International Journal of Neuropsychopharmacology, 2024,pyae055

https://doi.org/10.1093/ijnp/pyae055
Advance access publication 10 November 2024
Regular Research Article

Regular Research Article

Anhedonia is associated with a specific depression profile and poor antidepressant response

Antonina Luca, MD, Msc, PhD[1], Maria Luca, MD, Msc, PhD[2], Siegfried Kasper, MD[3,4], Basilio Pecorino, MD[1], Joseph Zohar, MD, PhD[5,6], Daniel Souery, MD[7], Stuart Montgomery, MD, MBBS, FRCPsych[8], Panagiotis Ferentinos, MD, PhD[9], Dan Rujescu, MD[3], Antonino Messina, MD, PhD[10], Raffaella Zanardi, MD[11,12], Raffaele Ferri, MD[13], Mariangela Tripodi, MD[13], Bernhard T. Baune, MD, PhD, MPH, FRANZCP[14,15,16], Giuseppe Fanelli, MD, PhD[17,18], Chiara Fabbri, MD, PhD[17], Julien Mendlewicz, MD, PhD[19], Alessandro Serretti, MD, PhD[*,1,13],

[1]Department of Medicine and Surgery, Kore University of Enna, Enna, Italy, [2]Centre for Addiction, Adrano-Bronte, Italy, [3]Department of Psychiatry and Psychotherapy, Medical University Vienna, Vienna, Austria, [4]Department of Molecular Neuroscience, Center for Brain Research, Medical University Vienna, Vienna, Austria, [5]5Department of Psychiatry, Sheba Medical Center, Tel Hashomer, Israel, [6]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [7]Psy Pluriel – Epsylon Caring for Mental Health Brussels and Laboratoire de Psychologie Médicale Université libre de Bruxelles, Bruxelles, Belgium, [8]Imperial College School of Medicine, London, United Kingdom, [9]Department of Psychiatry, Athens University Medical School, Athens, Greece, [10]Psychiatry Unit, Department of Mental Health, ASP Enna, Enna, Italy, [11]Department of Clinical Neurosciences, Vita-Salute San Raffaele University, Milan, Italy, [12]Mood Disorder Unit, IRCCS San Raffaele Hospital, Milan, Italy, [13]Oasi Research Institute-IRCCS, Troina, Italy, [14]Department of Psychiatry and Psychotherapy, University of Münster, Münster, Germany, [15]Department of Psychiatry, Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia, [16]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Victoria, Australia, [17]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, [18]Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands, [19]Université Libre de Bruxelles, Brussels, Belgium

[*]Corresponding author: Alessandro Serretti, MD, PhD, Oasi Research Institute-IRCCS, Troina, Italy; Department of Medicine and Surgery, Kore University of Enna, Italy. (alessandro.serretti@icloud.com)

Abstract

Background: Anhedonic features within major depressive disorder (MDD) have been associated with worse course and outcome and may predict nonresponse to treatment. However, a detailed clinical profile of anhedonia in MDD is still lacking.

Materials and Methods: One thousand two hundred ninety-four patients with MDD were selected from the cross-sectional European multicenter Group for the Study of Resistant Depression study. Anhedonia was assessed through the Montgomery–Åsberg Depression Rating Scale anhedonia item "inability to feel." Clinical and demographic features were then analyzed.

Results: The presence of anhedonia related to a distinct demographical (living alone) and clinical profile (thyroid diseases, diabetes, suicide risk, high number of previous depressive episodes, more severe MDD, and more frequent inpatient status). Furthermore, anhedonia was associated with nonresponse to treatment and treatment resistance, even after adjusting for confounding variables.

Conclusions: Our findings support the role of anhedonia as a modulating feature of MDD, being associated with a more severe depression profile. Moreover, anhedonic features are independent predictors of poor treatment response.

Keywords: anhedonia, antidepressants, major depression, treatment-resistant depression (TRD), treatment outcomes.

Significant Statement

We analyzed the clinical profile of anhedonia in patients with major depression disorder and observed that it was related to a distinct demographic and clinical profile, and it was associated with nonresponse to treatment and treatment resistance. We concluded that anhedonia is correlated with a more severe depression profile.

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders 5th edition, text revision, defines anhedonia as a "marked diminished interest or pleasure in all, or almost all, activities."[1] Originally considered a depressive symptom, at present, anhedonia is defined as an independent and trans-diagnostic construct.[2] Its conceptualization has been expanded, linking anhedonia to

Received for publication: September 12, 2024. **Accepted:** November 6, 2024. **Editorial decision:** November 5, 2024.

reward processing deficits encompassing, among others, interest, reward anticipation, and pleasure.[3–5] Despite being a transdiagnostic construct, anhedonia is a core feature of major depressive disorder (MDD), whereby up to 70% of individuals with depression may experience it.[6]

From a clinical point of view, depressive episodes with prominent anhedonic features may show peculiarities compared to those without such features. More specifically, patients with MDD and anhedonia may be more likely to present social withdrawal, mood reactivity, rumination on the past, diurnal mood variation, and loss of appetite.[7] In addition, the presence of anhedonia during a depressive episode has been linked to lower positive affect, melancholic features, and more severe psychomotor retardation.[8,9] In light of this evidence, it would be inappropriate to consider anhedonia as a simple symptom of MDD.

Most importantly, the prognostic value of anhedonia has been repeatedly investigated. Anhedonia has been suggested to be a risk factor for suicidality, independent from depression itself.[10–12] Moreover, the construct has been consistently linked to poor outcomes of MDD, more severe depressive symptoms, and persistence of psychosocial impairment, despite overall response to monoamine enhancers (antidepressants).[13,14] Anhedonic features have been associated with nonresponse to treatment and non-remission in depressed adults.[15] In addition, anhedonia has been reported to predict a longer time to remission and fewer depression-free days among adolescents suffering from treatment-resistant depression (TRD).[16] Among adolescents, anhedonia was also a predictor of greater severity, higher number of MDD episodes, longer duration, and suicidality, representing a key feature of MDD.[17] Other studies confirmed the strong association between anhedonia and TRD, as it was listed among the variables with high discriminatory validity.[18] Consistently, in adults with TRD, the antidepressant action of ketamine was mediated by the reduction of anhedonic features with an indirect effect of anhedonia in the relationship between ketamine infusions and the severity of depression,[19] and anhedonia may predict, along with bipolarity, response to intranasal esketamine.[20]

However, further research on the topic is needed, as a study[21] suggests that the impact of anhedonia on treatment outcomes might not be independent of other variables, such as depressed mood. Moreover, it is still not clear whether sex and age might lead to any difference in terms of anhedonic features among patients with MDD. Although a study reported a higher prevalence of social anhedonia among men from the general population,[22] depressed females might show higher rates of anhedonia compared to their male counterparts.[23] Imaging studies indicate that depressed females might show a distinct profile of aberrant activity in anhedonia-related brain areas (ie, insula, putamen, hippocampus), which in turn could relate to the severity of anhedonia.[24] Regarding age, a study[9] reported an association between older age and anhedonia in a sample of depressed individuals. Hence, further research is needed to clarify the impact of anhedonia in MDD.

In this study, we investigated the demographic and clinical features associated with anhedonia in patients with MDD, testing also treatment response and possible sex and age differences.

METHODS

Patients included in the present research were selected from the cross-sectional European multicenter Group for the Study of Resistant Depression study. As detailed elsewhere,[25,26] adults with current MDD, diagnosed according to DSM IV-TR criteria, were enrolled; participants were naturalistically treated with at least one antidepressant drug at a sufficient dose for at least 4 weeks. Demographic and clinical data were collected as previously reported.[25,27] The Montgomery–Åsberg Depression Rating Scale (MADRS)[28] was administered at inclusion and to assess retrospectively symptoms at the beginning of the current episode (considering patients' interview and medical records).

Patients were classified as responders if a reduction in total MADRS score ≥50% from baseline was obtained after ≥4 weeks of treatment; otherwise, they were considered as nonresponders. In case of insufficient response after 2 or more monoamine enhancer trials, patients were defined as TRD. Considering that both nonresponders and TRD represent a challenge in routine clinical practice, in the present study, they were analyzed together as one group.

The retrospective MADRS item 8 was used to categorize patients into nonanhedonic (nA_MDD) and anhedonic MDD (A_MDD), using a cutoff score of ≤3 to identify the first group and >3 for the second one.[29,30] Specific anhedonia measurements were not available in our sample; however, MADRS has previously been widely used to assess anhedonia. In particular, prior studies[31,32] used the MADRS anhedonia factor score, computed by combining the 2 MADRS items addressing sadness (1: apparent sadness; 2: reported sadness) with the 3 items addressing detachment (6: concentration difficulties; 7: lassitude; 8: inability to feel). However, the literature is not uniform on this definition, also because the pooling of 5 sadness and detachment items covers a much broader depression domain. Moreover, a comparison with the Snaith-Hamilton pleasure scale, specific for anhedonia, showed that the anhedonia score mainly correlates with item 8 in depressed subjects.[33] Other MADRS items showed a correlation ranging from $r = 0.01$ to $r = 0.49$, while item 8 showed a correlation of $r = 0.53$, interestingly, items 6 (concentration difficulties) and 7 (lassitude), included in the anhedonia factors used in the abovementioned papers, showed relatively low correlations of $r = 0.19$ and $r = 0.21$, respectively, thus suggesting that these are less valid measures of Snaith-Hamilton pleasure scale measured anhedonia. In the present study, to strictly adhere as much as possible to the classical definition of anhedonia, only item 8 (inability to feel) of the MADRS was therefore considered as a proxy for anhedonia, similar to previous studies.[30] Though we are aware that item 8 partially correlates with the Snaith-Hamilton pleasure scale measure, it may not cover the whole range of interest, reward anticipation, and pleasure facets of anhedonia.

Concerning medications, scarcely represented drug classes (administered to less than 5% of the whole sample) were excluded from the analyses. In the present study, the MADRS retrospective total score, excluding item 8 "Inability to feel" (MADRS-rEx8), was used to assess the severity of depression independent from item 8.

All the Ethical Committees of the participating centers approved the study protocol. The enrolled subjects signed a written informed consent prior to participation.

Statistical Analysis

Demographic and clinical characteristics of nA_MDD and A_MDD were compared with T-tests and chi-square tests. A univariate analysis was carried out to test possible associations between anhedonia and response to treatment (responders vs nonresponders/TRD). Multivariate logistic regression models were then applied by adjusting for variables associated with anhedonia in the univariate analyses and categorized into demographic and systemic conditions. A further multivariate model included overall depression severity (MADRS-rEx8). Given the possible influence

of age and sex on anhedonia,[22,23] we performed a further analysis stratifying for sex and age (considering age median value).

The statistical significance level was set at $P = .05$, uncorrected, because of the confirmative nature of the analysis, given the previously reported studies on anhedonia and depression. Data were analyzed with STATA v.18.[34] In our sample, we had a power of 0.8 to detect a small effect size of $d = 0.16$ with an alpha of 0.05 (2-tailed).

RESULTS

Sample Characteristics

A total of 1294 patients with MDD and complete MADRS assessment were included (mean age 51.6 ± 13.9 years; 861 women [66.6%]), among which 749 (57.9%) patients showed A_MDD. Comparing nA_MDD and A_MDD, no differences were found in terms of age (respectively, 51.3 ± 14.4 vs 51.9 ± 13.6; $P = .937$) and sex (374 [68.6%] vs 487 [65.0%] women; $P = .175$). As shown in Table 1, patients with A_MDD were more likely to be living alone (separated, single, or divorced), had more frequent welfare benefits, and showed more frequent comorbidities with thyroid diseases and diabetes mellitus. Moreover, A_MDD was associated with increased suicide risk, a higher number of previous depressive episodes, more severe MDD, and a greater likelihood of inpatient status.

Therapeutic Regimen

Concerning therapy, norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, and monoamine oxidase inhibitors were prescribed to less than 5% of patients

Table 1. Clinical demographic characteristics of the sample

	Whole sample (n = 1294)	nA_MDD (n = 545)	A_MDD (n = 749)	OR	95% CI	*P*-value
Thyroid disease (any), yes	181 (13.9)	63 (11.6)	118 (15.7)	1.4	1.03–1.98	**.032**
Diabetes mellitus, yes	76 (5.9)	21 (3.8)	55 (7.3)	1.9	1.18–3.31	**.010**
Any somatic disease, yes	712 (55.1)	290 (53.2)	422 (56.4)	1.1	0.91–1.42	.253
Marital status (obs n = 1293)						
Married/living with partner	637 (49.3)	288 (52.9)	349 (46.6)	1.2	1.03–1.41	**.016**
Widowed	65 (5.0)	24 (4.4)	41 (5.5)	1.7	1.03–2.82	**.037**
Separated	114 (8.8)	45 (8.3)	69 (9.2)	1.5	1.05–2.23	**.026**
Single	327 (25.3)	129 (23.7)	198 (26.4)	1.5	1.22–1.91	**<.001**
Divorced	150 (11.6)	58 (10.7)	92 (12.3)	1.6	1.14–2.20	**.006**
Has children (obs n = 1293)	841 (65)	356 (65.4)	485 (64.7)	0.9	0.76–1.22	.798
Number of children	1.3 ± 1.2	1.3 ± 1.2	1.2 ± 1.2	0.9	0.90–1.08	.836
Living status (obs n = 1293)						
Alone	384 (29.7)	146 (26.8)	238 (31.8)	1.6	1.32–2.00	**<.001**
At home with spouse/partner/children	790 (61.1)	354 (65.1)	436 (58.2)	1.2	1.07–1.41	**.004**
At parents or children's home	78 (6)	32 (5.9)	46 (6.1)	1.4	0.91–2.25	.115
At nursing home	2 (0.2)	/	2 (0.3)	/	/	/
With someone else (roommate/cousins)	33 (2.5)	10 (1.8)	23 (3.1)	2.3	1.09–4.83	**.028**
With others	6 (0.5)	2 (0.4)	4 (0.5)	2.0	0.36–10.91	.423
Working status (obs n = 1288)						
Unemployed/on social benefits	326 (25.3)	110 (20.3)	216 (28.9)	1.9	1.56–2.47	**<.001**
Blue-collar worker	94 (7.3)	39 (7.2)	55 (7.4)	1.4	0.93–2.12	.101
White-collar worker/retired/student	826 (64.1)	372 (68.6)	454 (60.9)	1.2	1.06–1.39	**.004**
Management position	42 (3.3)	21 (3.9)	21 (2.8)	1.0	0.54–1.83	.999
Characteristics of depression						
Suicide risk, yes (obs n = 1293)	594 (45.9)	193 (35.4)	401 (53.6)	2.1	1.67–2.64	**<.001**
Duration of depression, days (obs n = 1213)	219.8 ± 193.6	214.8 ± 201.9	223.4 ± 187.5	1.0	0.99–1.00	.467
Previous MDD episodes (obs n = 999)	3.5 ± 2.5	3.1 ± 2.2	3.8 ± 2.7	1.1	1.05–1.18	**<.001**
Previous MDD episodes ≥3 (median value)	579 (57.9)	199 (52.6)	380 (61.2)	1.4	1.09–1.83	**.008**
Duration since onset, years (obs n = 1213)	14.8 ± 12.9	14.0 ± 13.1	15.3 ± 12.9	1.0	0.99–1.01	.084
Psychotic symptoms (obs n = 902)	62 (6.9)	14 (4.1)	48 (8.6)	2.2	1.20–4.10	**.010**
Panic disorder (obs n = 1294)	115 (8.9)	46 (8.4)	69 (9.2)	1.1	0.74–1.62	.630
Generalized anxiety disorder (obs n = 1294)	143 (11.0)	64 (11.7)	79 (10.5)	0.9	0.62–1.25	.498
Number of previous antidepressants (obs n = 1293)	1.5 ± 1.6	1.4 ± 1.6	1.6 ± 1.6	1.1	0.99–1.13	.085
Inpatient status (obs n = 1285)	422 (32.8)	134 (24.7)	288 (38.7)	1.9	1.50–2.45	**<.001**
MADR-rEx8 (obs n = 1294)	30.4 ± 6.9	26.8 ± 5.7	33.1 ± 6.5	1.2	1.15–1.21	**<.001**
Nonresponders/TRD (obs n = 1294)	989 (76.4)	388 (71.2)	601 (80.3)	1.6	1.26–2.12	**<.001**

Abbreviations: A_, anhedonic; CI, confidence intervals; MADR-rEx8, Montgomery–Åsberg Depression Rating Scale-retrospective item 8 excluded; N, number; nA_MDD, non anhedonic major depressive disorder; obs, number of observations; OR, odd ratio. Data are expressed as number and percentage or mean ± standard deviation.
P-values < .05 are reported in bold.

and were therefore not considered in further statistical analyses. Serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, noradrenergic and specific serotonergic antidepressants, serotonin antagonist and reuptake inhibitors, benzodiazepines and antipsychotics were more frequently prescribed to patients with A_MDD. On the other hand, selective serotonin reuptake inhibitors (SSRIs) were more frequently prescribed to nA_MDD patients. Finally, A_MDD patients were prescribed higher equivalent doses of monoamine enhancers than nA_MDD patients (Supplementary Table S1).

MADRS and Treatment Response Profiles

A_MDD patients presented a higher MADRS-rEx8 than nA_MDD patients, as expected (Table 1). Out of the 1294 patients, 305 (23.6%) were responders, and 989 (76.4%) were nonresponders/TRD. Nonresponders/TRD were more frequent among A_MDD than in nA_MDD (Table 1; Figure 1). The strength of association was also confirmed across multivariate analyses: (1) Model 1 (*adjusted for marital status/living status, working status*): odd ratio (OR) = 1.6; 95% confidence interval (CI) [1.27, 2.15]; $P < .001$; (2) Model 2 (*adjusted for thyroid disorder and diabetes*): OR = 1.7; 95% CI [1.29, 2.17]; $P < .001$; (3) Model 3 (*adjusted for depression severity*): OR = 1.4; 95% CI [1.06, 1.88]; $P < .019$.

Sex- and Age-Stratified Analysis

This analysis included 861 women and 433 men, with no difference in mean age (51.5 ± 13.9 and 51.8 ± 13.9 years, respectively, $P = .78$). No significant differences were found comparing the MADRS-rEx8 between women (30.2 ± 6.9) and men (30.9 ± 6.9; $P = .068$). Out of the 861 women, 662 (76.9%) were nonresponders/TRD, and 487 (56.6%) had A_MDD. An association between A_MMD and poor treatment response was observed: OR = 1.9; 95% CI [1.35, 2.56]; $P < .001$. The association was confirmed also in the following models of multivariate analyses: (1) Model 1: OR = 1.9; 95% CI [1.35, 2.58]; P-value < 0.001; (2) Model 2: OR = 1.9; 95% CI [1.39, 2.66]; P-value < 0.001; (3) Model 3: OR = 1.5; 95% CI [1.07, 2.19]; $P = .018$. Out of the 433 men, 327 (75.5%) were nonresponders/TRD, and 262 (60.5%) had A_MDD. Among men, A_MDD was not associated with nonresponders/TRD (OR = 1.3; 95% CI [0.83, 2.03]; $P = .241$).

In the whole group, the median age was 52, and 431 (50.1%) women and 208 (48.1%) men were younger than 52 years. As shown in Figure 1, regardless of age and sex, nonresponders/TRD were more frequent in A_MDD than nA_MMD. However, in sex- and age-stratified analyses, a significant association between anhedonia and poor treatment response was found only in women aged ≥52 years (OR = 2.3, 95% CI [1.45, 3.58]; $P < .001$).

DISCUSSION

In this study, more than 57% of patients with MDD reported clinically relevant anhedonia. From a socio-demographic point of view, anhedonia in our cohort was associated with unemployment, being separated or divorced, and living alone, which likely exacerbated feelings of loneliness. In line with these findings, previous studies reported a strong association between impairment in work function, unemployment, and anhedonia in MDD.[14,35] Moreover, recent studies involving nondepressed individuals suggested that anhedonia may lead to poor social engagement and communication difficulties between partners, reducing relationship quality.[36]

From a clinical perspective, anhedonia was also associated with somatic medical conditions, specifically thyroid dysfunctions and diabetes mellitus in our cohort. Although the relationship between MDD and thyroid diseases is well-established,[37,38] the specific relationship between anhedonia and thyroid function still needs to be clarified, as only one study reported a nonsignificant trend toward higher TSH level in subjects with anhedonia compared to those without.[39] More compelling is the emerging evidence highlighting the impact of insulin resistance, which is a hallmark of diabetes mellitus type 2, on brain function, particularly in regions integral to mood regulation and reward processing.[40–42] Insulin resistance has been shown to induce dendritic

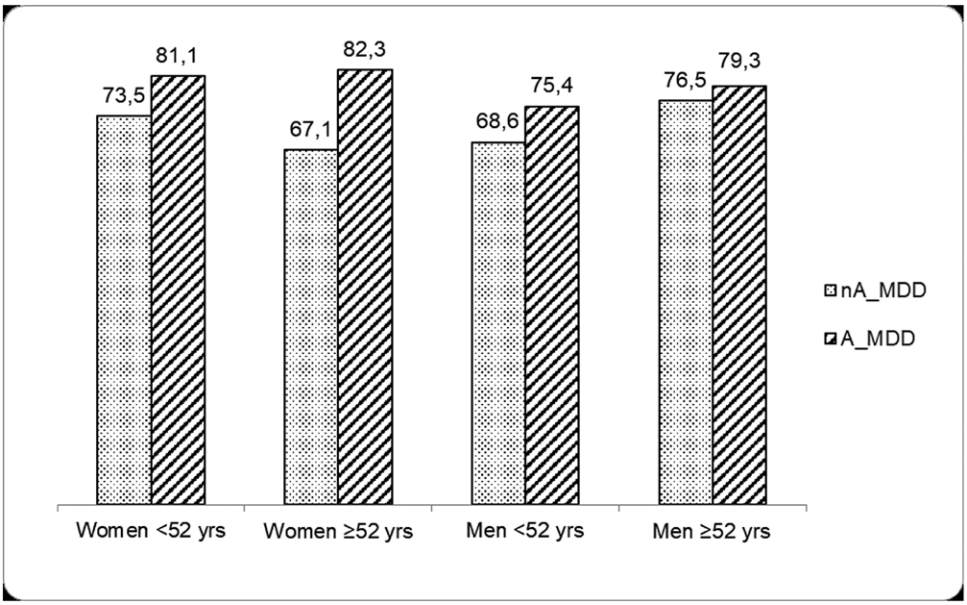

Figure 1. Percentage of nonresponders/TRD in anhedonic and nonanhedonic MDD, stratified by age and sex. Abbreviations: A_MDD, anhedonic major depression disorder; nA_MDD, non anhedonic major depression disorder; TRD, treatment-resistant depression; yrs, years.

atrophy in the hippocampus, a region essential for cognitive and emotional processing in depression.[43] Additionally, insulin receptors are abundant in key brain regions involved in emotional regulation and reward processing, such as the ventral tegmental area and nucleus accumbens.[40] Disruptions in insulin signaling within these regions can lead to significant alterations in dopamine transmission, directly affecting the experience of pleasure and motivation.[40] Recent studies further underscore that individuals with MDD who exhibit insulin resistance are disproportionately affected by anhedonia.[44] Targeting insulin signaling pathways in the development of novel therapeutic strategies could thus represent a promising avenue for managing anhedonia, a symptom notoriously resistant to current treatments.[45,46] Overall, systemic medical comorbidities are generally considered detrimental in MDD.[47]

In agreement with previous data linking anhedonia to a more severe MDD course,[10–14] our sample of patients with A_MDD showed a more severe clinical phenotype, characterized by higher suicide risk, a high number of previous depressive episodes, and more frequent inpatient status. Moreover, regardless of depression severity, an association between nonresponders/TRD and anhedonia was observed. These data suggest that anhedonia may be not only a core feature of depression, characterizing a more severe phenotype, but also a possible independent predictor of poor response. Targeted treatments could therefore be particularly important in these patients[5,48]). Consistently, in our naturalistic study, A_MDD showed a different treatment profile compared to nA_MDD, in line with suggestions provided by previous studies that SSRI may be less effective in A_MDD.[6] However, ketamine was still not available at the time of recruitment of this sample, and it has been suggested to target anhedonia and suicidality[49]; other tailored approaches should be considered, such as agomelatine, vortioxetine, or bupropion.[5]

Regarding sex differences, in our cohort, anhedonia was slightly more common in men (60.5%) than in women (56.6%). Sex differences in anhedonia prevalence are far from being clear. Although in the general population anhedonia has been reported to occur slightly more frequently in men,[22] among depressed individuals, anhedonia has been reported as more frequent in women.[23] Furthermore, in our study, the association between anhedonia and poor response was observed in women only, while it was a nonsignificant trend in men. Interestingly, when age was considered, the association between anhedonia and poor response was confirmed only for women aged 52 years or older; therefore, this combined effect of age and sex could explain inconsistencies found in previous studies that considered only sex and not also age-stratified effects. Previous data on the prevalence of anhedonia during the life span are scarce. A previous study reported a progressive increase in anhedonia during adolescence and adulthood, followed by a decrease.[22] However, this sample was poorly comparable to our study, as it was extracted from the general population. Although the higher prevalence of TRD among middle-aged women has been previously reported,[50] the role of anhedonia as a possible predictor of poor response has not yet been defined in this group of patients. From a biological point of view, poor response to treatment in older women with A_MDD may be related to the depletion of circulating estradiol due to menopause, thus leading to a more severe and difficult-to-treat depression characterized by anhedonia.[51,52] However, the sex differences observed in anhedonia and TRD likely stem from a more complex interplay of biological, psychological, and social factors. Biologically, sex hormones like estrogen and progesterone play crucial roles in mood regulation, with differences expected to diminish after menopause. However, the persistence of these differences in women over 52, a predominantly postmenopausal age group, is intriguing and suggests that other factors might be at play. This could include neurobiological differences in brain regions associated with reward processing or alternative endocrine influences. The unexpected continuation of sex differences postmenopause highlights the need for further research into how these factors interact across the lifespan, particularly in understanding the hormonal and nonhormonal mechanisms that might drive these differences in older adults. The findings suggest that sex differences in anhedonia and TRD could inform more personalized treatment approaches. For women, especially those postmenopause, clinicians might consider the role of hormonal fluctuations and their impact on mood, potentially incorporating hormone therapy or targeting specific neurobiological pathways. For men, addressing different coping mechanisms or social factors could be key. Overall, recognizing these sex-specific differences can lead to more tailored and effective treatment strategies, improving outcomes for both men and women with TRD.

Some limitations should be mentioned when interpreting our findings. First, the presence of anhedonia was evaluated with the MADRS item 8 and not with a questionnaire or scale specifically developed and validated for the assessment of anhedonia. However, as detailed in the Methods section, it demonstrated to be a substantial valid proxy for anhedonia, though not covering the whole anhedonia domain. In addition, the MADRS to assess symptoms at baseline was administered retrospectively. Therefore, we cannot exclude the possibility of recall bias, though retrospective depression assessment has been demonstrated to be substantially reliable.[53] Although we controlled for possible confounders, the independence of treatment resistance predictors from other variables is difficult to assess, given that many clinical features are reciprocally correlated. As an example, anhedonia may increase suicidal behaviors[11,12]; therefore, it may not be correct to include it into multivariate models. However, multivariate models helped to at least partition the variance explained at a cross-sectional level; furthermore, machine learning analyses may help in controlling reciprocal effects.[54] Furthermore, our sample was not specifically recruited for this study, which is a secondary analysis. The sample was recruited to investigate the clinical and genetic correlates of TRD, with a numerical balance of responders, nonresponders, and TRD. The sample is therefore not representative of the general population of depressed subjects because of an excess of nonresponders and TRD (76.4%). While this may on one hand reduce the representativeness of the sample, and on the other hand, it offers more power for detecting differences across the outcome groups. In the present study, results were not corrected for multiple comparisons due to the strong previous evidence of a detrimental effect of anhedonia in depression and its outcome, and because of our interest in investigating the impact of anhedonia on depressive features and outcomes in a detailed and fine-grained way. However, also applying a strict Bonferroni correction, the main finding on treatment outcome remains significant, with the exception of the model including overall baseline depressive severity. This is not surprising given the correlation of anhedonia with overall depressive severity; however, the nominal significance of the multivariate model, including baseline depressive severity, may suggest that anhedonia has a partially independent modulating effect on treatment outcome. Univariate analyses with clinical and demographic variables also showed associations with anhedonia that are partly due to baseline depressive severity, however,

as previously mentioned, given the reciprocal correlations with anhedonia makes it difficult to disentangle unique effects. Finally, the naturalistic design of our study may have influenced our findings. Specifically, the lower rate of SSRI prescriptions in anhedonic patients likely reflects current prescribing practices,[5] given the potential emotional blunting induced by SSRIs and their limited efficacy on anhedonia.[55] However, this potential bias might have reduced the observed association with poor response, not the opposite.

In conclusion, our findings support the role of anhedonia as a key modulating feature of MDD, associated with a more severe depression profile and serving as an independent predictor of nonresponse/TRD. Future research should explore the mechanisms underlying persistent sex differences in anhedonia and TRD in postmenopausal women, focusing on hormonal, neurobiological, and psychosocial factors. Longitudinal studies examining these differences across various life stages, particularly before, during, and after menopause, are needed to provide deeper insights. Additionally, research into personalized treatment approaches based on sex-specific factors could enhance therapeutic outcomes for TRD.

Supplementary Material

Supplementary data are available at *International Journal of Neuropsychopharmacology* (IJNPPY) online.

Acknowledgments

We thank research teams working at the mental health centers of the GSRD consortium in Austria, Belgium, France, Germany, Greece, Israel, Italy, and Switzerland. We also thank the authors of previous publications in this dataset. However, our warmest thanks go to all the patients who agreed to participate in the study and to all their families.

Author Contributions

Antonina Luca (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Methodology [equal], Software [equal], Writing—original draft [equal], Writing—review & editing [equal]), Maria Luca (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Siegfried Kasper (Conceptualization [equal], Investigation [equal], Methodology [equal], Project administration [equal], Writing—review & editing [equal]), Basilio Pecorino (Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Joseph Zohar (Conceptualization [equal], Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Daniel Souery (Conceptualization [equal], Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Stuart Montgomery (Conceptualization [equal], Data curation [equal], Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Panagiotis Ferentinos (Conceptualization [equal], Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Dan Rujescu (Conceptualization [equal], Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Antonino Messina (Investigation [equal], Writing—review & editing [equal]), Raffaella Zanardi (Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Raffaele Ferri (Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Mariangela Tripodi (Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Bernhard Baune (Conceptualization [equal], Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Giuseppe Fanelli (Investigation [equal], Visualization [equal], Writing—review & editing [equal]), Chiara Fabbri (Investigation [equal], Methodology [equal], Visualization [equal], Writing—review & editing [equal]), Julien Mendlewicz (Investigation [equal], Visualization [equal], Writing—review & editing [equal]), and Alessandro Serretti (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Software [equal], Supervision [equal], Writing—original draft [equal], Writing—review & editing [equal]).

Funding

Bernhard T. Baune, Chiara Fabbri, and Alessandro Serretti received support from Psych-STRATA, a project funded from the European Union's Horizon Europe research and innovation program under Grant Agreement No. 101057454.

Conflict of Interest

Dr Rujescu served as a consultant for Janssen, received honoraria from Boehringer Ingelheim, Gerot-Lannacher, Janssen, and PharmaGenetix, received research/travel support from Angelini, Boehringer Ingelheim, Janssen, and Schwabe, and served on advisory boards of AC Immune, Boehringer Ingelheim, Roche, and Rovi. Dr Souery has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GlaxoSmithKline, Jazz, and Solvay. Dr Montgomery has served as a consultant or on advisory boards for AstraZeneca, BioNevia, Bristol Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, PharmaNeuroBoost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis, and Wyeth. Dr Serretti has served as a consultant or speaker for Abbott, AbbVie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, InnovaPharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier, and Taliaz. Dr Kasper has received grant/research support from Lundbeck; he has served as a consultant or on advisory boards for Angelini, Biogen, Esai, Janssen, IQVIA, Lundbeck, Mylan, Recordati, Sage and Schwabe; and he has served on speakers bureaus for Aspen Farmaceutica S.A., Angelini, Biogen, Janssen, Lundbeck, Neuraxpharm, Recordati, Sage, Sanofi, Schwabe, Servier and Sun Pharma. Dr Baune received honoraria for serving as a consultant or on advisory boards for Angelini, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Janssen, LivaNova, Lundbeck, Medscape, Neurotorium, Novartis, Otsuka, Pfizer, Recordati, Roche, Rovi, Sanofi, Servier, and Teva. The other authors declare no potential conflicts of interest.

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5-TR. American Psychiatric Association Publishing, 2022.
2. Naguy A, Alwetayan S, AlKhadhari S. Anhedonia as a transdiagnostic construct. Asian J Psychiatr. 2020;48:101604.
3. Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH. Assessing anhedonia in depression: potentials and pitfalls. Neurosci Biobehav Rev. 2016;65:21–35.
4. Wang S, Leri F, Rizvi SJ. Anhedonia as a central factor in depression: neural mechanisms revealed from preclinical to clinical evidence. Prog Neuropsychopharmacol Biol Psychiatry. 2021;110:110289.
5. Serretti A. Anhedonia and depressive disorders. Clin Psychopharmacol Neurosci. 2023a;21:401–409.
6. Cao B, Zhu J, Zuckerman H, *et al*. Pharmacological interventions targeting anhedonia in patients with major depressive disorder: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2019b;92:109–117.
7. Buckner JD, Joiner TE, Jr, Pettit JW, *et al*. Implications of the DSM's emphasis on sadness and anhedonia in major depressive disorder. Psychiatry Res. 2008;159:25–30.
8. Lemke MR, Puhl P, Koethe N, Winkler T. Psychomotor retardation and anhedonia in depression. Acta Psychiatr Scand. 1999;99:252–256.
9. Lin J, Su Y, Rizvi SJ, *et al*. Define and characterize the anhedonia in major depressive disorder: an explorative study. J Affect Disord. 2022;313:235–242.
10. Ducasse D, Loas G, Dassa D, *et al*. Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. Depress Anxiety. 2018;35:382–392.
11. Bonanni L, Gualtieri F, Lester D, *et al*. Can anhedonia be considered a suicide risk factor? A review of the literature. Medicina. 2019;55:458.
12. Auerbach RP, Pagliaccio D, Kirshenbaum JS. Anhedonia and suicide. Curr Top Behav Neurosci. 2022;58:443–464.
13. Spijker J, Bijl RV, de Graaf R, Nolen WA. Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand. 2001;103:122–130.
14. Vinckier F, Gourion D, Mouchabac S. Anhedonia predicts poor psychosocial functioning: results from a large cohort of patients treated for major depressive disorder by general practitioners. Eur Psychiatry. 2017;44:1–8.
15. Vrieze E, Demyttenaere K, Bruffaerts R, *et al*. Dimensions in major depressive disorder and their relevance for treatment outcome. J Affect Disord. 2014;155:35–41.
16. McMakin DL, Olino TM, Porta G, *et al*. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. J Am Acad Child Adolesc Psychiatry. 2012;51:404–411.
17. Gabbay V, Johnson AR, Alonso CM, *et al*. Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. J Child Adolesc Psychopharmacol. 2015;25:194–200.
18. Liu X, Read SJ. Development of a multivariate prediction model for antidepressant resistant depression using reward-related predictors. Front Psychiatry. 2024;15:1349576.
19. Wilkowska A, Wiglusz MS, Gałuszko-Wegielnik M, Włodarczyk A, Cubała WJ. Antianhedonic effect of repeated ketamine infusions in patients with treatment resistant depression. Front Psychiatry. 2021;12:704330.
20. Pettorruso M, Guidotto R, d'Andrea G, *et al*.; REAL-ESK Study Group. Predicting outcome with Intranasal Esketamine treatment: a machine-learning, three-month study in Treatment-Resistant Depression (ESK-LEARNING). Psychiatry Res. 2023;327:115378.
21. Khazanov GK, Xu C, Dunn BD, Cohen ZD, DeRubeis RJ, Hollon SD. Distress and anhedonia as predictors of depression treatment outcome: a secondary analysis of a randomized clinical trial. Behav Res Ther. 2020;125:103507.
22. Dodell-Feder D, Germine L. Epidemiological dimensions of social anhedonia. Clin Psychol Sci. 2018;6:735–743.
23. Adewuya AO, Coker OA, Atilola O, *et al*. Gender difference in the point prevalence, symptoms, comorbidity, and correlates of depression: findings from the Lagos State Mental Health Survey (LSMHS), Nigeria. Arch Womens Ment Health. 2018;21:591–599.
24. Wang X, Xia Y, Yan R, *et al*. The sex differences in anhedonia in major depressive disorder: a resting-state fMRI study. J Affect Disord. 2023;340:555–566.
25. Dold M, Kautzky A, Bartova L, *et al*. Pharmacological treatment strategies in unipolar depression in European tertiary psychiatric treatment centers—a pharmacoepidemiological cross-sectional multicenter study. Eur Neuropsychopharmacol. 2016;26:1960–1971.
26. Bartova L, Dold M, Kautzky A, *et al*. Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice. World J Biol Psychiatry. 2019;20:427–448.
27. Panariello F, Kasper S, Zohar J, *et al*. Characterisation of medication side effects in patients with mostly resistant depression in a real-world setting. World J Biol Psychiatry. 2023;24:439–448.
28. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–389.
29. Billones RR, Kumar S, Saligan LN. Disentangling fatigue from anhedonia: a scoping review. Transl Psychiatry. 2020;10:273.
30. Diaz AP, Fernandes BS, Teixeira AL, *et al*. White matter microstructure associated with anhedonia among individuals with bipolar disorders and high-risk for bipolar disorders. J Affect Disord. 2022;300:91–98.
31. Cao B, Park C, Subramaniapillai M, *et al*. The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. Front Psychiatry. 2019a;10:17.
32. McIntyre RS, Loft H, Christensen MC. Efficacy of vortioxetine on anhedonia: results from a pooled analysis of short-term studies in patients with major depressive disorder. Neuropsychiatr Dis Treat. 2021;17:575–585.
33. Ameli R, Luckenbaugh DA, Gould NF, *et al*. SHAPS-C: the Snaith-Hamilton pleasure scale modified for clinician administration. PeerJ. 2014;2:e429.
34. StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.
35. Rizvi SJ, Cyriac A, Grima E, *et al*. Depression and employment status in primary and tertiary care settings. Can J Psychiatry. 2015;60:14–22.
36. Tan K, Jarnecke AM, South SC. Social anhedonia, communication, and marital satisfaction in newlywed couples. J Pers. 2023;91:1239–1252.
37. Chiera M, Draghetti S, Ronchi DD, *et al*. Hyperthyroidism and depression: a clinical case of atypical thyrotoxicosis manifestation. Int Clin Psychopharmacol. 2023;38:269–272.

38. Fan T, Luo X, Li X, *et al*. The association between depression, anxiety, and thyroid disease: a UK Biobank prospective cohort study. Depress Anxiety. 2024;2024:8000359.
39. Su M, Li E, Tang C, Zhao Y, Liu R, Gao K. Comparison of blood lipid profile/thyroid function markers between unipolar and bipolar depressed patients and in depressed patients with anhedonia or suicidal thoughts. Mol Med. 2019;25:51.
40. Gruber J, Hanssen R, Qubad M, *et al*. Impact of insulin and insulin resistance on brain dopamine signalling and reward processing—an underexplored mechanism in the pathophysiology of depression? Neurosci Biobehav Rev. 2023;149:105179.
41. Possidente C, Fanelli G, Serretti A, Fabbri C. Clinical insights into the cross-link between mood disorders and type 2 diabetes: a review of longitudinal studies and Mendelian randomisation analyses. Neurosci Biobehav Rev. 2023;152:105298.
42. Kasyanov E, Pinakhina D, Rakitko A, *et al*. Genetic associations of anhedonia: insights into overlap of mental and somatic disorders. Consort Psychiatr. 2024;5:5–15.
43. Reagan LP, Cowan HB, Woodruff JL, *et al*. Hippocampal-specific insulin resistance elicits behavioral despair and hippocampal dendritic atrophy. Neurobiol Stress. 2021;15:100354.
44. Brouwer A, van Raalte DH, Lamers F, Rutters F, Elders PJM, Van Someren EJW, Snoek FJ, Beekman ATF, Bremmer MA. Insulin resistance as a marker for the immune-metabolic subtype of depression. J Affect Disord. 2021;295:1371–1376.
45. Hamer JA, Testani D, Mansur RB, *et al*. Brain insulin resistance: a treatment target for cognitive impairment and anhedonia in depression. Exp Neurol. 2019;315:1–8.
46. Fanelli G, Serretti A. Depression, antidepressants, and insulin resistance: which link? Eur Neuropsychopharmacol. 2022;60:4–6.
47. Serretti A. The interplay of psychopharmacology and medical conditions. Int Clin Psychopharmacol. 2023b;3:365–388.
48. Scala M, Fanelli G, Ronchi DD, *et al*. Clinical specificity profile for novel rapid acting antidepressant drugs. Int Clin Psychopharmacol. 2023;38:297–328.
49. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. Transl Psychiatry. 2014;4:e469.
50. Liu X, Mukai Y, Furtek CI, Bortnichak EA, Liaw K-L, Zhong W. Epidemiology of treatment-resistant depression in the United States. J Clin Psychiatry. 2021;83:21m13964. doi:10.4088/JCP.21m13964
51. Vivian-Taylor J, Hickey M. Menopause and depression: is there a link? Maturitas. 2014;79:142–146.
52. Serretti A. Modulating factors in mood disorders treatment. Int Clin Psychopharmacol. 2024;39:47–50.
53. Birk SL, Olino TM, Klein DN, Seeley JR. Validity of retrospectively-reported depressive episodes. J Affect Disord. 2020;277:908–913.
54. Kautzky A, Dold M, Bartova L, *et al*. Refining prediction in treatment-resistant depression: results of machine learning analyses in the TRD III Sample. J Clin Psychiatry. 2018;79:16m11385. doi:10.4088/JCP.16m11385
55. Serretti A, Calati R, Goracci A, Di Simplicio M, Castrogiovanni P, De Ronchi D. Antidepressants in healthy subjects: what are the psychotropic/psychological effects? Eur Neuropsychopharmacol. 2010;20:433–453.