportions of first-degree relatives with affective disorders. Such differences may elucidate a poorer prognosis independent of gender role distinctions.

It is noteworthy that this study was conducted in the midst of the COVID-19 pandemic. First, the differential impact of factors such as access to visits and changes in pharmacological treatment for men and women warrants further study. Second, it is possible that women necessitate greater social activity than men to regulate their emotions.[13] Consequently, in circumstances conducive to social distancing, such as a pandemic, women may encounter heightened susceptibility to depression. This phenomenon could elucidate the inferior outcomes observed among women in our experimental setting, particularly in instances where the social support facilitated by the protocol was significantly diminished. In general, research conducted during this time has consistently indicated a controversial gender effect on mental health.[14] Generally, women have exhibited higher levels of depressive symptoms resulting from the impact of quarantine measures compared to men.[15] Despite

consensus on women facing a heavier burden due to societal norms and gender disparities, especially in adulthood, this study emphasizes the positive impact of social support interventions. Acknowledging this, it's crucial for research and clinical practice to address gendered norms, mitigating biases in healthcare. By recognizing these nuances, healthcare professionals can deliver equitable care, fostering satisfaction in caregiving for both men and women.

Therefore, there is a pressing need to improve clinical trial designs by incorporating gender analysis as a primary focus. Implementing such an approach in the future would enhance the potential for providing women with depression a tailored treatment that could significantly improve outcomes.

Strengths

This study adds to the body of evidence that there are differences between men and women regarding the evolution of depression after an intervention carried out during the COVID-19 pandemic. We had a homogeneous sample of participants suffering from TRD, as well as a prospective design with various active groups and time points. This fact has allowed us to make exploratory contributions to this field of study.

Limitations

Because this is an exploratory secondary data analysis of an RCT, there were no sample size estimates or *p*-value adjustments made. Future research will require a larger sample size to investigate these research questions. Furthermore, the measurement instruments relied on self-report, which may be influenced by social desirability. Finally, the study was conducted online during the COVID-19 pandemic, so these research questions should be investigated in different contexts.

Because this is an exploratory secondary data analysis of an RCT, there were no sample size estimates or *p*-value adjustments made. Additionally, the study is limited by the comparatively smaller sample size of males compared to females, potentially impacting the generalizability of our findings and necessitating careful interpretation of gender-specific differences observed. Moreover, comprehensive information on potential explanatory variables, such as adherence to interventions and social support, as well as other confounding factors that could have influenced the observed disparities between male and female groups, was not collected. Future research endeavors will necessitate larger sample sizes to adequately investigate these research questions. Furthermore, the reliance on self-report measurement instruments introduces the possibility of social desirability bias. Lastly, it's worth noting that the study was conducted online during the COVID-19 pandemic, suggesting the importance of replicating these investigations in diverse contexts.

Conclusions

Our data indicate a less favorable prognosis for women in terms of therapeutic response in the context of treatment-resistant depression following lifestyle-based interventions. Nevertheless, our findings also suggest the potential benefit of increased psychological support in mitigating this circumstance.

Data availability

The data that support the findings of this study are available from the corresponding author, AAL, upon reasonable request.

Conflict of interest

The authors report there are no competing interests to declare.

Funding and acknowledgments

Ethical considerations

Ethics approval was granted by the Research Ethics Committee of the Balearic Islands (IB3925/19PI; 29-05-2019). The study was developed in accordance with the Helsinki Declaration and its updates. All subjects provided informed consent before group allocation. All collected data were processed as stipulated in the current Spanish legislation regarding the protection of personal data (Law 3/18, Dec 5th). Once the data was collected it was anonymized for data analysis and only used for the study purposes.

References

1. Malhi GS, Bell E, Singh AB, Bassett D, Berk M, Boyce P, et al. The 2020 royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: major depression summary. Bipolar Disord. 2020;22(8):788−804. [cited 2023 May 16] Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bdi.13035.

2. Aguilar-Latorre A, Oliván-Blázquez B, Algorta GP, Serrano-Ripoll MJ, Olszewski LE, Turón-Lanuza A. One-year follow-up of the effectiveness of a lifestyle modification programme as an adjuvant treatment of depression in primary care: a randomised clinical trial. J Affect Disord. 2023;332:231−7.

3. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. BMC Psychiatry. 2014;14(1):1−13. [cited 2023 May 16] Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-14-107.

4. Aemissegger V, Lopez-Alcalde J, Witt CM, Barth J. Comparability of patients in trials of ehealth and face-to-face psychotherapeutic interventions for depression: meta-synthesis. J Med Internet Res. 2022;24(9):e36978.

5. Navarro C, Yáñez AM, Garcia A, Seguí A, Gazquez F, Marino JA, et al. Effectiveness of a healthy lifestyle promotion program as adjunctive teletherapy for treatment-resistant major depression during COVID 19 pandemic: a randomized clinical trial protocol. Medicine (Baltimore). 2020;99(45):e22958.

6. Garcia A, Yáñez AM, Bennasar-Veny M, Navarro C, Salva J, Ibarra O, et al. Efficacy of an adjuvant non-face-to-face multimodal lifestyle modification program for patients with treatment-resistant major depression: a randomized controlled trial. Psychiatry Res. 2022;319:114975. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165178122005662.

7. Serrano-Ripoll MJ, Oliván-Blázquez B, Vicens-Pons E, Roca M, Gili M, Leiva A, et al. Lifestyle change recommendations in major depression: do they work? J Affect Disord. 2015;183:221—8.

8. Segal ZV, Williams JMG, Teasdale JD. Mindfulness-based cognitive therapy for depression. 2nd ed. New York: The Guilford Press; 2013.

9. Aguilar-Latorre A, Navarro C, Oliván-Blázquez B, Gervilla E, Magallón Botaya R, Calafat-Villalonga C, et al. Effectiveness and cost-effectiveness of a lifestyle modification programme in the prevention and treatment of subclinical, mild and moderate depression in primary care: a randomised clinical trial protocol. BMJ Open. 2020;10(12):e038457.

10. Aguilar-Latorre A, Pérez Algorta G, Navarro-Guzmán C, Serrano-Ripoll MJ, Oliván-Blázquez B. Effectiveness of a lifestyle modification programme in the treatment of depression symptoms in primary care. Front Med (Lausanne). 2022;9(954644):1—10.

11. Sanz J, García-Vera MP, Espinosa R, Fortún M, Vázquez C, Obreg R, et al. Spanish adaptation of the Beck Depression Inventory-II (BDI-II): 3. Psychometric features in patients with psychological disorders. Clin Salud. 2005;16(2):121—42. Available from: http://www.redalyc.org/resumen.oa?id=180616104001.

12. Di Fazio N, Morena D, Delogu G, Volonnino G, Manetti F, Padovano M, et al. Mental health consequences of COVID-19 pandemic period in the European population: an institutional challenge. Int J Environ Res Public Health. 2022;19(15):9347.. [cited 2023 May 17] Available from: https://www.mdpi.com/1660-4601/19/15/9347/htm.

13. Ryba MM, Hopko DR. Gender differences in depression: assessing mediational effects of overt behaviors and environmental reward through daily diary monitoring. Depress Res Treat. 2012;2012:1—9.

14. Zheng D, Liu P, Chen H, Wang X, Li J. Worse psychological traits associated with higher probability of emotional problems during the Omicron pandemic in Tianjin, China. Eur J Psychiatry. 2023;37 (2):84—91.

15. Amendola S, Spensieri V, Hengartner MP, Cerutti R. Mental health of Italian adults during COVID-19 pandemic. Br J Health Psychol. 2021;26(2):644—56. Available from: https://onlinelibrary.wiley.com/doi/10.1111/bjhp.12502.