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Prevalence of anhedonia in women with deep endometriosis

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Anhedonia, characterized by diminished motivation and pleasure sensitivity, is increasingly recognized as prevalent among patients with chronic pain. Deep Endometriosis (DE), the most severe endophenotype of the disease, is commonly presented with chronic pelvic pain. This cross-sectional study reports, for the first time, the prevalence of anhedonia in a sample comprised by 212 premenopausal women with suspected DE referred to a tertiary hospital. Our findings show that 27,8% [95% CI 22.1, 26.5] of DE patients experience abnormal hedonic tone. Severity of DE pain-related symptoms significantly correlated with anhedonia, consistent with previous findings. Chronic pelvic pain emerged as a significant predictor of anhedonia (OR 1.5, 95% CI 1.0–1.22, $p < 0.05$) with the odds increasing to 2.28 [95% CI 1.12, 4.23] when pain was severe. The most affected areas in DE patients were interests, social interaction and food pleasure. The present results are representative of DE patients under multimodal treatment, limiting generalizability. Overall, our study highlights the impact of chronic pain on hedonic functioning in DE. Therapeutic approaches targeting hedonic capacity in DE patients are crucial for restoring health and well-being.

Keywords Anhedonia, Endometriosis, Deep endometriosis, Chronic pelvic pain, Chronic pain, Inflammation

Anhedonia is traditionally defined as a diminished ability to experience pleasure derived from sensory experiences or social interactions. It is considered a transdiagnostic symptom present in mental health disorders such as schizophrenia and substance use disorders, and also one of the most reliable behavioral endophenotypes for depression[1,2]. Regarding therapeutic approaches, anhedonia presents resistance to change and a poor response to antidepressant medication with a potential to worsen as a negative consequence of treatment[3–5]. In 2008, the APA RDoC (American Psychiatric Association Research Domain Criteria), a research framework based on a dimensional approach to mental health that aims to overcome the traditional categorical perspective in psychiatry, considered anhedonia as a behavioral correlate of the negative valence system responsible of the responses to aversive situations such as fear, anxiety, or loss.

Anhedonia is not a unitary concept and is not solely related to the loss of pleasure. Its presence represents a myriad of multifaceted reward-related deficits involving multiple complex psychological processes, such as: (i) reward valuation, (ii) behavioral motivation (i.e., anticipation of pleasure), (iii) affective responses (i.e., liking), and (iv) learning mechanisms that may lead to seeking and interacting with specific reward stimuli in the future. The study of the neural bases of the reward system using neuroimaging techniques has identified a systematic network of dopamine regulated mesocorticolimbic areas involved in regulating the impact and anticipation of hedonic experiences[6–9].

In recent years, studies have begun to address the presence of anhedonia in samples affected by chronic pain and neurological diseases demonstrating a steady relationship between them[10,11]. In 2020, Trøstheim and colleagues published a systematic review and meta-analysis of anhedonia in adults with and without mental illness, demonstrating higher anhedonia levels in persons with chronic pain and Parkinson's disease than in healthy controls[12]. In the same year, Garland and colleagues, by means of a sample of chronic pain patients, demonstrated that 25% reported anhedonia scores above the standard cut-off compared to a well-matched

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large sample of healthy controls. Importantly, these results were independent from a Major Depressive Disorder diagnosis, revealing a more nuanced relationship between anhedonia and health than the traditional assumption of anhedonia as a precursor to an underlying mental health disorder.

Endometriosis has traditionally been considered a benign chronic gynecological disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process[13]. However, current specialists in the field advocate for an expansion of this perspective in order to capture the multifaceted effects of the disease throughout the body[14]. In this sense, endometriosis can be also characterized as a chronic, systemic, inflammatory disease affecting 10% of biological females of reproductive age worldwide. Although clinical presentation varies considerably, studies indicate that 40% to 87% of patients report chronic pelvic pain, making it the leading identified cause[15]. Diagnosis delay, 10 years on average, and misdiagnosis are common issues faced by patients. These challenges are partly explained by the complex nature of the disease and, most significantly, by social normalization of dysmenorrhea[14,16,17]. Within endometriosis, deep endometriosis (DE) represents the most severe phenotype of the illness. DE is diagnosed when endometriotic lesions penetrate deeper than 5 mm under the peritoneal surface. This form of the disease can disrupt the functionality of vital organs such as urinary bladder, ureters, and bowel. DE is usually associated with severe pelvic pain, dysmenorrhea and other pain symptoms and can be more aggressive than in other types of endometrioses, and may even lead to irreversible severe complications. The diagnose and multidisciplinary treatment of these type of endometriosis are often challenging[18–20].

Beyond its physical symptoms, endometriosis patients present psychological distress and may develop mental health disorders. Previous studies have consistently found a significantly higher prevalence of depression and anxiety in this population compared to healthy controls[21]. In 2021, a systematic review and meta-analysis reported a prevalence of 28.9% and 31% for depression and anxiety, respectively. Regarding full-blown comorbid psychiatric disorders, Chen and colleagues (2016), utilizing the Taiwan National health Insurance research Database, identified an increased risk of developing Major Depressive Disorder and Anxiety Disorders (hazard ratio: 1.56, 95%, CI 1.24–1.97 and 1.44, 95% CI 1.22–1.70 respectively)[22]. Additionally, the same group reported an increased prevalence of bipolar disorders in this population[23]. Further studies aiming to address psychological impact of endometriosis in a more detailed and explicative manner have reported disrupted perceptions of the self, low self-esteem, problems with emotional self-efficacy, and reduced optimism[24,25]. Interestingly, the literature highlights chronic pelvic pain as the main symptom contributing to psychological distress severity and detrimental quality of life[26,27].

Interestingly, stress, and particularly chronic stress, has been claimed as a contributing factor to the proliferation of endometriotic lesions and inflammatory parameters as demonstrated in rodent studies. Clinical findings also indicate that endometriosis is associated with chronic levels of stress largely attributed to the daily experience of symptoms, particularly pain-related ones, and their impact on personal, relational and social aspects of life[28,29]. Furthermore, prologued stress, specially involving social rejection or defeat, is associated with reduced hedonic capacity and impaired reward motivation and learning. Additionnally, social anhedonia has been observed in sickness states along with elevated inflammation markers in experimental human studies, with females presenting heightened susceptibility[30,31]. Overall, these findings suggest that stress plays a role both in exacerbating endometriosis and contributing to the development of anhedonia.

Overall, the psychosocial impact of endometriosis is widely recognized throughout the scientific literature[14,24,26]. However, despite the wealth of data demonstrating the deleterious effects of this condition on wellbeing and mental health, no model has successfully integrated the psychological correlates of endometriosis with the specific effects of stress on the disease symptoms, consequently, the resulting perspective has limited clinical explanatory potential[24,32]. The present study aims to stablish an initial step in this direction by estimating, for the first time, the prevalence of anhedonia in a large sample of DE patients receiving multidisciplinary treatment at a tertiary hospital. In this regard, we hypothesized that women with DE would present levels of anhedonia comparable to those observed in previous reported samples with chronic pain[12]. Ultimately, we also predicted that anhedonia would be associated with pain severity as well as with an increased presence of diverse pain symptoms including not only chronic pelvic pain, but also dysuria, dyschezia, and dyspareunia.

Materials and methods

Participants

Participants were recruited during an in-person specialized gynecological endometriosis consultation in a tertiary hospital. Participants were required to have a diagnosis of DE obtained surgically or via a high-resolution transvaginal ultrasound. After giving informed consent, participants were sent an online survey containing self-reported sociodemographic, endometriosis, and psychological variables relevant for the study. The study received ethical approval from our center previous to sample recruitment (HCB/2021/0674). The sample recruitment was conducted consecutively in a 7-month period, form September 2022 to March 2023. All procedures involving participants were conducted in accordance with the ethical standards of the Ethics Committee for Drug Research of Hospital Clínic and with the 1964 Helsinki Declaration and its later amendments.

All the participants underwent a clinical examination and a two—or three- dimensional transvaginal ultrasound (TVU) using and endovaginal probe (type RIC5-9, Voluson S10; GE Healthcare, Milwaukee, WI, USA). The ultrasound examination was performed to diagnose the presence of DE, as it has been reported that a systematic evaluation of endometriosis by TVU can accurately replace diagnostic laparoscopy[33]. For patients with DE, description of the sonographic features of the different phenotypes of endometriosis lesions was performed, following the consensus guidelines stablished by the International Deep Endometriosis Analysis (IDEA group)[33]. All patients with previous surgeries were classified as stage IV of the rASRM classification.

Patients were excluded if they had a history of past or present malignancy, endocrine, severe psychiatric disorders (psychoses, bipolar disorders and substance abuse disorders), neurodegenerative disorders,

cardiovascular and systemic diseases, premature ovarian failure or menopausal status, endometrial hyperplasia or polyps, uterine leiomyomata, adenomyosis, having had an inflammatory disease or infectious conditions ≤6 months and comorbid pain syndromes such as chronic migraines, irritable bowel syndrome, bladder pain syndrome, central sensitization or fibromyalgia. Neurodegenerative diseases and psychiatric disorders were excluded for their potential impact on behavioral assessment.

Measures

Anhedonia was assessed using the Snaith-Hamilton Scale (SHAPS). The SHAPS is considered a gold standard for measuring anhedonia. It consists of 14 items covering four domains of hedonic experience: interests, social interactions, food/drink, and sensory experiences. Each item is self-rated using a Likert scale with four alternatives indicating level of agreement with the statement (definitely/strongly agree, agree, disagree and strongly disagree). Total scores can range from 14 to 56, with higher scores indicating higher anhedonia[34]. Internal reliability of the SHAPS has been demonstrated previously in chronic pain samples with alpha coefficient ranging from 0.78 to 0.92. An alternative scoring method for the SHAPS collapses "agree" responses as a score of 1, and "disagree" responses as 0, resulting in a total score ranging from 0 to 14, where higher punctuations indicate higher anhedonia[10,12,34] A punctuation of 3, in this short scoring format, is considered the limit between a normal and an abnormal hedonic tone[34].

Four items of the BDI-II were used as a secondary measure of anhedonia (Beck Depression Inventory–II, 1996). The BDI-II is a gold-standard scale for measuring depression and includes 4 items related to the loss of pleasure, which have been considered an alternative method for assessing anhedonia in both clinical and healthy samples[35]. The subscale comprises items assessing loss of pleasure (item 4), loss of interest (item 12), loss of energy (item 15), and loss of interest in sex (item 21). Scores on this subscale range from 0 to 12, with higher scores indicating higher anhedonia.

Depression and anxiety were also assessed using the "Hospital Anxiety and Depression Scale" (HADS). The HADS is a 14-item scale comprising 7 statements measuring depression and the remaining 7 anxiety. Respondents rated each statement according to the frequency experienced during the past week. The HADS has previously been used with endometriosis samples[24]. The total score of both subscales ranges from 0 to 21, with higher scores indicating higher severity of depression or anxiety. Additionally, the HADS allows obtaining a total score.

Endometriosis clinical profile of patients was assessed by using a comprehensive endometriosis symptom list graded by participants based on their perceived severity of symptoms. Participants utilized an 11-point Numerical Self-Rating Scale (NRS) ranging from 0: "absence of symptom" to 10: "the highest severity ever experienced". The 11-point NRS is a widely measure for assessing chronic pain severity[36,37]. The symptom list included the following items: (1) heavy menstrual bleeding (HMB), (2) gastrointestinal symptoms during menstruation, (3) fatigue, (4) dyschezia, (5) dysuria, (6) dyspareunia, (7) periovulation pain, (8) dysmenorrhea, (9) chronic pelvic pain, and (10) abnormal uterine bleeding (AUB). Additionally, (11) infertility was assessed in a single item asking participants if they have found themselves unable to achieve pregnancy after attempting, at least, for one consecutive year.

Finally, we created a composite measure, the pain severity subscale, by summing all DE pain-related symptoms: (1) dyschezia, (2) dysuria, (3) dyspareunia, (4) periovulation pain, (5) dysmenorrhea, and (6) chronic pelvic pain. The rationale for this composite measure is based on the understanding that patients experience these symptoms with varying pain profiles and intensities, both across different symptoms and throughout the progression of the disease. This scale was comprised by the sum of the NRS given to each individual pain-related symptom. Therefore, the subscale presents a range from 0 to 60, with higher scores indicating a more intense experience of pain.

Data analysis

Descriptive analysis, sample size calculation and prevalence estimates

The mean and standard deviation (SD) were calculated for the quantitative variables: age, endometriosis symptoms score (measured with the 11-point NRS), anxiety and depression scores (measured with HADS), and anhedonia score (measured with SHAPS and BDI-II). Absolute frequencies and percentages were calculated for the categorical variables: level of studies, previous pregnancy, civil status, infertility, previous surgery, hormonal treatment, the presence of severity in the endometriosis symptoms (scoring NRS ≥ 7; a cutoff stablished for chronic pain severity by Oldenmenger[38]), and the presence of anhedonia measured with SHAPS (scoring > 2 is considered the limit between normal and abnormal hedonic functioning[34]).

Regarding sample size, with a confidence level of 95% and taking as reference the 17.6% prevalence of anhedonia in patients with inflammatory bowel diseases and chronic abdominal pain[39], we estimated that 223 patients with DE would be needed in order to reach a statistically accurate prevalence of anhedonia in deep endometriosis.

Prevalence is provided by means of a percentage with a 95% confidence interval.

Correlation and logistic regression analysis

To explore the direction and strength of the association between anhedonia and the clinical profile of patients we conducted an exploratory correlation analysis and developed a predictive logistic regression model. The anhedonia scores (both from SHAPS and BDI-II) were correlated with the scores of all endometriosis symptoms (heavy menstrual bleeding, gastrointestinal symptoms, fatigue, dysuria, dyschezia, dyspareunia, dysmenorrhea, pain during ovulation, abnormal uterine bleeding, and chronic pelvic pain), as well as with the pain severity subscale. We used Spearman's test to check correlations since anhedonia scores showed a nonparametric distribution.

Logistic regression models were conducted to assess the likelihood of developing anhedonia based on the intensity of pain, as reflected both by the composite measure and the single chronic pelvic pain symptom. Anhedonia was treated as a binary variable, utilizing the short correction of the SHAPS, with a score of 3 as the cutoff for abnormal hedonic tone. Both the pain severity scale and the single chronic pelvic pain item were treated as continuous variables in the model. Additionally. we conducted a third model treating chronic pelvic pain as binary variable, using an NRS score of 7 or higher as the cutting point.

The descriptive, correlation and regression statistical analyses were conducted using the R (version 4.2.2) and RStudio (version 2022.12.0 + 353), and the level of significance was set at 0.05.

Comparison of anhedonia levels considering chronic pelvic pain severity

In order to provide a clearer understanding of how more severe chronic pelvic pain may impact patients' mental state, we compared patients with higher pain severity to those with less pain. Specifically, we compared anhedonia, anxiety, and depression scores between patients reporting high chronic pelvic pain severity (NRS ≥ 7) and those reporting lower severity (NRS < 7). We applied t-test to assess the differences between both groups.

Item level analysis: dimensions of pleasure affected in deep endometriosis

To assess whether patients with different levels of pain experience anhedonia for the same types of pleasures, we conducted an exploratory item-level comparison of anhedonia scores among DE patients with greater (NRS ≥ 7) or lesser (NRS < 7) severity of chronic pelvic pain. Table S1 (included in the Supplementary materials), shows the mean and 95% CI for each anhedonia item (from SHAPS and BDI-II), accompanied by forest plots (Figs. 4 and 5). To provide a reference level of anhedonia in other chronic pain populations, we also included data from a meta-analytical chronic pain sample[12].

Results

A total of 225 consecutive women diagnosed with DE were enrolled in the study (see Table 1). Of these, we finally gathered information from 212 patients that completed all the questionnaires. 13 patients completed the questionnaires partially and therefore were excluded from the analysis here presented. Mean age of participants was 40 years old, being 36% of the sample previously pregnant. From the total sample, 47.6% reported infertility problems, 64.8% were taking hormonal treatment, and 38.7% had undergone surgery, with 16.2% reporting multiple surgery interventions. All recruited patients had DE lesions confirmed by TVS. Additionally, 49 patients had concomitant ovarian endometriomas (OE): 12 cases of right OE, 28 cases of left OE, and 9 cases of bilateral OE. Seventy-eight patients had undergone previous surgeries for DE lesions. Among them, 54% had surgical treatment for OE, and 32% had treatment for superficial endometriosis.

Regarding the endometriosis symptom profile, dysmenorrhea and fatigue were reported by 75% of the sample with both symptoms obtaining the highest NRS severity: 7.3 and 7.2, respectively. Gastrointestinal symptoms during menstruation were present in 67% of patients with a mean NRS severity score of 7. Half of the sample reported symptoms of dyspareunia, pain during ovulation, and abnormal uterine bleeding, with means NRS scores of 6.1 for the first two symptoms, and 5.6 for abnormal uterine bleeding. Around 40% of patients reported dyschezia. Dysuria was the symptom less reported (15.56%). Chronic pelvic pain was reported by almost 40% of DE patients, with an average mean of 5.

Prevalence of anhedonia in deep endometriosis

The SHAPS mean scores (± SD) for the sample was 24.2 (± 8.1) and 2 (± 3.1) for the long and short scoring versions, respectively. A total of 27,8% [95% CI: 22.1, 26.5] of women with DE were considered anhedonic (see distribution of scores depicted in Fig. 1). A Cronbach Alpha of 0.94 was obtained for the SHAPS scores indicating high internal reliability of the measure.

Our sample obtained a mean score of 10.3 (± 4.66) for anxiety and 6.99 (± 4.51) for depression, indicating moderate scores in both measures without reaching the clinical cutoff point of 11 for depression and anxiety[40]

Correlation of anhedonia with endometriosis symptoms: the predictive value of chronic pelvic pain

A very robust correlation was observed between the two anhedonia measures used in the present investigation (SHAPS and BDI-II anhedonia subscale). Considering the relation between anhedonia and pain, at least five of the endometriosis pain-related symptoms (dysuria, dyschezia, dyspareunia, pain during ovulation, and chronic pelvic pain) systematically correlated significantly with the three measures of anhedonia (see Fig. 2). The strongest correlation was obtained with the pain severity subscale, which reflects the contribution of the different pain symptoms (with a range of 0.31–0.33). Importantly, we did not observe strong correlations between fatigue and anhedonia (except a marginal correlation with the BDI-II anhedonia subscale). Finally, the correlation matrix showed also a strong positive association between all pain-related symptoms and anhedonia.

The logistic regression models applied to our data showed good fit, with p-value < 0.05. For each unit increase in the NSR symptom scale, the odds of being part of the anhedonic group increses by a factor of 1.11 (95% CI [1.00, 1.22]). On the other hand, the pain severity composite scale indicated that for a unit increase in this measure, the odds of having an abnormal hedonic tone increase by a factor of 1.05 (95% CI [1.02,1.08]). The results, using chronic pelvic pain as a binary variable considering a NRS of 7 or above as the cutoff point, increased the odds of being part of the anhedonic group by a factor of 2.28 [95% CI: 1.12, 4.23].

Comparison of anhedonia levels considering chronic pelvic pain severity

A comparison of the levels of anhedonia, anxiety and depression was conducted between patients presenting severe chronic pelvic pain (NRS ≥ 7) and those who did not (NRS < 7) to gain a more nuanced understanding of

Deep endometriosis patients (N = 212)		
Demographic variables		
Age—*mean (SD)*	39.7 (7)	
Studies—*n (%)*		
Primary education	9 (4.2%)	
Secondary education	29 (13.7%)	
Professional degree	45 (21.2%)	
Bachelor's	76 (35.8%)	
Master's	48 (22.6%)	
Doctorate	5 (2.4%)	
Pregnancy – *n (%)*	75 (35.4%)	
Civil status (single / in couple / divorced) – *n (%)*	35 (16.6%) / 166 (78.7%) / 10 (4.7%)	
Endometriosis variables—*n (%)*		
Infertility (Y/N)	101 (47.6%)	
Previous surgery *(single surgery / multiple surgeries)*	55 (38.7%) / 23 (16.2%)	
Hormonal treatment (Y/N)	92 (64.8%)	
Symptoms of endometriosis	**NRS SCORE** ***mean (SD)***	**NRS ≥ 7** ***n (%)***
Abnormal uterine bleeding	5.6 (3.6)	109 (51.4%)
Gastrointestinal symptoms	7 (3)	142 (67%)
Fatigue	7.2 (2.9)	158 (74.5%)
Dysuria	2.3 (3.1)	32 (15.1%)
Dyschezia	4.8 (3.5)	85 (40.1%)
Dyspareunia	6.1 (3.2)	115 (54.2%)
Dysmenorrhea	7.3 (3.2)	159 (75%)
Pain during ovulation	6.1 (3.1)	117 (55.2%)
Heavy menstrual bleeding	2.8 (3.4)	41 (19.3%)
Chronic pelvic pain	5 (3.3)	81 (38.2%)
Pain severity subscale	31.5 (13.8)	127 (59.9%)
Emotional variables – *mean (SD)*		
Anxiety, HADS score	10.3 (4.6)	
Depression, HADS score	7 (4.5)	
Anhedonia (SHAPS 0–1) score	2 (3.1)	
Anhedonia prevalence (SHAPS ≥ 3) – *n (% [95% CI])*	59 (27.8% [95% CI: 22.1, 26.5])	
Anhedonia (SHAPS 1- 4) score	24.2 (8.1)	
Anhedonia (BDI-II subscale) score	9 (2.5)	

Table 1. Descriptive variables of the study group. Absolute frequencies and percentages are shown for the categorical variables. The mean and the SD are shown for the quantitative variables. The presence of severity in the endometriosis symptoms was defined following the cutoffs established for chronic pain severity by Oldenmenger[38], indicating severity of the symptom when scoring NRS ≥ 7. All participants completed the whole evaluation, except for three participants who did not answer the Anhedonia BDI-II subscale.

their psychological impact. As shown in Table 2, levels of anhedonia were significantly higher in those patients with severe chronic pelvic pain (mean ± SD = 26.62 ± 8.49) compared to those without chronic pelvic pain (mean ± SD = 22.70 ± 7.43). Anxiety and depression levels followed the same pattern, being significantly higher in the former group indicating that an increase in anhedonia is associated with a worse general mental state. Consistently, our DE sample showed higher punctuations in anxiety compared to depression in both cases.

Comparison of anhedonia in deep endometriosis with other chronic pain samples

A comparison of anhedonia measures with samples of individuals with chronic pain is displayed in Table 3 for illustrative purposes. These data have been selected from an anhedonia article that presented data across different chronic pain samples and conditions[10]. As a reference we have also included data on a meta-anality sample of healthy subjects to stablish a proxy level of hedonia in healthy individuals. As shown in Table 3, the endometriosis group obtained scores coherent with the rest of chronic pain samples. Interestingly, patients with severe chronic pelvic pain presented a marked increase in anhedonia scores as can be observed in both Table 3 and Fig. 3.

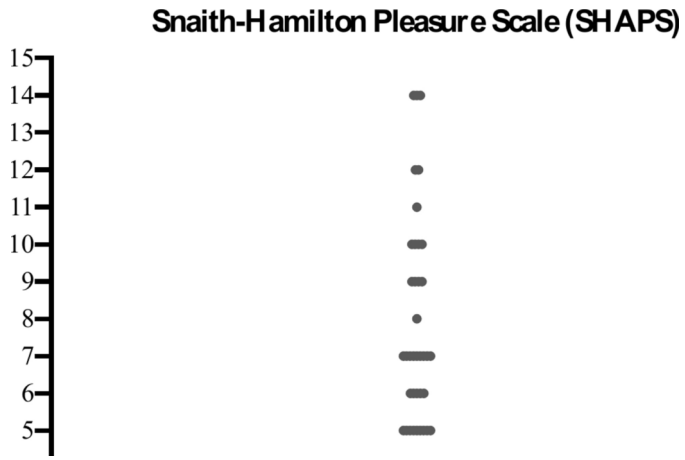

Fig. 1. Distribution of SHAPS (0–1) anhedonia scores in deep endometriosis sample. 27.8% of the sample presented significant alterations in the hedonic tome according to the SHAPS scale.

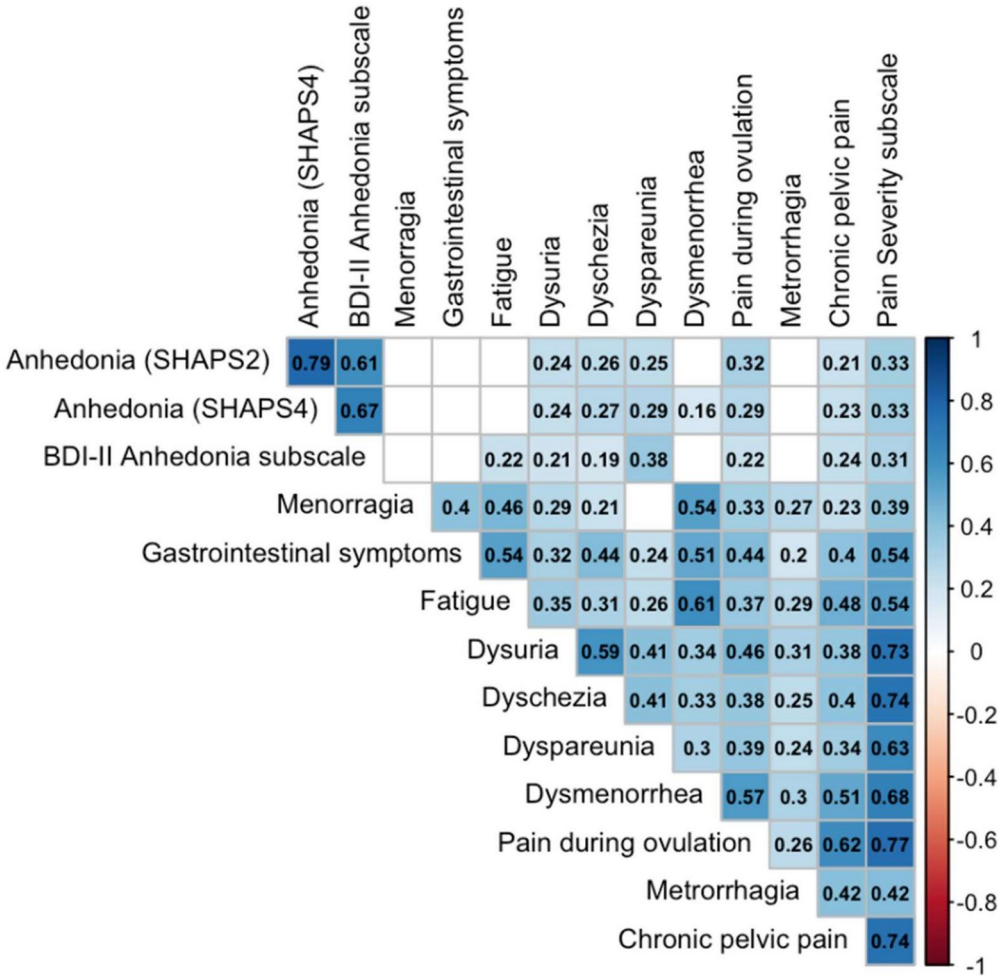

Fig. 2. Correlations between anhedonia and endometriosis symptoms. Significant correlation coefficients are shown for the group of women with endometriosis. $P < 0.05$. (SHAPS: Snaith-Hamilton Pleasure Scale; BDI-II: Beck Depression Inventory II).

	Chronic pelvic pain (NRS* ≥ 7) (n = 81)	Chronic pelvic pain (NRS < 7) (n = 131)	*p*-value
Anhedonia	26.62 ± 8.49	22.7 ± 7.43	0.001
Anxiety (HAD)	12.35 ± 4.38	9.04 ± 4.31	< 0.001
Depression (HAD)	8.81 ± 4.78	5.85 ± 3.95	< 0.001

Table 2. Comparison of patients reporting chronic pelvic pain NRS* ≥ 7 vs. NRS < 7. Means ± SD are presented for anhedonia measured by SHAPS (1-4 scoring), Anxiety (HADS-A) and depression (HADS-D). *NRS: Numeric Ragin Scale ranging from 0 to 10 with higher scores indicating higher intensity of pain.

	n	Age	Female	Primary pain condition	SHAPS (1–4)	SHAPS (0–1)	Anhedonia prevalence (%)
DE Total Sample	225	40 (10)	225 (100%)	Deep Endometriosis	24.2 [23.12, 25.29]	2 [1.58, 2.43]	27.83
DE Chronic pelvic pain sample (NRS > 7)	87	40 (6.9)	87 (100%)	Deep Endometriosis	26.62 [24.77, 28.47]	2.85 [2.07, 3.63]	38.27
Sample 1 Chronic Pain[10]	115	48.3 (13.6)	78 (68%)	Low back (56.5%) Fibromyalgia (20%)	24.40 [23.18, 25.62]	1.60 [1.12, 2.08]	19.1
Sample 2 Chronic Pain[10]	35	32.9 (8.4)	3 (9%)	Low back (68,6%)	25.12 [22.81 – 27.42]	2.30 [1.41, 3.19]	34.3
Sample 3 Chronic Pain[10]	282	52 (12.5)	178 (63%)	Low back (52,3%)	24.66 [23.81 – 25.51]	1.80 [1.50, 2.10]	28.5
Sample 4 Chronic Pain[10]	56	67.8 (9.7)	32 (57%)	Low back	23.91 [22.35 – 25.47]	1.30 [0.80, 1.80]	14
Chronic Abdominal Pain Sample40	120	40.80 (14.50)	57%	Inflammatory bowel dis	23.40 [22.90 – 23.90]	1.30 [1.03, 1.57]	17.6
Meta-analysis Sample Healthy Controls 12	6541	33.95 (11.34)	55%	Healthy Individuals	20.2 [19.7 – 20.8]	0.6 [0.4 – 0.8]	14

Table 3. SHAPS scores for chronic pain patients using both scoring methods (1–4) and (0–1). Data were extracted from studies addressing anhedonia in chronic pain patients[10]. Samples description include the number of participants, age, sex, and primary pain condition if known. Anhedonia measures, including means and confidence intervals (CI), along with prevalence values, are presented. Additionally, data from healthy participants taken from the anhedonia menta-analysis by Trøstheim[12] are included for illustrative purposes.

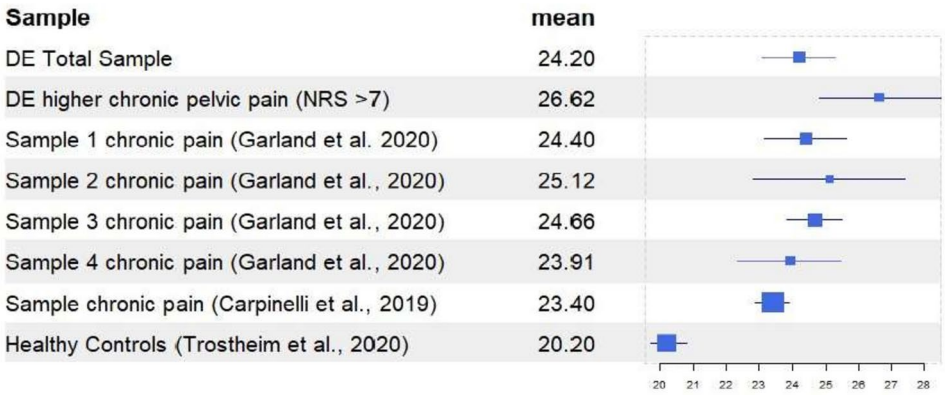

Fig. 3. Forest plot of anhedonia SHAPS measures (1–4 scoring), means and CI are plotted in blue. We present the anhedonia results from DE patients. Separately, we present the anhedonia scores of those DE patients suffering from severe chronic pelvic pain (NRS > 7). Additionally, anhedonia scores from previous studies examining chronic pelvic pain are included for comparison and illustrative purposes[10,12,39].

Item level analysis: dimensions of pleasure affected in deep endometriosis

To assess whether patients with different levels of pain experience anhedonia for the same types of pleasures, we conducted an exploratory item-level comparison of anhedonia scores among DE patients with greater (NRS ≥ 7) or lesser (NRS < 7) severity of chronic pelvic pain. Table S2 (included in the Supplementary Materials) shows the mean and 95% CI for each anhedonia item (from SHAPS and BDI-II). This information was used to plot Figs. 4 and 5, which appear throughout the present text. To facilitate comparison and as reference values, we also presented data from a meta-analytical chronic pain sample[12].

Discussion

Anhedonia is a behavioral trait characterized by a blunted reactivity to rewarding stimuli[1,41]. To the best of our knowledge, our study is the first to explore the presence of anhedonia in a large sample of DE patients. Our

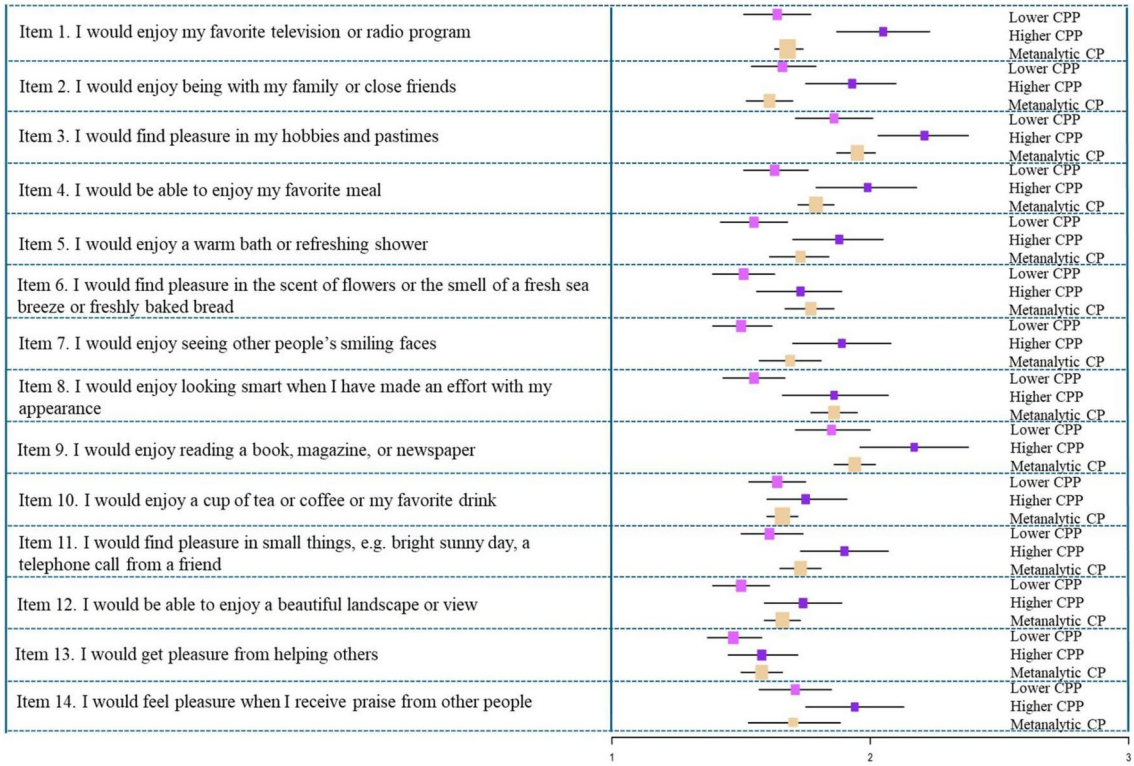

Fig. 4. Item-level analysis. Anhedonia SHAPS item-level analysis illustrating DE patients with high and chronic pelvic pain (NRS ≥ 7) and low chronic pelvic pain (NRS < 7), alongside a meta-analytical sample[12], for the sake of comparison. Means and CI are plotted for each group.

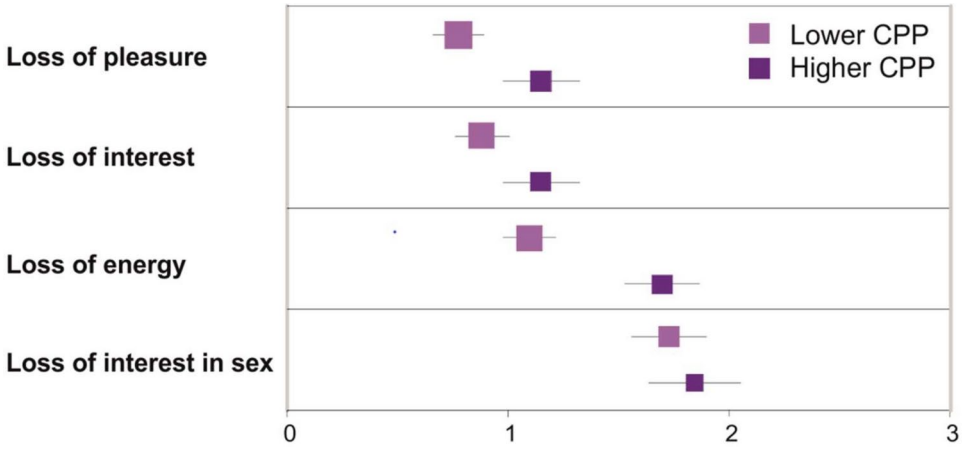

Fig. 5. Item level analysis. BDI-II anhedonia subscale, item-level analysis comparing DE patients with high and chronic pelvic pain (NRS ≥ 7), [Lower CPP], and low chronic pelvic pain (NRS < 7), [Higher CPP]. Means and CI are plotted for both groups in each item of the scale.

results showed that women affected with DE report higher levels of anhedonia comparable to those observed in other chronic pain populations (see Table 3) demonstrating the presence of anhedonia in individuals without a primary diagnosis of depression. Furthermore, we observed significant correlations between anhedonia and the intensity of DE pain-related symptoms (see Fig. 2). Notably, anhedonia was more pronounced in DE patients affected by more severe chronic pelvic pain. These findings were supported by three different predictive models that demonstrated the impact of pelvic pain on the odds of presenting impaired levels of anhedonia, with a marked increase in cases of severe chronic pelvic pain. Overall, the present results highlight the strong impact of DE and chronic pelvic pain in subjective hedonism, clearly diminishing the capacity of patients to experience pleasure derived from daily life experiences as assessed by anhedonia scales.

Anhedonia has emerged in the last years as a central transdiagnostic construct in diverse psychopathological and neurological conditions as well as in diseases involving chronic pain and inflammatory processes. Its presence has been documented in social phobia[42], schizophrenia[43], depression[1], obsessive–compulsive disorder[44], substance use disorders[45] opioid misuse[10,46], stroke[11], chronic pain[12], and inflammatory bowel disease[39]. Moreover, anhedonia has been linked to a higher incidence of life-time suicide attempts[47], an increased risk of suicide[48], and has been identified as a robust predictor of poor psychosocial functioning[49]. This global overview portrays anhedonia as a significant contributor to the development of severe and long-lasting negative effects of some diseases emerging as an essential therapeutic target for restoring health and well-being.

Our results show that nearly 30% of patients with DE exhibit abnormal hedonic functioning. However, the scores obtained in anxiety and depression measures, despite being more elevated than in healthy population, do not surpass the clinical threshold for a psychiatric disorder[41]. In this sense our study is consistent with findings demonstrating that anhedonia in chronic pain patients is unlikely to result exclusively from a comorbid depression. Importantly, even in mental health disorders such as schizophrenia, major depressive disorder and substance use disorders, when results are adjusted for general depression severity, anhedonia remains as an independent factor underscoring its potential to compromise mental health[10,12].

DE patients can present symptoms of central sensitization[20,50], a phenomenon characterized by synaptic plasticity and incremented neural responsiveness in central pain pathways in the presence of normal and subthreshold afferent inputs[51,52] Notably, neuroinflammation has emerged as a mechanism underpinning both central sensitization[51] and reward system dysregulation[53,54]. Our results add a first step in contributing to this understanding by showing a gradient between anhedonia and chronic pelvic pain severity, as reflected in the positive correlation of anhedonia and the pelvic pain severity subscale, along with the significative predictive value of chronic pelvic pain in anhedonia. Further studies should include a validated measure of central sensitization to explore this potential relationship in greater depth. Although we excluded patients with diagnosed chronic pain conditions, we did not specifically use questionnaires to ensure the exclusion of all syndromes, thereby limiting the scope of our conclusions in this regard.

Regarding the facets of pleasure compromised by anhedonia in DE patients, our item-level analysis (see Fig. 4) aligns with findings from a meta-analytical sample of chronic pain patients. Although statistical comparisons cannot be made due to the different nature of the statistics, we believe that the meta-analytical results provide a valuable reference. Interestingly, DE individuals affected by severe chronic pelvic pain, present the highest impairment in nearly all anhedonia SHAPS items, underscoring the widespread impact of chronic pelvic pain in daily life pleasures. Particularly affected are areas associated with interests, social interactions and food. Besides, drinking and sensory experiences show impairment levels comparable to other chronic pain patients. Interests such as reading may be affected due to the impairment observed in chronic pain conditions of attentional resources[55,56]. Additionally, DE is normally accompanied by gastrointestinal symptoms that could impact the hedonic quality of eating[57]. And finally, social behavior and inflammation processes, although seemingly unrelated, influence each other, as demonstrated by research indicating that induced inflammation can lead to social withdrawal in human experimental paradigms[30,54,58–60]. Although these observations were obtained through content analysis and lack statistical precision, exploring the affected areas could provide insights for designing individualized intervention programs targeting specific areas. However, further studies employing more robust statistical methods are needed to address the limitations of our study in this regard.

To further explore item-level results and refine the DE anhedonia profile we also present the item analysis of the BDI-II anhedonia subscale (see Fig. 5). This subscale provides data regarding pleasure associated, among others, with sex which is an area not covered by the SHAPS. Sexuality, which encompasses both physical and interpersonal pleasure (i.e. physical and social anhedonia) is particularly relevant for understanding the impact of endometriosis. Interestingly, all the DE participants showed high scores in this item with almost no differentiation between those experiencing high and low chronic pelvic pain. This underscores the importance of exploring this deleterious effect on DE patients in future studies using more robust statistical methodology to address some of our limitations. Other areas such as interests, general pleasure and energy exhibited positive associations with severity of pain. Importantly, the BDI-II item related to energy encompasses fatigue, as evidenced by our correlational findings (see Fig. 2). While the SHAPS presents a well-delimited construct of pleasure that is not affected by fatigue, the BDI-II anhedonia subscale weights fatigue in the scoring of anhedonia. This topic about the relationship between fatigue and anhedonia has started to gain attention recently[61,62]. Overall, the affected facets of anhedonia in chronic pelvic pain patients reflect DE manifestations clearly recognizable for clinicians and suggest interesting lines for further research.

A relevant limitation of our study is the impact of medical treatment on the hedonic tone. In our sample, 64.6% of DE patients were receiving hormonal treatment, primarily in the form of combined oral contraceptives (COC) and progestins, which are considered first-line therapies for endometriosis[63,64]. Both COC and progestins have demonstrated efficacy in alleviating endometriosis-related pain symptoms in approximately two-thirds of endometriosis patients[65,66]. In general, the use of these treatments is associated with an increase in patient satisfaction, quality of life and emotional well-being[65,67]. However, the positive effects of these treatments in controlling pain may potentially influence the levels of anhedonia in our sample. Conversely, the use of COC and progestins in the general population has been associated with a subsequent use of antidepressants and a first depression diagnose particularly among adolescents[68]. This highlights the need for further research to understand the specific effects of treatment on hedonic capacity in the context of endometriosis and DE, as well as the necessity to adjust for the appropriate age range representing our patients.

Finally, although our results are based on a validated psychometric measure of anhedonia with a standardized cutoff, and we recruited a large cohesive sample of diagnosed DE patients, some concerns regarding generalizability of our results arise. Thirteen patients completed the evaluation only partially and were therefore excluded from the final analysis, preventing us from reaching the desired sample size of 223. Second, the study

included a group of patients with DE from a tertiary referral center receiving multimodal treatment, potentially contributing to an overestimation of the reported symptoms and limiting the generalizability of our findings to other large referral centers with comparable patient populations and demographics. Additionally, the average age of 40 years in our sample suggests a long diagnostic delay, which we did no assess but could have influenced symptom severity. A significant proportion of our sample (78 patients) had previous surgeries and were referred to our hospital due to recurrence of lesions and symptoms. However, despite the impact on external validity, these aspects reflect the real-life experiences of endometriosis patients, who often face prolonged diagnostic delays and persistent or recurrent symptoms despite treatment[69].

To the best of our knowledge, this is the first study in the scientific literature to demonstrate, in a large sample of DE patients, that DE patients suffer from anhedonia. Furthermore, our findings show a significant positive association between pain severity and anhedonia as assessed using golden standard measures and show that chronic pelvic pain predicts the presence of anhedonia in DE patients. Importantly, our results align with meta-analytic results of anhedonia in chronic pain populations demonstrating a more nuanced relationship between chronic pain and anhedonia not sole explainable by a comorbid depression. Notably, DE patients with severe pelvic pain showed the highest levels of anhedonia. In these cases, comorbid central sensitization processes could share pathophysiological mechanisms with anhedonia via sustained inflammation. Our findings underscore overlooked consequences of DE, emphasizing the need for further exploration. Importantly, they highlight the necessity of developing specific therapeutic approaches to restore a healthy hedonic capacity in endometriosis and DE.

Data availability

The data supporting this study are not publicly available to preserve individuals' privacy under the European General Data Protection Regulation (GDPR), but may be obtained from the corresponding author upon reasonable request and appropriate permissions.

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Author contributions

MAMZ, FC, and AM designed the study protocol. MAMZ and FC supervised the study. AF and MAMZ collected the data. ES and GC conducted all the statistical analysis and design graphics and tables. AMM drafted the manuscript. ME and EAA reviewed the first draft and provided psychological insight. LQM and MG reviewed the first draft and contributed in refining gynecological scientific terminology and perspectives.

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Competing interests

The authors declare no competing interests.

Additional information

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