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Sex-Specific Effects of Psilocybin Versus Escitalopram on Anxiety and Anhedonia: A Bayesian Reanalysis of Antidepressant Treatment Outcomes

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Abstract

Rationale:

Major depressive disorder (MDD) shows marked sex differences in prevalence, symptomatology, and treatment response. However, women remain underrepresented in many clinical trials, and sex-specific treatment outcomes are rarely examined.

Objectives

This study reanalyzed data from a randomized controlled trial comparing psilocybin and escitalopram for MDD to evaluate sex differences across multiple psychological domains.

Methods

We reanalyzed data from a six-week, double-blind randomized controlled trial comparing psilocybin with escitalopram in adults with moderate-to-severe MDD. Post-treatment depressive symptoms (MADRS, QIDS-SR-16, BDI), anhedonia (SHAPS), anxiety (STAI), thought suppression (WBSI), and well-being (WEMWBS) were modeled as a function of sex, treatment condition, their interaction, and baseline symptom severity. Sexual dysfunction severity (PRSexDQ-SALSEX), assessed only at the six-week follow-up, was analyzed separately as an ordinal outcome.

Results

Sex-related patterns emerged for anxiety and anhedonia. Women receiving psilocybin showed greater reductions in anxiety than men (STAI: 95% CrI − 17.5 to − 3.29), whereas women receiving escitalopram showed greater reductions in anhedonia than men (SHAPS: 95% CrI − 4.63 to 0.00). For the remaining continuous outcomes, sex differences were generally small and uncertain. Sexual dysfunction severity was lower overall in the psilocybin group than in the escitalopram group and lower in women than in men, although the treatment-by-sex interaction was not significant.

Conclusions

This reanalysis identified domain-specific sex-related patterns in anxiety and anhedonia, suggesting that responses to psilocybin and escitalopram may differ between women and men. These preliminary findings support adequately powered, sex-balanced, and hormone-informed trials of serotonergic treatments for MDD.

1. Introduction

Major depressive disorder (MDD) is a leading contributor to global disability, characterized by low mood, anhedonia, irritability, and pervasive guilt or worthlessness (Wu et al., 2025). Comorbid psychiatric conditions, including anxiety, personality disorders, and substance use, affect up to 80% of individuals with MDD, contributing to its complexity and treatment resistance (Gorwood et al., 2020). Forecasts suggest MDD will become the leading cause of disease burden by 2030 (Malhi & Mann, 2018).

Sex-based differences in the prevalence, symptomatology, and outcomes of MDD are robust and well-documented (Li et al., 2023; Williams et al., 2022), with females nearly twice as likely as males to be diagnosed with MDD and related mood disorders (Labaka et al., 2018). This disparity emerges after puberty and appears to shift again during periods of marked hormonal transition, including the perimenopausal and menopausal years, suggesting that female biology may play a significant role in disease onset, recurrence, and clinical expression (Williams et al., 2022). Women more frequently experience recurrent and severe episodes, often accompanied by somatic symptoms and comorbid anxiety. Males often present with atypical or externalizing symptoms such as irritability, risk-taking behavior, and substance misuse and are over three times more likely to die by suicide (Martin et al., 2013). These divergent phenotypic expressions may contribute to sex-specific diagnostic biases and under recognition in men (Cochran & Rabinowitz, 2003; Streb et al., 2021). Despite the clinical importance of these disparities, the neurobiological mechanisms underlying sex differences in MDD remain poorly characterized, hindering progress toward precision psychiatry and the development of sex-informed interventions (Carvalho Silva et al., 2023).

Sex differences manifest not only in the incidence of depression but also potentially in antidepressant mechanisms, tolerability, and clinical efficacy. Pharmacokinetic variability of antidepressants has been widely reported to be influenced by sex hormones (Xu et al., 2017; Kashuba & Nafziger, 1998; Khan et al., 2005; Wang et al., 2025). In selective serotonin reuptake inhibitor (SSRI) research, both treatment response and adverse effects vary across menstrual phases and reproductive transitions, with estradiol shown to potentiate serotonergic signaling and antidepressant responsiveness (Kornstein et al., 2000; Rubinow et al., 1998; Schmidt et al., 2000). A recent preclinical study demonstrated that escitalopram produced stronger antidepressant effects in female than male mice. This finding, consistent with previous reports, suggests that estrogen may enhance the serotonergic response to escitalopram by maintaining higher 5-HT levels through the downregulation of monoamine oxidase (MAO), the key enzyme responsible for serotonin degradation (Wang et al., 2025).

Although SSRIs remain first-line treatments for depression, they have well-documented limitations, including delayed onset of action and partial or absent efficacy in a substantial portion of patients (Cipriani et al., 2018). Over the past decade, there has been a resurgence of clinical research investigating classic psychedelics and entactogens as novel treatments for mood disorders (Reiff et al., 2020). These compounds exert their effects primarily through serotonergic mechanisms, particularly 5-HT_2A receptor signaling, and have demonstrated rapid and sustained antidepressant effects in early clinical trials (Dos Santos et al., 2021; Reiff et al., 2020).

Psilocybin, a serotonergic psychedelic with agonism at the 5-HT_2A receptor, has emerged as a promising novel treatment for depressive disorders, including MDD (Madsen et al., 2019). Both psilocybin and

escitalopram modulate the serotonin system, yet via distinct neurobiological routes. Escitalopram stabilizes mood by enhancing synaptic serotonin availability and dampening limbic reactivity, while psilocybin transiently amplifies 5-HT_2A-mediated signaling, promoting neural plasticity, emotional re-engagement, and global network integration (Liebnau et al., 2025). However, despite growing therapeutic interest, critical questions remain regarding individual variability in treatment response, including the role of sex and ovarian hormone fluctuations (Cohen & Blest-Hopley, 2025; Shadani et al., 2024). Understanding whether these mechanistically distinct serotonergic interventions differentially affect men and women is crucial for advancing precision psychopharmacology, accounting for sex as a biological variable and developing sex-informed psychedelic therapies.

1.1 Hormonal modulation of serotonergic systems

Sex hormones exert profound effects on mood regulation, stress responsivity, and antidepressant response (Marwick et al., 2025; Seifert et al., 2025, 2026; Zan et al., 2025; Zang et al., 2025; Mengelkoch & Slavich, 2024; Derntl et al., 2024; Dalla et al., 2011). Preclinical and clinical studies show estrogen and progesterone modulate stress responsivity, emotional regulation, and reward sensitivity through actions on the hypothalamic–pituitary–adrenal (HPA) axis, serotonergic expression, and limbic plasticity (Williams et al., 2022; Del Rio et al., 2018; Kauffmann et al., 2025).

More broadly, ovarian hormones and neuroactive steroids, particularly estradiol and progesterone, regulate serotonergic gene expression, receptor density, synaptic plasticity, and interhemispheric communication and are increasingly implicated in dynamic changes in functional connectivity within and between intrinsic brain networks such as the default mode network (DMN) (Bethea et al., 2002; Rubinow & Schmidt, 2019; Pletzer et al., 2010; Pritschet et al., 2020; Hidalgo-Lopez et al., 2021).

Estradiol has been shown to exert neuroprotective and mood-stabilizing effects through modulation of serotonergic transmission by reducing monoamine oxidase (MAO) activity, increasing glutamatergic signaling and synaptic plasticity within the hippocampus and prefrontal cortex, and upregulating 5-HT_2A receptor expression and brain-derived neurotrophic factor (BDNF) (Bethea et al., 2002). This is particularly relevant in the context of psychedelic treatment, given the central role of 5-HT_2A receptor signaling, neuroplasticity, and large-scale network reorganization in proposed mechanisms of psilocybin action.

In addition, progesterone and its neuroactive metabolite allopregnanolone act on GABA-A receptors to modulate stress sensitivity, emotional lability, and inhibitory regulation of anxiety-related states (Del Rio et al., 2018). Through these effects, ovarian hormones may shape both the neurobiological and affective context in which serotonergic treatments are experienced.

Fluctuations in estrogen and progesterone across the menstrual cycle are associated with predictable changes in mood, emotional regulation, and stress sensitivity. In particular, periods of rapid hormonal change, rather than absolute hormone levels alone, may be especially relevant for affective vulnerability. Furthermore, fluctuations in these hormones across the menstrual cycle, peripartum, and perimenopausal phases are closely linked with serotonergic sensitivity and mood vulnerability, as seen in conditions such as premenstrual dysphoric disorder (PMDD), peripartum depression, and perimenopausal affective

disturbances (Bencker et al., 2025). Relatedly, premenstrual exacerbation (PME) in major depressive disorder highlights that cyclical hormone-related changes may not only trigger distinct reproductive mood disorders but may also worsen symptoms of ongoing psychiatric conditions. This is particularly relevant in MDD, where anxiety, anhedonia, and affective instability may vary across the cycle and potentially influence both baseline symptom severity and apparent treatment response (Nolan & Huges, 2022; Kuehner & Nayman, 2021).

In contrast, androgens such as testosterone appear also to influence affective regulation through dopaminergic and GABAergic mechanisms (Reddy & Jian, 2010; Campbell et al., 2010). Although testosterone is present in both sexes, it is the primary sex hormone in males and typically varies more across developmental stages and diurnal rhythms than across a monthly cycle (Derntl et al., 2014). This distinction is relevant because it suggests that sex-related variability in affective symptoms may arise from different temporal endocrine patterns in males and females.

Psilocybin and SSRIs appear to engage partly different serotonergic and plasticity-related mechanisms, which may be differentially modulated by ovarian hormones (Fonzo et al., 2025; Ekoh et al., 2025). A better understanding of these interactions and their pharmacological targets may support the development of more sex-sensitive and mechanism-based treatments for depression. More broadly, sex-related neuromodulatory processes may contribute to differences in stress vulnerability and antidepressant response (Williams et al., 2022).

However, in clinical trials there is a widespread requirement for effective contraceptives for women of childbearing age, most commonly achieved through hormonal contraceptives, which may suppress endogenous ovarian hormone fluctuations (Pletzer et al., 2010; 2014; 2024). Recent PET evidence indicates that women using combined oral contraceptives show reduced cortical and subcortical 5-HT_2A/2C receptor binding compared with naturally cycling women (Kauffmann et al., 2025), suggesting that suppressed estradiol levels may lower serotonergic receptor availability and alter sensitivity to 5-HT_2A-mediated treatments such as psilocybin.

Despite increasing therapeutic interest, women remain underrepresented in psilocybin trials (≈ 25–35%) (Gill et al., 2022; Madson et al., 2022; Roseman et al., 2018; Carhart-Harris et al., 2021), and the majority do not control for menstrual phase, hormonal contraceptive use, or menopausal status. Factors that likely influence serotonergic pharmacodynamics and subjective response (Cohen & Blest-Hopley, 2025).

To address this gap, we conducted a retrospective Bayesian analysis of data from a phase 2 double-blind randomized controlled trial (N = 59; 20 females; NCT03429075) comparing psilocybin and escitalopram for moderate-to-severe MDD (Carhart-Harris et al., 2021). The original trial found that both treatments reduced depressive symptoms, with no significant difference on the primary outcome (QIDS-SR-16), although several secondary measures favored psilocybin. Importantly, no sex-specific analyses were conducted.

1.2 Present Study

In the present study, we evaluated sex-by-treatment interactions across multiple clinical domains using eight validated psychological measures. We test the hypothesis that males and females may differ in post-

treatment outcomes and that these differences may vary across treatment conditions. To examine these questions, we implemented Bayesian linear models with sceptical priors, which shrink estimates toward zero and provide a conservative inferential framework, and conducted sensitivity analyses using wider priors to assess robustness. This approach was intended to provide a more nuanced assessment of possible sex-specific treatment effects while accounting for the uncertainty inherent in a relatively small sample. In addition, sexual dysfunction severity at the 6-week follow-up was examined separately as an ordinal outcome.

2. Methods

2.1 Study Design

Detailed study procedures have been described in a previous publication (Carhart-Harris et al., 2021). In brief, adults with moderate-to-severe depression (HAM-D ≥ 17) were randomly assigned to the psilocybin (n = 30) or escitalopram (n = 29) group and completed a total of six study visits over a six-week period. All participants gave written informed consent prior to participation. The baseline visit (V1) included a preparatory psychotherapy session. On the first and second dosing days (V2 and V4 spaced three weeks apart), individuals in the psilocybin group received 25 mg of psilocybin, while those in the escitalopram group were given 1 mg of psilocybin. This is a sub-threshold dose intended to maintain expectancy consistency and align procedural elements across groups.

Between the two dosing sessions, participants were instructed to take daily oral capsules. Initially, one capsule per day was administered. This was increased to two capsules daily starting at the three-week mark. Therapeutic support was provided by trained clinicians before, during, and after each dosing session, including integration therapy during V3 and V5. Optional follow-up support was also available after the final visit (V6), which marked the end of the primary six-week study window. All participants consented to take part in the study; however, consent was not required for this reanalysis of previously collected data.

2.2 Participant

A total of 59 participants (20 females) were included in the trial, with 30 allocated to the psilocybin group and 29 to the escitalopram group. Prior to enrollment, 39% of participants (n = 23) were taking psychiatric medications, all of which were discontinued before the start of the intervention. In addition, four participants (7%) withdrew from ongoing psychotherapy in accordance with predefined exclusion criteria (Carhart-Harris et al. 2021). Within the escitalopram condition, four individuals discontinued treatment prematurely due to adverse effects attributed to the medication. In the psilocybin group, one participant reported continued cannabis use throughout the study period, and two others were unable to attend the second dosing session as a result of COVID-19-related restrictions. The average participant age was 41 years.

2.3 Measures and Outcomes

Data were collected at baseline and post-treatment (post 6 weeks) using a validated battery assessing depressive symptom severity, anxiety, anhedonia, well-being, thought suppression, and sexual dysfunction

severity. Depressive symptoms were measured with the Montgomery–Åsberg Depression Rating Scale (MADRS, Montgomery & Åsberg, 1979), Quick Inventory of Depressive Symptomatology (QIDS-SR-16, Rush et al., 2003), and Beck Depression Inventory (BDI, Beck et al., 1961). Anxiety was assessed with the State–Trait Anxiety Inventory (STAI, Spielberger et al., 1983), anhedonia with the Snaith–Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995), well-being with the Warwick–Edinburgh Mental Well-being Scale (WEMWBS, Tennant et al., 2007), thought suppression with the White Bear Suppression Inventory (WBSI, Wegner & Zanako, 1994) and sexual dysfunctioning with the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ-SALEX, Montejo et al., 2000).

For the MADRS, QIDS-SR-16, BDI, SHAPS, STAI, WEMWBS, and WBSI, baseline and 6-week post-treatment scores were available, and post-treatment outcomes were modeled with adjustment for baseline symptom severity. Because the PRSexDQ-SALSEX was collected only at the 6-week follow-up, it was analyzed as an endpoint measure of sexual dysfunction severity. Higher scores indicated greater symptom severity on the MADRS, QIDS-SR-16, BDI, SHAPS, STAI, and WBSI, greater well-being on the WEMWBS, and greater sexual dysfunction on the PRSexDQ-SALSEX

2.4 Statistical Analysis

Analysis was conducted on data collected at two timepoints, baseline and 6 weeks post-treatment, for all continuous clinical measures. Participants were analyzed according to their randomized treatment assignment. Initial data preprocessing was conducted using Microsoft Excel (Office 16 for macOS), and all statistical modeling and visualization procedures were implemented in RStudio using the brms and rstanarm packages. Missing data were handled using complete case analysis. Participants were included in the analysis only if they had complete data for all variables of interest: baseline scores, post-treatment scores, treatment condition, and sex. Sexual dysfunction severity was analyzed separately as an endpoint outcome.

2.4.1 Descriptive and Variance Analysis

Descriptive statistics were computed to characterize the sample, including age distributions to provide contextual information on the possible proportion of female participants in the menopausal transition. For the seven continuous self-reported and clinician-rated questionnaires (MADRS, SHAPS, STAI, QIDS-SR-16, BDI, WEMWBS, and WBSI), group-level means, standard deviations, and change scores were calculated and stratified by treatment condition (psilocybin vs. escitalopram) and sex (male vs. female). To assess the assumption of equal variance across sex, F-tests were used to compare post-treatment score variances between males and females within each treatment arm.

For the PRSexDQ-SALSEX, descriptive distributions across severity categories (none, mild, moderate, and severe) were summarized within each treatment-by-sex subgroup.

2.4.2 Bayesian Modeling Framework

Sex differences in treatment outcomes were analyzed using Bayesian linear regression models applied separately to each of the seven continuous clinical scales (MADRS, SHAPS, STAI, QIDS, BDI, WEMWBS, and

WBSI). The dependent variable was the post-treatment score, and baseline scores were included as covariates. The model structure was defined as

$$YPost = \beta 0 + \beta 1\, Condition + \beta 2\, Sex + \beta 3\ (condition\, x\, Sex) + \beta 4\ \ Ybaseline + \epsilon$$

Condition was coded as 0 for escitalopram and 1 for psilocybin, and sex was coded as 0 for males and 1 for females. Three main contrasts were evaluated for each outcome: (1) female minus male differences within the escitalopram group, (2) female minus male differences within the psilocybin group, and (3) sex by treatment interaction. Posterior draws from each model were transformed into these three contrasts and used for subsequent Bayesian hypothesis testing.

2.4.3 Interpretation and Evidence Thresholds

To quantify evidence for sex differences, we computed two-sided Bayes factors for each of the three contrasts. These Bayes factors were evaluated:

(1) whether a given contrast differed from zero (BF_{any}),

$$H0 : \triangle = 0\ vs.\ H1 : \triangle = 0$$

(2) whether it exceeded a minimally clinically important difference (BF_{MCID}), and

$$H0 :\ |diff|\ > MCID\ vs.\ \ H1 :\ |diff| \leq\ MCID.$$

(3) whether it lay within a predefined non-inferiority margin indicating a small or negligible effect (BF_{NI}).

$$H0 :\ |diff|\ \leq\ NI\ vs.\ \ H1 :\ |diff|\ >\ NI$$

Bayes factors were calculated by comparing the ratio of posterior to prior odds that each contrast lay inside the relevant region of interest. Values greater than 3 were interpreted as moderate-to-strong evidence for an effect, between 0.33 and 3 as weak or inconclusive, and below 0.33 as moderate evidence favoring the null (Lee & Wagenmarker, 2013). Where MCIDs were not available for a given instrument, we applied standardized effect size benchmarks: medium effects as 0.5 times the baseline standard deviation (SD). This approach allowed for interpretation grounded in clinical relevance while addressing the limitations of small-sample Bayesian estimation (Mouheli et al., 2020). Sceptical priors were applied to promote conservative inference, with Normal(0, 7.5) distributions assigned to condition, sex, and interaction coefficients; Normal(0, 5) to the baseline covariate; and Normal(0, 10) to the intercept. Posterior estimates were summarized using posterior means and 95% credible intervals (CrIs), providing probabilistic estimates of sex differences and their interaction with treatment condition.

2.4.4 Sensitivity Analyses

To examine the robustness of our findings, all seven continuous outcome models were re-estimated with wider priors (Normal(0, 15)) for the regression coefficients. Comparisons of posterior distributions and BFs under these relaxed prior assumptions were used to assess the consistency of inference.

2.4.5 Analysis of Sexual Dysfunction

PRSexDQ-SALSEX sexual dysfunction severity was analyzed as an ordinal outcome using cumulative link ordinal regression with treatment condition, sex, and their interaction as predictors. Follow-up Mann-Whitney U tests compared males and females separately within the escitalopram and psilocybin groups.

3. Results

3.1 Descriptive and Variance Statistics

Information on the use of hormonal contraceptives was not available. The median age of female participants was 38 years (SD = 9.17; range = 22–60), and the median age of male participants was 42.8 years (SD = 11.46; range = 21–64). Descriptive statistics for each sex-by-treatment subgroup across continuous outcome measures indicated that female participants tended to show greater symptom reductions than male participants within each treatment condition (Supplementary Table S1).

To assess equality of score variability between sexes, Levene's F-tests were conducted for baseline, post-treatment, and change scores (Supplementary Table S2). Levene's F-tests indicated broadly comparable variability of post-treatment scores between men and women within each treatment arm. The only clear exception was SHAPS post-treatment scores under escitalopram, where males showed greater dispersion than females ($F = 4.15$, $p = .045$). For WEMWBS, variance in change scores under escitalopram also differed by sex ($F = 0.31$, $p = .048$), reflecting more heterogeneous improvements among women. All other variance comparisons were non-significant (all $p > .10$).

Welch's t-tests of mean differences within treatment arms identified two statistically significant findings. First, post-treatment anhedonia scores on the SHAPS were lower in women than in men in the escitalopram group ($t = 2.61$, $p = .015$), consistent with greater reduction in anhedonia among women. Second, change scores on the STAI in the psilocybin arm indicated larger anxiety reductions in women than in men ($t = 2.64$, $p = .018$). No other questionnaire showed statistically significant sex differences in mean baseline, post-treatment, or change scores within either treatment arm (Supplementary Table S2).

3.2 Posterior Estimates and Bayes Factors

Across the seven psychological domains, the strongest sex-related patterns emerged for anxiety and anhedonia, whereas depression severity, thought suppression, and well-being showed smaller and more uncertain effects. Bayesian results for depression outcomes are presented in Table 1, followed by anxiety, anhedonia, thought suppression, and well-being in Tables 2–5. Sensitivity analyses are provided in the Supplementary Materials.

3.2.1 Depression Severity (MADRS, QIDS, BDI)

Across all three depression scales, posterior estimates of sex differences were small with wide CrIs that included zero. For MADRS, the female–male contrast in the escitalopram group had a posterior mean of 1.12 (95% CrI − 4.37 to 7.03), while under psilocybin, the mean contrast was − 2.57 (CrI − 8.63 to 3.65). The interaction contrast (difference of differences) was − 3.70 (CrI − 11.1 to 3.81). Bayes factors for any non-

zero effect were close to or below 1 (BF_any = 1.79, 0.25, and 0.20 for escitalopram, psilocybin, and the interaction, respectively), providing at most weak evidence and favoring neither substantial sex differences nor strong equivalence.

For the BDI, in the escitalopram group, the female–male contrast had a posterior mean of − 1.58 (CrI − 7.82 to 4.78); in the psilocybin group, it was − 5.46 (CrI − 12.1 to 1.09). The interaction mean was − 3.88 (CrI − 12.0 to 4.31). All CrIs comfortably overlapped zero, and BFs again indicated weak evidence (BF_any = 0.43, 0.05, and 0.21, respectively), suggesting that the data did not clearly support either meaningful sex differences or strict non-inferiority.

For QIDS, posterior contrasts were closest to zero. The mean female–male differences were − 0.55 (CrI − 4.65 to 3.47) for escitalopram and − 2.04 (CrI − 6.15 to 1.90) for psilocybin, with an interaction mean of − 1.49 (CrI − 6.83 to 3.82). All associated Bayes factors fell within the inconclusive range (BF_any between 0.17 and 0.65). Across the depression scales, all credible intervals included zero, and corresponding Bayes factors remained in the weak or inconclusive range.

Table 1
Bayesian Analysis of Depression Outcomes

Depression Measure	Comparison	BF_any	BF_MCID	BF_NI	Posterior, mean	95% CrI
MADRS	Escitalopram	1.76	0.0269	2.82	1.12	[− 4.37, 7.03]
MADRS	Psilocybin	0.251	0.307	3.06	−2.57	[− 8.6, 3.65]
MADRS	Interaction	0.202	0.796	1.20	−3.7	[− 11.1, 3.81]
QIDS	Escitalopram	0.646	0.133	4.24	-0.55	[− 4.65, 3.47]
QIDS	Psilocybin	0.171	0.201	3.48	-2.04	[− 6.15, 1.90]
QIDS	Interaction	0.417	0.288	2.80	-1.49	[− 6.83, 3.82]
BDI	Escitalopram	0.432	0.285	2.63	-1.58	[− 8.27, 5.18]
BDI	Psilocybin	0.049	0.894	0.867	−5.37	[− 12.6, 1.88]
BDI	Interaction	0.213	0.730	1.15	−3.79	[− 12.3, 4.85]

Notes: BF_any = evidence for any nonzero effect; BF_MCID = effect ≥ minimally clinically important difference. BF_NI = non-inferiority. Posterior values represent the mean estimate with the associated 95% credible interval (CrI). BFs < 1 favor the null; BFs > 1 favor the alternative. Interpretive thresholds: BF < 0.33 = moderate evidence for the null, BF 0.33–3 = weak/inconclusive evidence, and BF > 3 = moderate-to-strong evidence for an effect.

3.2.2 Anxiety (STAI)

The STAI revealed a pronounced sex difference within the psilocybin group. The posterior mean female–male contrast under psilocybin was − 10.5, with a 95% CrI from − 17.5 to − 3.29, indicating that women had substantially lower post-treatment anxiety than men after adjusting for baseline scores. The corresponding contrast under escitalopram was smaller and more uncertain (mean − 2.54, CrI − 9.33 to 4.07). The sex × treatment interaction contrast was also negative (mean − 7.97, CrI − 16.3 to 0.45), suggesting a tendency for the female advantage to be more pronounced under psilocybin than escitalopram, although the CrI narrowly included zero.

Bayes factors provided strong evidence that the psilocybin female–male difference exceeded a minimally clinically important difference (MCID; BF_MCID = 13.0). Corresponding Bayes factors for escitalopram and for the interaction contrast were smaller and remained below conventional thresholds for strong evidence.

Table 2
Bayesian Analysis of Anxiety

Contrast	BF_any	BF_MCID	BF_NI	Mean Difference	95% Credible Interval
Escitalopram	0.293	0.470	1.67	−2.54	−9.33 to 4.07
Psilocybin	0.00231	13.0	0.062	−10.5	−17.5 to − 3.29
Interaction	0.0342	3.10	0.293	−7.97	−16.3 to 0.45

Notes: BF_any = evidence for any nonzero effect; BF_MCID = effect ≥ minimally clinically important difference. BF_NI = non-inferiority. Posterior values represent the mean estimate with the associated 95% credible interval (CrI). BFs < 1 favor the null; BFs > 1 favor the alternative. Interpretative thresholds: BF < 0.33 = moderate evidence for the null, BF 0.33–3 = weak/inconclusive evidence, BF > 3 = moderate-to-strong evidence for an effect.

3.2.3 Anhedonia (SHAPS)

For SHAPS, both drugs reduced anhedonia in men and women, but posterior contrasts suggested a possible female advantage under escitalopram. The female–male contrast in the escitalopram group had a posterior mean of − 2.36 (CrI − 4.63 to 0.00), indicating lower anhedonia scores among women, with the upper bound of the CrI just touching zero. Under psilocybin, the mean contrast was − 1.03 (CrI − 3.25 to 1.16), reflecting a smaller and more uncertain difference. The interaction contrast, representing differential female benefit between conditions, had a mean of 1.34 (CrI − 1.87 to 4.49).

Bayes factors for escitalopram on SHAPS supported the presence of some sex difference (BF_any ≈ 0.03 when framed against a null centered at zero and the observed negative effect), although evidence that this exceeded the MCID was modest, and non-inferiority BFs were close to 1. For psilocybin, BFs favored neither strong effects nor strict equivalence. The interaction contrast yielded a BF_any of about 4, suggesting moderate evidence for some difference between treatment arms in the size of the female–male contrast, but CrIs remained wide. Taken together, SHAPS findings suggest a tendency for greater reduction in

anhedonia in women, particularly under escitalopram, but do not establish a robust treatment-by-sex interaction.

Table 3
Bayesian Analysis of Anhedonia

Contrast	BF_any	BF_MCID	BF_NI	Mean Difference	95% Credible Interval
Escitalopram	0.0259	0.520	0.957	−2.36	−4.63 to 0.00
Psilocybin	0.220	0.0493	8.17	−1.03	−3.25 to 1.16
Interaction	4.05	0.164	4.00	1.34	−1.87 to 4.49

Notes: BF_any quantifies evidence for any group difference relative to the null model. BF_MCID assesses evidence that the effect exceeds the minimally clinically important difference. BF_NI evaluates evidence for non-inferiority. Posterior values represent the mean estimate with the associated 95% credible interval (CrI)

3.2.4 Thought Suppression (WBSI)

For thought suppression, female–male contrasts were small and highly uncertain. In the escitalopram group, the posterior mean contrast was − 0.76 (CrI − 7.38 to 5.84); in the psilocybin group it was − 2.52 (CrI − 9.51 to 4.49). The interaction mean was − 1.76 (CrI − 10.4 to 6.71). All Bayes factors were close to 1 (BF_any between 0.31 and 0.70), indicating that the data were consistent with both small effects and practical equivalence. Thus, WBSI provided no evidence for sex-specific treatment differences.

Table 4
Bayesian Analysis of Thought Suppression

Contrast	BF_any	BF_MCID	BF_NI	Mean Difference	95% Credible Interval
Escitalopram	0.695	0.256	2.55	−0.76	−7.38 to 5.84
Psilocybin	0.315	0.273	2.72	−2.52	−9.51 to 4.49
Interaction	0.538	0.451	2.11	−1.76	−10.4 to 6.71

Notes: BF_any = evidence for any nonzero effect; BF_MCID = effect ≥ minimally clinically important difference. BF_NI = non-inferiority. Posterior values represent the mean estimate with the associated 95% credible interval (CrI). BFs < 1 favor the null; BFs > 1 favor the alternative. Interpretative thresholds: BF < 0.33 = moderate evidence for the null, BF 0.33–3 = weak/inconclusive evidence, BF > 3 = moderate-to-strong evidence for an effect

3.2.5 Well-being (WEMWBS)

Posterior estimates for WEMWBS indicated slightly higher post-treatment well-being in women than in men across both treatment arms. In the escitalopram group, the mean female–male contrast was 1.81 (CrI − 4.62 to 8.37); in the psilocybin group, it was 2.50 (CrI − 4.25 to 9.38). The interaction contrast was close to zero (mean 0.69, CrI − 7.59 to 9.04). Bayes factors for any effect were modest (BF_any ≈ 2.4–3.2) and did not reach thresholds typically interpreted as strong evidence. Thus, while women tended to report

numerically higher well-being, uncertainty remained substantial, and no clear sex-specific treatment effect was demonstrated.

Table 5
Bayesian Analysis of Well-being

Contrast	BF_any	BF_MCID	BF_NI	Mean Difference	95% Credible Interval
Escitalopram	2.38	0.363	2.09	1.81	−4.62 to 8.37
Psilocybin	3.20	0.279	2.64	2.50	−4.25 to 9.38
Interaction	1.24	0.438	1.96	0.69	−7.59 to 9.04

Notes: BF_any = evidence for any nonzero effect; BF_MCID = effect ≥ minimally clinically important difference. BF_NI = non-inferiority. Posterior values represent the mean estimate with the associated 95% credible interval (CrI). BFs < 1 favor the null; BFs > 1 favor the alternative. Interpretative thresholds: BF < 0.33 = moderate evidence for the null, BF 0.33–3 = weak/inconclusive evidence, BF > 3 = moderate-to-strong evidence for an effect.

3.3 Sensitivity Analyses

All analyses were repeated using wider prior distributions to assess the robustness of Bayes factors and posterior intervals to prior specification.

Posterior means and CrIs for all contrasts were very similar to those obtained with the main sceptical prior, and the direction of effects was unchanged across all questionnaires.

Bayes factors varied slightly in magnitude but did not alter the qualitative interpretation for any outcome: Depression (MADRS, BDI, QIDS), well-being (WEMWBS), and thought suppression (WBSI) measures remained inconclusive with respect to sex differences, whereas STAI continued to show a pronounced female advantage under psilocybin, and SHAPS suggested a possible, but uncertain, female benefit under escitalopram. Overall, the results appear robust to reasonable changes in prior specification but remain constrained by the limited sample size and associated uncertainty (Supplementary Table S3 and Fig. 1).

3.4 Sexual Dysfunction Severity (PRSexDQ-SALSEX)

Descriptive distributions of PRSexDQ-SALSEX severity at the 6-week follow-up suggested lower sexual dysfunction severity in women than in men across both treatment conditions and a more favorable overall distribution in the psilocybin group than in the escitalopram group (Fig. 2). In the escitalopram group, 89% of women were classified as having no sexual dysfunction, compared with 25% of men; among men receiving escitalopram, the remaining cases were distributed across mild (10%), moderate (25%), and severe (40%) dysfunction. In the psilocybin group, 91% of women and 68% of men were classified as having no sexual dysfunction.

Ordinal regression supported these descriptive patterns (Table 6). Participants receiving psilocybin had lower odds of being classified in a more severe sexual dysfunction category than those receiving escitalopram ($p = .013$), and women had lower odds of greater dysfunction severity than men ($p = .008$).

The treatment-by-sex interaction was not significant (p = .411), indicating no clear evidence that the sex difference differed between treatment conditions. Follow-up within-arm comparisons showed that males had significantly greater sexual dysfunction severity than females in the escitalopram arm (p = 0.0026), whereas no significant sex difference was observed in the psilocybin arm (p = 0.1306).

Table 6
Analysis of sexual dysfunction at 6-week follow-up

Predictors	Estimate	SE	z	p
Psilocybin vs Escitalopram	-1.62	0.65	-2.50	.013
Female vs Male	-3.06	1.15	-2.66	.008
Treatment × Sex	1.33	1.62	0.82	.411

Notes: Estimates are from a cumulative link ordinal logistic regression model of PRSexDQ-SALSEX severity at a 6-week follow-up. Severity categories were ordered from none to severe, with higher categories reflecting greater sexual dysfunction. Escitalopram and male served as the reference categories. Negative coefficients indicate lower odds of greater dysfunction severity. The treatment × sex interaction tests whether the female–male difference differed between treatment conditions.

4. Discussion

This study presents a retrospective reanalysis of sex differences in treatment response to psilocybin and escitalopram, using a well-characterized dataset from a recent clinical trial in participants with MDD. Eight validated psychological and psychiatric scales were examined, including measures of depression, anxiety, anhedonia, thought suppression, well-being, and sexual dysfunction severity. The primary aim was to determine whether men and women differed in their responses to these treatments and whether any differences reached clinically meaningful magnitudes.

Across the examined domains, the clearest sex-related patterns emerged for anxiety and anhedonia. Women in the psilocybin arm showed greater reductions in anxiety than men, whereas women in the escitalopram arm showed greater reductions in anhedonia than men. For the remaining domains, credible intervals generally overlapped zero, and Bayes factors were weak or inconclusive, consistent with either small effects or insufficient precision. In addition, sexual dysfunction severity at follow-up was lower in women than in men and lower overall in the psilocybin group than in the escitalopram group, although the treatment-by-sex interaction was not significant. Taken together, these findings suggest that sex-related variation in treatment response may be more apparent in specific clinical domains than across broad depressive symptom severity alone.

In the psilocybin group, females exhibited greater reductions in anxiety compared with males. One possible explanation involves the combined influence of estradiol and progesterone on fear and anxiety circuitry, particularly within the amygdala and hippocampus, where ovarian hormones shape synaptic plasticity, stress sensitivity, and inhibitory regulation (Adkins et al., 2020; Cover et al., 2014). Progesterone withdrawal and altered sensitivity to changing progesterone levels have also been linked to heightened anxiety in some women, particularly when HPA-axis responsivity is elevated. Within this framework, psilocybin may interact

with hormonally sensitive stress-regulation pathways in a way that preferentially facilitates anxiolytic effects in at least a subset of female participants. However, given the absence of direct hormonal measures in the present dataset, these mechanisms remain speculative. Preclinical evidence also suggests that stress may differentially modulate psilocybin's anxiolytic effects in males and females. Farinha-Ferreira et al. (2025) reported that psilocybin reduced anxiety-like behaviour in both sexes under non-stressed conditions. However, when animals were exposed to an additional acute stressor during the psychedelic phase, these anxiolytic effects were attenuated, particularly in males. In contrast, females retained more of the post-acute anxiolytic benefit and showed a less reactive corticosterone profile, suggesting that ovarian hormones may buffer stress-related interference with psilocybin's effects.

By contrast, reductions in anhedonia were more pronounced in females receiving escitalopram than in males. This aligns with evidence that women often respond more favorably to SSRIs, potentially due to sex differences in serotonin transporter binding, pharmacokinetics, and serotonergic metabolism (Sramek et al., 2016). One possible implication is that stronger serotonergic enhancement in women may translate more readily into improvements in reward processing and hedonic tone, particularly when baseline anhedonia is closely tied to serotonergic dysregulation. Moreover, progesterone and its metabolite allopregnanolone may further enhance SSRI efficacy in women through GABAergic mechanisms. SSRIs have been shown to increase allopregnanolone, which in turn enhances GABA-A-mediated inhibitory signaling and may reduce stress-related interference with reward responsiveness. Through this pathway, serotonergic and neurosteroid effects could jointly contribute to improved hedonic tone in women, whereas these hormonal influences may interact less directly with the mechanisms primarily targeted by psilocybin (Schüle et al., 2014).

A related pattern was observed for sexual dysfunction severity. Participants receiving psilocybin showed lower sexual dysfunction severity overall than those receiving escitalopram, and women showed lower severity than men across treatment conditions. Although the treatment-by-sex interaction was not significant, this finding is clinically relevant because sexual side effects are among the most common reasons for reduced tolerability and poorer adherence during SSRI treatment (Jing & Straw-Wilson, 2016; Montejo et al., 2019). In that sense, the sexual dysfunction results complement the domain-specific findings for anxiety and anhedonia by suggesting that sex-related differences may extend beyond efficacy outcomes to tolerability-related domains (Jacobsen et al., 2020). Given the well-established burden of SSRI-related sexual side effects on quality of life and treatment adherence, this aspect may be particularly important in future comparative trials of serotonergic interventions (Fried and Nesse, 2014; Dagostin Ferraz et al., 2026). At the same time, these findings should be interpreted cautiously, as sexual functioning is influenced by multiple biological and psychosocial factors, and the female subgroup likely spanned different reproductive stages, including possible perimenopausal or menopausal transition, which may independently affect sexual functioning (Christmas and Reed, 2024; Nappi et al., 2010).

Taken together, the stronger female response to psilocybin in anxiety and to escitalopram in anhedonia suggests that distinct neurobiological mechanisms underlie these domain-specific outcomes. By contrast, sex differences across the broader depression measures were small and uncertain, with the QIDS showing the most attenuated pattern of the three depression scales. This is notable because in the original trial, the

QIDS-SR-16 was the primary endpoint and did not significantly differentiate psilocybin from escitalopram, despite several secondary outcomes favoring psilocybin (Carhart-Harris et al., 2021). Accordingly, the near-null QIDS findings in the present reanalysis may reflect the relative conservativeness of this measure in this dataset rather than the absence of sex-related effects across all symptom domains. More broadly, the lack of robust sex differences on depressive symptom scales may also reflect limited statistical power, smaller domain-general effects, and unmeasured hormonal variables such as menstrual phase or contraceptive use that could be used in our analysis. These mechanistic patterns generate specific, testable hypotheses for future hormone-stratified psychedelic trials.

Beyond these clinical findings, the results contribute to the growing recognition that sex hormones modulate antidepressant response (Kauffmann et al., 2025; Wei & Chiu, 2025; Del Rio et al., 2018). Yet, most psychedelic studies continue to overlook sex as a biological variable and do not measure key hormonal variables, including menstrual cycle phase, hormonal contraceptive use, and endogenous hormone levels (Cohen & Blest-Hopley, 2025). Incorporating these factors into future study designs will be essential for improving reproducibility, interpretability, and equity in psychedelic research and therapy.

5. Limitations

Several limitations should be considered when interpreting these findings.

First, this was a secondary analysis of a trial that was not originally designed or powered to detect sex-by-treatment interactions. Although the Bayesian framework enabled a more graded assessment of uncertainty, the relatively small sample size and unequal sex distribution, particularly the low number of female participants, limited statistical precision. Further stratification by treatment arm reduced power still further, meaning that the observed sex-related differences should be interpreted cautiously and regarded as preliminary.

Secondly, information on hormonal status was unavailable, including hormonal contraceptive use, menstrual cycle phase, premenstrual exacerbation of symptoms, and menopausal stage. This heterogeneity among female participants likely introduced variability in estradiol and progesterone exposure, both of which influence emotional regulation and treatment responsiveness. Ovarian hormones and their neuroactive metabolites modulate 5-HT_2A receptor signaling, glutamatergic plasticity, and GABAergic tone, thereby shaping subjective and clinical responses to serotonergic compounds. The use of combined oral contraceptives may blunt endogenous hormonal fluctuations and alter serotonergic receptor architecture, as described in a recent brain imaging study in which women using combined oral contraceptives reported lower cortical and subcortical 5-HT_2A receptor binding, suggesting a potential mechanism through which synthetic hormones could influence treatment sensitivity (Kaufmann et al., 2025). Consequently, the observed outcomes may reflect not only biological sex differences but also the hormonal context shaped by contraceptive use or perimenopausal transition. This limits the translatability of the findings of this and other clinical studies that do not account for hormonal phase or recruit women across hormonal life stages and with and without exogenous hormone exposure.

In addition, the population had a wide age range of female participants, which raises the possibility that some may have been in the menopausal transition. Age-related endocrine changes may therefore have contributed to variability in treatment response, but this could not be formally evaluated in the present analysis. Finally, this retrospective analysis relied on clinical questionnaire data and did not include biological or neurophysiological measures that could directly test the mechanisms discussed in the interpretation of the findings. Accordingly, explanations involving ovarian hormones, serotonergic sensitivity, or stress-related neurobiology remain speculative. The present results should therefore be viewed as hypothesis-generating rather than confirmatory.

6. Implications for future research

Future research should examine hormonal context as a potentially meaningful contributor to antidepressant and psychedelic treatment response. In the present study, the absence of information on menstrual cycle phase, hormonal contraceptive use, and menopausal status limited interpretation of the observed sex-related patterns. Future trials should therefore incorporate more systematic characterization of these factors as they may differentially influence serotonergic signaling, stress responsivity, and affective regulation.

Such characterization is important not only for mechanistic understanding but also for improving interpretability of clinical outcomes. Hormone-related fluctuations in anxiety, anhedonia, and mood symptoms may affect both baseline severity and post-treatment assessment, thereby influencing apparent treatment response. Future studies should also examine whether hormonal context is associated not only with treatment efficacy but also with tolerability, acute psychological distress, and adverse event profiles, particularly in psychedelic interventions where transient increases in emotional intensity may form part of the treatment process. In this context, accounting for within-person hormonal variability may help reduce unexplained variance, improve signal detection, and strengthen inference, particularly in psychedelic trials that often rely on relatively small samples and a limited number of dosing sessions.

Future studies should also aim to recruit women across a broader reproductive spectrum, including naturally cycling, hormonally contracepting, perimenopausal, and postmenopausal participants. Rather than collapsing female participants into a single category, stratified or phase-aware designs may offer a more informative approach to understanding when and for whom treatment effects differ. Where feasible, adaptive or cycle-informed trial designs could be used to evaluate whether the timing of psychedelic administration relative to hormonal state influences acute experience, post-acute symptom change, or durability of response.

In addition, mechanistic work will be needed to clarify how ovarian hormones interact with the neurobiological systems implicated in psychedelic and SSRI response. This includes serotonergic, glutamatergic, and GABAergic pathways, as well as stress-related and network-level processes that may shape domain-specific outcomes such as anxiety and anhedonia. Integrating clinical outcomes with hormonal measures, neuroimaging, and other biological markers may be particularly valuable for distinguishing general sex effects from more specific hormone-sensitive processes.

Taken together, future work should aim not only to include women more adequately in psychopharmacology and psychedelic trials but also to characterize female biological heterogeneity with greater precision. Such approaches will be important for determining whether the patterns observed here reflect true hormone-sensitive differences in treatment response and for advancing more biologically informed and equitable models of depression treatment.

Declarations

Ethical Considerations

This study reanalyzed data from a previously published randomized controlled trial (Carhart-Harris et al., 2021). Ethical approval for the original study was obtained from the Brent Research Ethics Committee (REC reference: 17/LO/1154), Imperial College London. The present reanalysis involved no new data collection. No additional ethical approval was required.

Declarations of Conflicting Interest

R.C.-H. reports receiving consulting fees from COMPASS Pathways, Entheon Biomedical, Mydecine, Synthesis Institute, Tryp Therapeutics, and Usona Institute. The other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Consent to Participate

All participants in the original trial provided informed written consent prior to enrollment. This reanalysis did not involve new participant recruitment or interaction.

Consent for Publication

Not applicable. No individual-level data, images, or videos are presented that require specific consent for publication.

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Author Contribution

A.F. performed the statistical analyses, interpreted the data, and drafted the manuscript. G.B.-H. contributed to the study concept, interpretation of the findings, and substantial revision of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Data Availability

The original trial dataset used in this reanalysis is not publicly available due to privacy and ethical restrictions but may be requested from the original authors (Carhart-Harris et al.) upon reasonable request and subject to appropriate ethical approvals. Analysis scripts and code for the Bayesian models are available upon request from the corresponding author.

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Figures

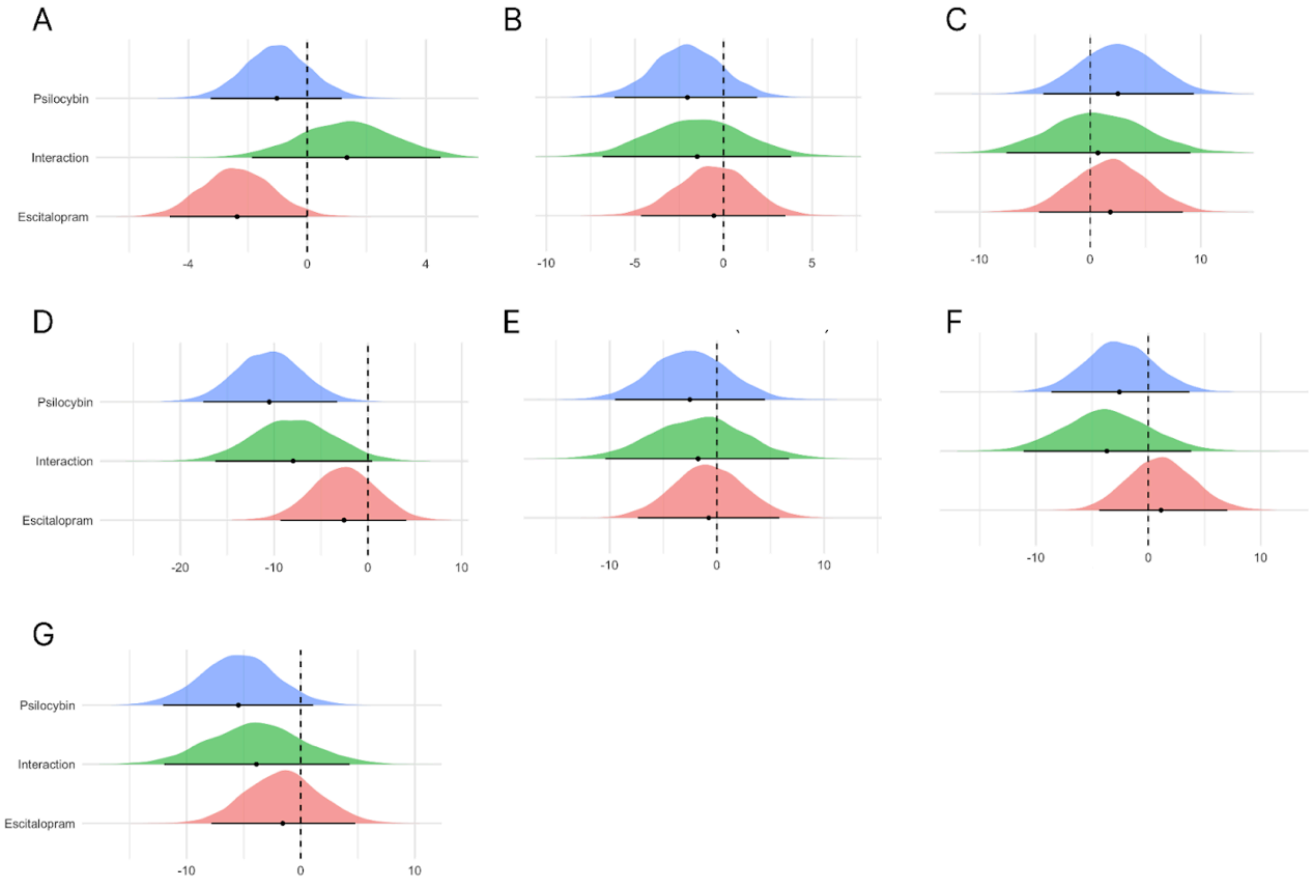


Figure 1

Posterior distribution of the female-male difference in post-treatment scores under sceptical priors

Notes: Posterior distributions for the female–male difference in post-treatment scores across all instruments. Panels A–G correspond to SHAPS (A), QIDS (B), WEMWBS (C), STAI (D), BDI (E), WBSI (F), and MADRS (G). For each model, posterior means and 95% credible intervals are shown for escitalopram, psilocybin, and the sex × condition interaction. The distributions reflect the sceptical prior and are adjusted for baseline scores. The dashed vertical line represents no sex difference. Across measures, credible intervals frequently include zero, indicating substantial uncertainty. The x-axis indicates the effect size (female-male).

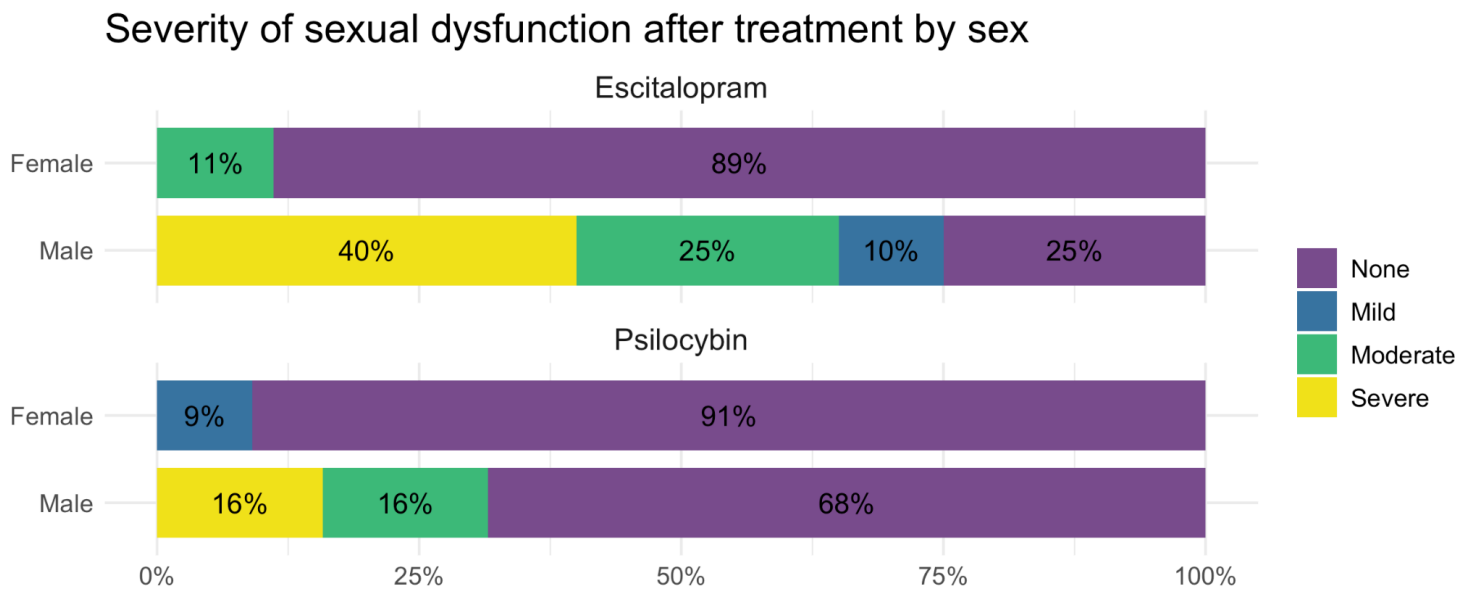


Figure 2

Sexual dysfunction severity at 6-week follow-up by sex and treatment condition

Notes: Bars represent the proportion of participants within each sex-by-treatment subgroup classified as having none (purple), mild (blue), moderate (green), or severe (yellow) sexual dysfunction on the PRSexDQ-SALSEX at the 6-week follow-up. Higher categories indicate greater sexual dysfunction. Percentages are shown within subgroups.

Supplementary Files

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