

# Sexual function improves as depressive symptoms decrease during treatment with escitalopram: results of a naturalistic study of patients with major depressive disorder

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## Abstract

**Background:** Major depressive disorder (MDD) is closely associated with sexual dysfunction, which may worsen during treatment with selective serotonin reuptake inhibitors (SSRIs) due to the side effects of pharmacologic treatment.

**Aim:** To examine the association between sexual function and severity of MDD in drug-naïve patients as compared with healthy controls and how treatment with SSRIs affects sexual function over time in individuals with MDD. Interaction with gender and treatment response was examined.

**Methods:** In 92 patients with MDD, we measured MDD severity with 6- and 17-item versions of the Hamilton Depression Rating Scale (HDRS<sub>6</sub> and HDRS<sub>17</sub>) and the level of sexual function with the Changes in Sexual Functioning Questionnaire at baseline and 4, 8, and 12 weeks after initiating treatment with escitalopram. Baseline sexual function was compared with the sexual function of 73 healthy controls. Linear regression models were used to assess differences in sexual function between healthy controls and patients and change in sexual function from baseline to week 12. Linear mixed models were used to assess differences in change in sexual function between treatment response groups.

**Outcomes:** Outcomes included total scores on the HDRS<sub>6</sub>, HDRS<sub>17</sub>, and Changes in Sexual Functioning Questionnaire and changes in total scores from baseline to week 12.

**Results:** Unmedicated patients with MDD reported impaired sexual function as compared with healthy controls. Level of sexual function was not associated with severity of MDD at baseline. Patients' sexual function improved significantly during treatment, which was coupled with amelioration of depressive symptoms. Treatment response groups (remitters, intermediate responders, nonresponders) did not predict change in sexual function. Gender had no effect on sexual dysfunction symptoms during treatment.

**Clinical Implications:** Major depression is a risk factor for sexual problems, and improvement in sexual function was coupled with amelioration of depressive symptoms.

**Strengths and Limitations:** Among its strengths, this was a naturalistic study reflecting real-world settings in clinical practice. It additionally included a baseline measurement of sexual function and MDD severity on drug-naïve patients prior to the initiation of treatment. Finally, the follow-up of 12 weeks extends beyond the acute phase of treatment in which previous research has observed a peak in sexual side effects. In terms of limitations, there was no placebo arm; thus, the study cannot attribute the effects on sexual function to treatment with antidepressants per se. Also, the patients were young, which may have served as a protective factor against sexual side effects.

**Conclusion:** Sexual dysfunction was strongly associated with MDD and improved in parallel with overall symptoms of depression across a standard 12-week treatment with SSRI antidepressants.

**Clinical Trial Registration:** NCT02869035 (<https://clinicaltrials.gov/ct2/show/NCT02869035>).

## Introduction

Major depressive disorder (MDD) is a serious mental disorder characterized by severe and persistent depressed mood, diminished interest and experience of pleasure, weight gain/loss, fatigue, feelings of worthlessness, psychomotor retardation including cognitive impairment, and recurrent thoughts of death.<sup>1</sup> It is one of the leading causes of disability worldwide with 163 million people currently affected, of whom approximately 70% are women.<sup>2,3</sup> A significant proportion of patients with MDD experience sexual dysfunction, which is observed in 50% to 90% of patients<sup>4-6</sup> and more frequently in women than men.<sup>7,8</sup> Sexual dysfunction can be defined as a “disturbance in a person’s ability to respond sexually or to experience sexual pleasure.”<sup>9(p493)</sup> This includes dysfunctions such as low sexual desire, arousal difficulties (lubrication difficulties in women and erectile dysfunction in men), anorgasmia, or pain during sexual activity.<sup>10</sup> The co-occurrence of MDD and sexual dysfunction is associated with reduced quality of life, lower self-esteem, and adverse effects on mood and partner relations.<sup>11,12</sup> In addition, impaired sexual function is correlated with more severe MDD symptoms<sup>13,14</sup> and may aggravate the depressed state.<sup>15</sup>

Selective serotonin reuptake inhibitors (SSRIs) are often considered the first-line drug treatment for moderate to severe MDD, depending on local clinical guidelines.<sup>16</sup> However, treatment with SSRIs has been found to further impair sexual function and cause treatment-emergent sexual dysfunction in up to 80% of patients with MDD.<sup>5,7,12,17,18</sup> Currently, little is known about the interplay among the effects of SSRIs, treatment response, patient characteristics, and sexual function, although some research suggests that response to antidepressant treatment may predict changes in sexual function.<sup>19-21</sup> As such, a better response to antidepressant treatment may predict improvement in sexual function, whereas worse or no response to treatment may predict no change or a deterioration in sexual function. Other research suggests that while sexual function at baseline tends to be more severely affected in women than men, it improves during treatment with antidepressants concurrent with the deterioration in the symptoms of depression in women, whereas the opposite is true for men.<sup>22-24</sup>

Many of the studies that investigated the effects of MDD and antidepressant treatment on sexual function did not specifically target patients who were drug naïve.<sup>6,25,26</sup> Since antidepressant treatment has been found to affect sexual function negatively, conclusions regarding the effects of MDD and/or treatment with antidepressants on sexual function are difficult to disentangle from such studies. Hence, studying unmedicated patients will allow a more accurate distinction to be made between sexual dysfunction attributed to antidepressant treatment and that to MDD.

## Aims of the study

The study aims were to examine (1) sexual function in medication-free patients with MDD as compared with healthy controls, (2) the effects of treatment with SSRIs on sexual function in patients with MDD, and (3) whether the response to treatment with SSRI antidepressants is associated with change in sexual function. For all 3 aims, we also analyzed the interaction effects of gender. Based on the current literature presented so far, our hypotheses were as follows:

Hypothesis 1: Medication-free patients with MDD will report lower sexual function than the group of healthy

controls, and sexual function will be negatively correlated with the severity of depression symptoms—more so in women than men.

Hypothesis 2: Treatment with antidepressants will lead to improved sexual function and a decrease in the number of patients with sexual dysfunction.

Hypothesis 3: Change in sexual function from baseline to week 12 will be positively associated with a change in the symptoms of depression in response to treatment with SSRIs, and remitters will show greater improvement in sexual function when compared with nonresponders to SSRI treatment—more pronounced in women than men.

## Methods

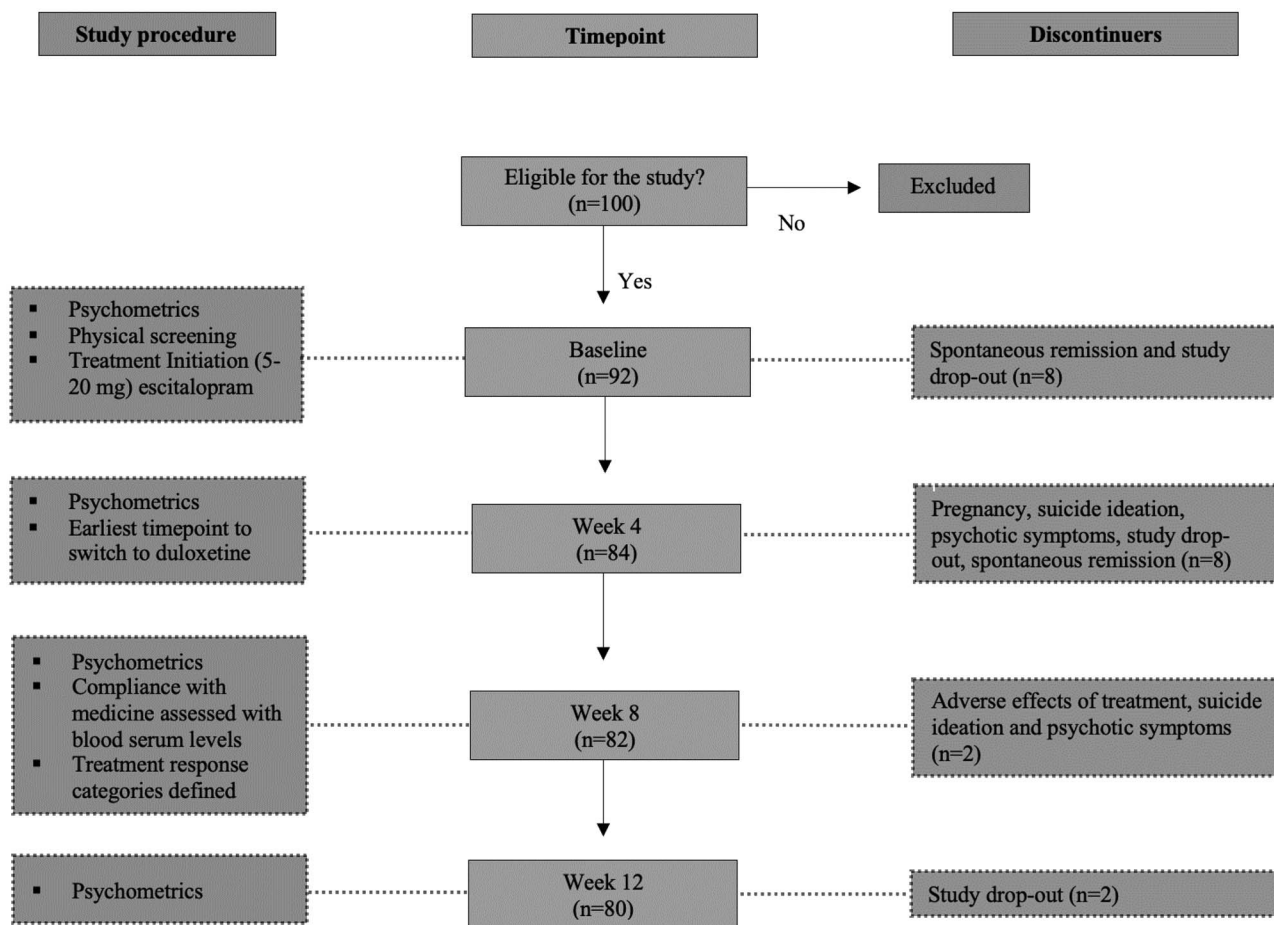
### Participants

Figure 1 is a flowchart of the study procedures and included/excluded patients.

One hundred patients aged 18 to 65 years and diagnosed with MDD were recruited in the 2016-2019 period for a study investigating prediction markers of treatment outcome in MDD using central and peripheral biomarkers (see Köhler-Forsberg et al<sup>27</sup> for more information). All participants who had filled in a Changes in Sexual Functioning Questionnaire (CSFQ) were included in the analysis. Of these, data on sexual function and depressive state were obtained from 92 patients (66 women, 26 men). Eighty patients completed the study.

The patient group consisted of medication-free outpatients with a moderate-severe single or recurrent case of MDD in accordance with the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* and *International Classification of Diseases, Tenth Revision*. Patients were recruited through a central referral center for “depression treatment packages” (ie, standard treatment in outpatient settings) within the Mental Health Services of the Capital Region of Denmark or through 1 of 5 general practitioners in collaboration with the study group.

Patients were included in the study if they scored a minimum of 17 on the 17-item Hamilton Depression Rating Scale (HDRS<sub>17</sub>), which indicates a moderate degree of depression.<sup>28</sup> Diagnosis was subsequently confirmed with the Mini International Neuropsychiatric Interview<sup>29</sup> and verified by a specialist in psychiatry prior to inclusion. The participants must not have received antidepressant medication for at least 2 months before inclusion (defined as “unmedicated”); the current depressive episode must not have lasted >2 years; and no more than 1 prior attempt with antidepressant medication was allowed. At baseline, 35 patients reported using medications other than contraceptive. Patients were not included if they were using medications that were psychoactive or contraindicated for SSRI use. Patients were also not included when using central nervous system drugs, which could not be washed out prior to treatment initiation (eg, ondansetron, clonidine, metoclopramide, or serotonergic treatment of migraine). Other exclusion criteria were contraindications to SSRIs, previous nonresponse to treatment with SSRIs, any severe neurologic or somatic illnesses, contraindications for magnetic resonance imaging and positron emission tomography as employed in the original study, insufficient Danish skills, substance or alcohol abuse, pregnancy, breastfeeding, learning disabilities, history of brain injury, or acute suicidal thoughts or psychosis. Patients with a



**Figure 1.** Flowchart showing the study procedure and the discontinuation between baseline and week 12 for the patients who were depressed.

present or prior history of any other primary axis I psychiatric disorder were excluded (MDD must be the primary diagnosis).

Data from 73 healthy controls aged 18 to 65 years (29 women, 9 men) were collected from an existing database at the Neurobiology Research Unit, Copenhagen University Hospital Rigshospitalet.<sup>30</sup> Data from the 73 healthy controls were originally collected in the 2020-2021 period as part of a study investigating the role of serotonin on cognition in humans, in which the CSFQ was administered. Healthy controls were comparable to the patient group in age and gender distribution. Exclusion criteria were a history of current or former psychiatric, somatic, or neurologic disease or severe head injuries, alcohol or drug abuse, use of psychoactive medication, contraindications to SSRI, magnetic resonance imaging or positron emission tomography, current or past learning disabilities, and nonfluency in oral and written Danish. The study from which the healthy controls were recruited was approved by the ethics committee for the capital region of Copenhagen (H-18038352) and preregistered at clinicaltrials.gov (NCT04336228).

### Study design

Having provided their written informed consent, the patients underwent a basic physical screening, which included somatic status, electrocardiogram analysis, and the collection of blood and urine samples to detect pregnancy or substance use within the last month. The patients were prescribed the antidepressant drug escitalopram in varying doses (5-20 mg/d). Initially,

5 mg was administered daily for 3 to 5 days, followed by 10 mg daily until first follow-up, after which doses were adjusted individually. Adjustments were made continuously depending on the patients' symptoms and side effects. Patients with a <25% decrease in HDRS<sub>17</sub> total score after 4 weeks of treatment or intolerable side effects were offered duloxetine instead. Patients had follow-up sessions at weeks 1, 2, 4, and 8 to evaluate the effect of the treatment and a final follow-up session at week 12 to evaluate the longer-term clinical outcome. At week 8, medication compliance was determined with a blood test.

At baseline and 4-, 8-, and 12-week follow-up after the initiation of antidepressant treatment, data on the severity of depression were assessed by a trained clinician during a face-to-face interview using the HDRS<sub>17</sub>, and self-reported sexual function was collected. A psychotherapeutic program was not provided during the trial. The study was approved by the ethics committee for the capital region of Copenhagen (H-15017713) as well as the Danish Medicines Agency (EudraCT: 2016-001626-34). The study was preregistered at clinicaltrials.gov (NCT02869035) and conducted in accordance with the Declaration of Helsinki.

Healthy controls were screened with respect to inclusion and exclusion criteria during an in-depth screening interview and were given written and oral information. After receipt of written informed consent, their medical history, blood pressure, and blood samples were obtained to ensure that the enrolled subjects were in good health.

Hereafter, measures of self-reported sexual function were obtained.

## Measures

The severity of depression was assessed with the HDRS<sub>17</sub>, which is a well-documented clinician-administered structured interview that assesses the severity of symptoms with a total score between 0 and 52.<sup>31</sup> A subset of 6 items reflecting core symptoms of depression was used when evaluating the percentage change in the severity of symptoms: item 1, depressed mood; item 2, feelings of guilt; item 7, work and activities; item 8, psychomotor retardation; item 10, psychic anxiety; and item 13, general somatic symptoms. The HDRS<sub>6</sub> yielded a total score of 0 to 22.<sup>32</sup>

A substantial body of research has shown greater sensitivity with the HDRS<sub>6</sub> than the HDRS<sub>17</sub> when assessing change in severity of depressive symptoms.<sup>33</sup> Thus, the treatment response categories for the current study were defined with reference to change in the severity score of the HDRS<sub>6</sub>. The categories were as follows: remitters,  $\geq 50\%$  remission from baseline to week 4 and a maximum score of 5 at week 8; nonresponders,  $< 25\%$  remission at week 4 and  $< 50\%$  remission in week 8. The patients who fell between the defined categories were categorized as intermediate responders.

Sexual function was assessed with the Danish validated version of the 14-item self-reported CSFQ, which the participants completed at home through a secure online survey system (<https://eprovide.mapi-trust.org/instruments/changes-in-sexual-functioning-questionnaire>). CSFQ-14 is well validated, has gender-specific items, and has been shown to be useful in assessing changes in sexual function in psychiatric populations.<sup>34</sup> The questionnaire measures global sexual functioning, with 5 subdomains measuring arousal, pleasure, desire/frequency, desire/interest, and orgasm. The scale ranges from 14 to 70 points for men and women, with lower scores indicating worse sexual function. The cutoff score that indicates a risk of sexual dysfunction is  $\leq 41$  for women and  $\leq 47$  for men (for a detailed description, see Clayton et al<sup>22</sup> and Keller et al<sup>34</sup>).

## Statistical analyses

All statistical analyses were performed with R, the free software programming language for statistics and graphs. Descriptive data are presented with mean, standard deviation, and range.

We found that the CSFQ data from the healthy control group were nonnormally distributed. Therefore, a nonparametric permutation test was performed, which showed no difference in outcome between the parametric tests; hence, the *P* values and estimates from the parametric tests are reported.

Chi-square was used to test the difference in gender distribution between healthy controls and patients and to test the difference in the proportion of patients and healthy controls that scored below the cutoff score indicating sexual dysfunction. A McNemar chi-square for dependent variables was used to determine the change in the proportion of patients exhibiting sexual dysfunction between baseline and week 12.

One-way analysis of variance was used to assess differences in the mean CSFQ at baseline between healthy controls and patients and to test for the presence of gender differences in the CSFQ scores of the patients and healthy controls. Furthermore, a 1-way analysis of variance was performed to

test for the presence of gender differences in the change in sexual function from baseline to week 12.

*T* tests were performed to test for differences in the mean age between patients and healthy controls and to compare the severity of the symptoms of depression and sexual function between study discontinuers and completers to control for attrition bias.

Linear regression models were run to assess associations (1) between the severity of depression and sexual function at baseline and (2) between change in severity of depression and change in sexual function from baseline to week 12. Change in sexual function and depressive symptoms was defined as the change in scores on the HDRS<sub>6</sub>, HDRS<sub>17</sub>, and CSFQ from baseline to week 12. The HDRS<sub>6</sub> and HDRS<sub>17</sub> were used in the analyses. For the baseline analysis, the HDRS<sub>17</sub> and HDRS<sub>6</sub> scores served as independent variables, while the CSFQ scores served as dependent variables. For the assessment of whether there was any association between change in sexual function and severity of depression, changes in HDRS<sub>17</sub> and HDRS<sub>6</sub> scores from baseline to week 12 served as independent variables, while change in CSFQ served as the dependent variable. To test the effect of gender, the following interaction terms were included in the models: gender  $\times$  either HDRS score (ie, 6- or 17-item scale) and gender  $\times$  change in either HDRS score.

A linear mixed model was used to analyze differences in mean change in sexual function over time for the 3 response groups: remitters, intermediate responders, and nonresponders. Time and treatment response group were fixed effects. A Gaussian model was used for repeated measurement in which we assumed an unstructured covariance pattern to account for possible changes in variance over time. Goodness of fit was assessed through a likelihood ratio test. An interaction term for treatment response group and time was included in the model, and a likelihood ratio test was performed to test goodness of fit. We found no evidence for difference in time evolution among treatment response groups; thus, the interaction term was excluded from the final model. A Wald test was applied to assess overall *P* value.

All models were controlled for age and gender. The *P* values reported in this article have been adjusted for multiple comparisons via the Bonferroni correction to prevent risk of a type I error. All models were assessed for violations of assumptions with a Shapiro-Wilks test for normality of distribution and a Bartlett test for homogeneity of variance and by visual inspection of data plots, density plot, and Q-Q plots for normality. We consider the results to be statistically significant at the level of  $P < .05$ .

## Results

Ninety-two patients with MDD and 73 healthy controls were included. The participants were predominantly women, and there was no significant difference between the groups in terms of gender ( $P = .94$ ) and age ( $P = .71$ ) distribution. There was no statistically significant correlation between age and CSFQ scores in healthy controls ( $P = .36$ ) or patients with MDD ( $P = .24$ ). No difference in CSFQ score was found between discontinuers (mean  $\pm$  SD;  $37.3 \pm 9.2$ ) and study completers ( $40.2 \pm 10.4$ ,  $P = .357$ ), nor were there any significant differences in the severity of depression symptoms (discontinuers,  $24 \pm 4$ ; completers,  $22.6 \pm 3.3$ ;  $P = .185$ ).



**Table 1.** Descriptive data for patient group and healthy controls.<sup>a</sup>

	Patients				Healthy controls
	Baseline	Week 4	Week 8	Week 12	Baseline
No. of responses					
HDRS <sub>6/17</sub>	92	84	82	80	0
CSFQ	92	69	67	75	73
Female, %	71.7	72.6	72.0	70.0	71.0
Age at baseline, y	26.8 ± 7.5 (18-56)	26.6 ± 7.4 (18-56)	27.0 ± 7.8 (18-56)	26.9 ± 7.4 (18-56)	26.4 ± 6.9 (19-52)
Measure <sup>b</sup>					
HDRS <sub>17</sub>	22.8 ± 3.4 (18-31)	14.0 ± 4.9 (2-29)	11.6 ± 6.4 (1-31)	9.6 ± 6.2 (0-25)	—
HDRS <sub>6</sub>	12.3 ± 1.6 (7-17)	7.3 ± 3.0 (1-16)	6.0 ± 3.7 (1-16)	4.9 ± 3.8 (0-14)	—
CSFQ	39.8 ± 10.3 (24-64)	39.7 ± 10.3 (18-61)	42.7 ± 10.4 (24-64)	43.8 ± 12.1 (21-66)	52.2 ± 9.5 (25-66)***
Women	35.7 ± 7.3 (22-53)	36.1 ± 8.2 (18-53)	39.3 ± 9.2 (24-61)	39.3 ± 10.2 (21-59)	49.0 ± 9.3 (25-64)***
Men	50.3 ± 9.3 (31-69)	49.2 ± 7.8 (33-61)	51.8 ± 8.0 (32-64)	54.6 ± 9.1 (33-66)	59.9 ± 4.4 (50-66)***
Sexual dysfunction, (total)%	60.8	58.0	40.3	38.7	12.3
Women	74.0	66.0	49.0	47.2	17.3
Men	27.0	36.8	16.7	18.2	0.0

Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire; HDRS<sub>6</sub>, 6-item Hamilton Depression Rating Scale; HDRS<sub>17</sub>, 17-item Hamilton Depression Rating Scale. <sup>a</sup>Data are shown as mean ± SD (range) unless noted otherwise. <sup>b</sup>HDRS<sub>17</sub> cutoff for mild depression: ≤17. CSFQ cutoff indicating sexual dysfunction: ≤41 for women, ≤47 for men. \*\*\**P* < .001 vs patients at baseline.

Demographics and clinical characteristics are presented in Table 1.

At baseline, the patients with depression scored significantly lower on the CSFQ than healthy controls (mean difference ± SE; 12.3 ± 1.5, *P* < .0001), indicating worse sexual function. Furthermore, significantly more patients with depression scored below the cutoff score, indicating sexual dysfunction, than healthy controls ( $\chi^2 = 40.17$ , *P* < .0001). Women scored significantly lower on the CSFQ than men in the group of patients with depression (14.6 ± 1.8, *P* < .0001) and the group of healthy controls (10.9 ± 1.6, *P* < .0001).

We found no significant association between the CSFQ and HDRS<sub>17</sub> at baseline (estimate [95% CI]; −0.3 [−0.78 to 0.18], *P* = .30). This was also the case when measured with the HDRS<sub>6</sub> (−0.46 [−1.42 to 0.51], *P* = .43). In these models, we observed no interactions with gender (all *P* > .57). An item correlation analysis showed that the sexual dysfunction item in the HDRS<sub>17</sub> was strongly negatively correlated with the CSFQ total score (coefficient; *r* = −0.55, *P* < .0001; for a full correlation matrix of the CSFQ and HDRS<sub>17</sub> items, see the supplementary material).

Figure 2 illustrates the distribution of CSFQ scores for each time point. The patients' mean CSFQ scores increased significantly from baseline to week 12 (mean difference ± SE; 4.0 ± 1.0, *P* = .001). We found no significant difference between the genders in terms of CSFQ score change from baseline to week 12 (*P* = .97).

The proportion of patients with sexual dysfunction significantly decreased from baseline to week 12 from 60.8% to 38.7% (*P* = .006), as illustrated in Figure 3 (for change in sexual function categories from baseline to week 12, see Table S1). At week 12, 20 patients (34% women, 9.1% men) no longer met the clinical threshold for sexual dysfunction, whereas sexual dysfunction emerging during treatment occurred in 6 patients (9.4% women, 4.5% men; for change in CSFQ subdomains between baseline and week 12, see supplementary material and Table S2).

Associations between changes in the CSFQ and the HDRS from baseline to week 12 were significantly and positively correlated for the HDRS<sub>17</sub> (estimate [95% CI]; 0.33 [0.10-0.56], *P* = .02) and borderline significant for the HDRS<sub>6</sub> after

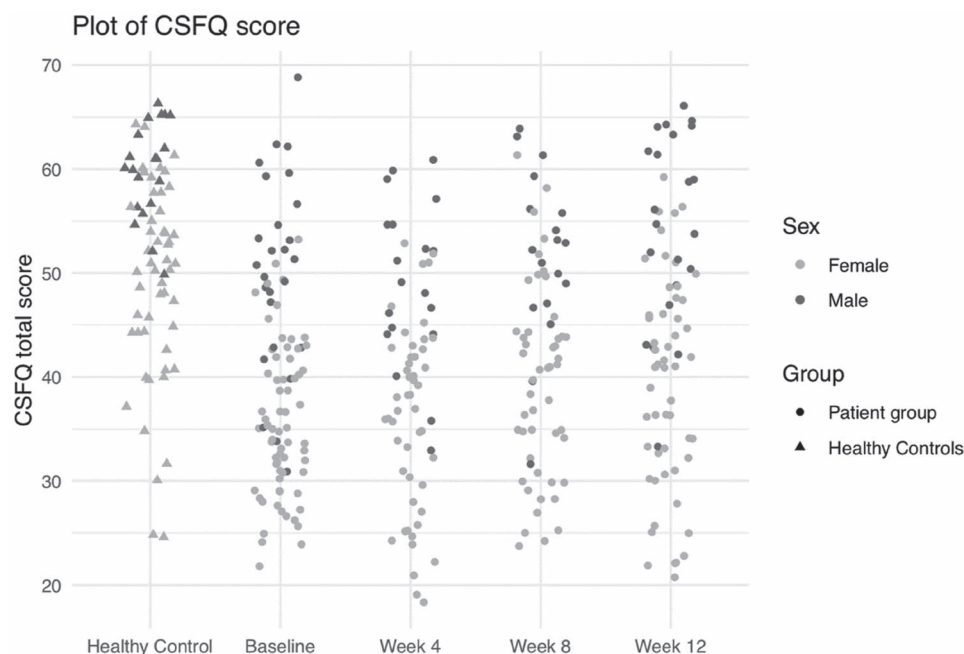
adjusting for multiple comparisons (0.27 [0.07-0.47], *P* = .028). No significant interactions with gender were observed in these models (all *P* > .1; see Figure S2 for an illustration).

At week 8, 28% (*n* = 23) of the depressed group met the criteria for remitter status, 55% (*n* = 45) for intermediate status, and 17% (*n* = 14) for nonresponder status. Our mixed model revealed no significant interaction among the treatment response groups in change in the CSFQ between baseline and week 12 (*P* = .62). At baseline, the CSFQ marginal mean was 39.3 for nonresponders and 42.0 for remitters (difference, 2.674), while at week 12, the marginal mean was 43.5 for nonresponders and 47.4 for remitters (difference, 3.945).

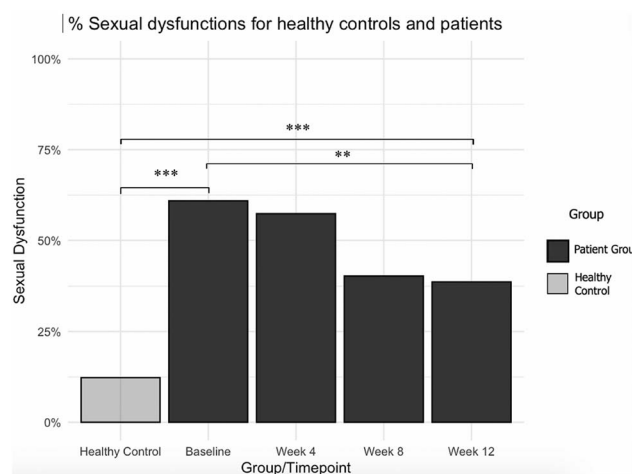
## Discussion

This study found that unmedicated patients with MDD reported impaired sexual function as compared with healthy controls. In patients and healthy controls, impaired sexual function was more pronounced in women than men. We did not find a significant association between the severity of MDD and sexual function in the unmedicated condition, nor were there any significant interaction effects with gender in this association. We found that treatment with antidepressants had an overall positive effect on sexual function for patients with MDD, which was associated with the amelioration of the symptoms of depression in a manner not dependent on gender. The treatment groups' response to SSRI did not predict change in sexual function.

The study shows that there was a high prevalence of impaired sexual function prior to treatment initiation in patients with MDD, with 60% scoring below the clinical cutoff indicating sexual dysfunction as opposed to only 12% of healthy controls. The prevalence of sexual dysfunction in the patients is in line with much of the previous research.<sup>8,20,21,35,36</sup> In contrast to our hypothesis, the severity of baseline MDD was not associated with the severity of sexual dysfunction, which to our knowledge has been reported once before, in a sample of 55 men and 79 women with MDD.<sup>8</sup> However, the majority of studies have reported a



**Figure 2.** Plot of the CSFQ scores for healthy controls and patients from baseline to week 12. Red, women; green, men. Circles, patients; triangles, healthy controls. CSFQ, Changes in Sexual Functioning Questionnaire.



**Figure 3.** Plot of the percentage of healthy controls and patients meeting the clinical cutoff score for sexual dysfunction for each time point. The CSFQ cutoff indicating sexual dysfunction is  $\leq 41$  for women and  $\leq 47$  for men. Light green, healthy controls; dark green, patients. \*\*  $P < .01$ . \*\*\*  $P < .001$ . CSFQ, Changes in Sexual Functioning Questionnaire.

significant association between the severity of MDD and the severity of sexual dysfunction,<sup>5,14,37</sup> as well as mood and sexual quality of life,<sup>38</sup> a divergence with our results perhaps explained by methodological and demographic differences. In the study by Bonierbale et al,<sup>5</sup> the data were obtained retrospectively, and the participants were already receiving an antidepressant treatment when the level of sexual function was assessed; however, all participants who had experienced a sexual problem before the onset of depression were excluded.<sup>5</sup>

Overall, patients with MDD experienced an improvement in sexual function after treatment with SSRI, which was significantly associated with a decrease in symptoms of depression. Over a third of the men and women who scored below

the clinical cutoff indicating sexual dysfunction at baseline changed category and were considered sexually functional at week 12, while the emergence of sexual dysfunction during treatment was observed in only 6 patients. The finding of an overall positive effect of SSRI treatment on sexual function is supported in other studies.<sup>7,39-41</sup> However, the findings are inconsistent with those in a comparable study by Khazaie et al,<sup>21</sup> who found a deterioration in sexual function during treatment with the SSRI fluoxetine. The authors noted that the proportion of patients exhibiting sexual dysfunction increased from 28% to 49% during 14 weeks of treatment. The diverging findings may be explained by the lower rate of baseline sexual dysfunction (28%) in the study by Khazaie et al as compared with ours (60%). In a study by Clayton et al,<sup>20</sup> the sexual function of patients with baseline sexual dysfunction improved during treatment with SSRI, whereas the sexual function of patients who were functional at baseline either improved minimally or deteriorated. Although previous studies have determined that treatment with SSRI is associated with sexual side effects,<sup>12</sup> our findings suggest that the alleviation of depressive symptoms generally outweighs the potential sexual side effects. Interestingly, the present study did not find any interaction effect of the response groups on sexual function during treatment with antidepressants. The sexual function of patients who were categorized as remitters did not improve more than that of nonresponders. This finding contrasts with that of Clayton et al, who found that change in sexual function was significantly associated with treatment response categories. In our study, the treatment response definition was much more conservative than in the study by Clayton et al. Consequently, our responder and nonresponder sample groups were substantially smaller, with less statistical power to detect any significant differences.

For healthy controls and patients with MDD, gender seemed to have an effect on sexual function, as the high prevalence of sexual dysfunction among the patients and

healthy controls was primarily or exclusively attributable to the women. While we did not find a statistically significant interaction with gender in the association between change in sexual function and change in severity of MDD, the overall significant association observed in this study is primarily attributable to the changes in women. Previous research has revealed that female sexuality is more sensitive to negative mood than is the case for men, whose sexual interest is less mood dependent.<sup>41</sup> Symptoms of depression and their alleviation may therefore have a greater impact on women than men.

There are some limitations to this study. First, the study does not include a placebo arm. Therefore, we cannot attribute the effects on sexual function to treatment with antidepressants per se. However, our finding that sexual function improved as depressive symptoms decreased during SSRI treatment, in spite of commonly reported sexual side effects associated with SSRIs, offers an important clinical perspective. Consequently, SSRI use might be a good first choice for patients with moderate to severe MDD, as well as in patients experiencing sexual dysfunctions due to MDD. Second, the sample size of our study population was relatively small. Consequently, our study might not have enough statistical power to detect significant interactions between treatment response groups and change in sexual function. The patients were young, which has been associated with fewer side effects of serotonergic antidepressant treatment.<sup>42</sup> We cannot rule out that the young age of the population serves as a protective factor against sexual side effects and the effect of decreased depressive symptoms on sexual function is therefore more pronounced.

The study has some strengths. It is a naturalistic study, reflecting the real-world settings in clinical practice. Importantly, our study included a baseline measurement of sexual function and MDD severity on drug-naïve patients prior to the initiation of treatment and revealed a strong negative association between depressive symptoms in unmedicated MDD and sexual function. The inclusion of a baseline sexual function measurement allowed us to differentiate between impaired sexual function attributable to MDD and impaired sexual function attributable to treatment with antidepressants. Furthermore, the study investigated clinically relevant changes and not “only” statistical changes based on the cutoffs of the CSFQ and HDRS<sub>17</sub>, as it was investigated whether the patients changed from the sexual dysfunctional level to the functional level or vice versa or had clinically relevant changes in their depression. The gender distribution in the current study reflects the distribution of patients diagnosed with MDD in clinical practice. The follow-up of 12 weeks—which extends beyond the acute phase of treatment in which previous research has observed a peak in sexual side effects<sup>22</sup>—is an additional strength to this study, heightening the ecologic validity. The inclusion of a healthy control group for comparison and the low dropout observed strengthen the quality of the data collected in the current study. Previous research has demonstrated that MDD and sexual dysfunction are bidirectional in nature and that they influence and potentially enhance each other.<sup>4</sup> Alleviating symptoms of sexual dysfunction is therefore pivotal in terms of addressing depression and vice versa. In clinical practice, this is important as 28% of patients have reported discontinuing their treatment due to sexual side effects.<sup>43</sup> This study clearly demonstrated that alleviating symptoms of depression was coupled with an improvement in sexual function. Providing information

about sexual dysfunction and the expected overall positive effect of treatment with antidepressants on sexual dysfunction should play a psychoeducative role in clinical practice when prescribing antidepressants to minimize treatment discontinuation and improve mental and sexual health.

## Acknowledgments

We thank all participants who took part in this study. We furthermore wish to thank Brice Ozenne for his assistance in performing the statistical analyses.

Conceptualization: V.G.F., G.M.K., M.B.J., A.G. Methodology: V.G.F., G.M.K., M.B.J., A.G. Project administration: V.G.F., M.B.J., A.G. Formal analysis: S.W., J.H.N. Writing—original draft: S.W., J.H.N. Writing—review and editing: V.G.F., A.G., D.S.S., J.H.N., M.B.J., S.A., G.M.K., S.W. Visualization: S.W. Supervision: V.G.F., A.G., D.S.S. Investigation: V.G.F., M.B.J. Funding acquisition: G.M.K., V.G.F. Data curation: S.W. Resources: A.M., S.A., V.G.F. V.G.F.: Lundbeck AS (lecturer), Sage Therapeutics (advisory board). AG: Lundbeck AS (lecturer), Pfizer/Viatris (lecturer, advisory board), Eli Lilly (consultant).

## Supplementary material

Supplementary material is available at *The Journal of Sexual Medicine* online.

## Funding

Economic support was granted from the Innovation Fund Denmark (5189-00087A), the Lundbeck Foundation (BrainDrugs: R279-2018-1145; Sahakian: R281-2018-131), the Research Fund of the Mental Health Services—Capital Region of Denmark, the Independent Research Fund Denmark (DFF-6120-00038), the G.J. Foundation, the Research Council of Rigshospitalet, the Augustinus Foundation (16-0058), and Savvaerksejer Jeppe Juhl og hustru Orita Juhls Mindelegat.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Conflicts of interest:** The authors have no personal or financial competing interests to declare.

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