Effects of Gepirone-ER on Sexual Function in Patients With Major Depressive Disorder

Tierney K. Lorenz, PhD; Mary F. Johnson, PhD; and Anita H. Clayton, MD

Abstract

Objective: To describe effects of gepirone extended-release (ER), an azapirone, on sexual function in patients receiving treatment for major depressive disorder (MDD).

Methods: Sexual function was assessed in 1,767 patients (67% women) across five Phase 3 randomized controlled clinical trials comparing gepirone-ER against placebo or active treatment with selective serotonin reuptake inhibitors (SSRIs) for treatment of MDD. All five trials assessed sexual functioning in the short term (8 weeks), with three including long-term extensions of 16, 20, or 44 weeks. Sexual function was assessed prospectively and throughout trials via clinical interview and well-validated survey measures.

Results: Across studies, gepirone-ER was equivalent to placebo on sexual side effects and treatment-emergent sexual dysfunction. Relative to SSRIs, gepirone-ER was associated with significantly better effect on sexual function across time points studied. Evidence from patients without sexual dysfunction at baseline demonstrates superiority of gepirone-ER over SSRIs in the first few weeks of treatment, when patients are most vulnerable to the negative effects of sexual side effects on medication nonadherence/discontinuation. Importantly, these benefits were maintained across treatment.

Conclusions: Gepirone-ER was not associated with sexual dysfunction in patients with MDD. Rates of sexual side effects and treatment-emergent sexual dysfunction with gepirone-ER were comparable to those reported for placebo and lower than sexual side effects reported for active treatment with SSRIs.

J Clin Psychiatry 2024;85(4):24m15357

Author affiliations are listed at the end of this article.

There is a critical need for treatment options for major depressive disorder (MDD) without risk of iatrogenic sexual dysfunction.[1] Although sexual problems are common in mood disorders, there is ample evidence of new or worsening sexual dysfunction with selective serotonin reuptake inhibitor (SSRI) or selective serotonin and norepinephrine inhibitor (SNRI) treatment.[1–5] Importantly, SSRI sexual side effects typically emerge within the first 2 weeks of treatment[6,7] before antidepressant efficacy is evident, causing significant issues with treatment noncompliance and potential relapse/persistence of depressive symptoms.[8] Treatment-emergent sexual dysfunction (TESD) contributes to relationship distress, worsening mood symptoms, and even suicidality.[9–12] Although sexual side effects are relatively less likely to cause discontinuation from treatment than other antidepressant side effects such as agitation,[13] they are also the most commonly experienced adverse event (impacting 40%–70% of patients)[13,14] and thus responsible for significantly decreased quality of life in the greatest number of patients. As such, the US Food and Drug Administration (FDA) requires providers to educate patients about sexual side effects, to consider this information when discussing patient preferences regarding adverse events and collaborating with patients on choice of medication prescribed.

The mechanism most often cited to explain SSRI and SNRI sexual side effects is their broad action on serotonin (5-hydroxytryptamine [5-HT]) systems that regulate sexual function and pleasure.[15–18] However, medications that do not act on serotonin reuptake and instead selectively target the 5-HT_{1A} receptor such as azapirones (e.g., buspirone) have considerably lower impact on sexual function and weight gain.[4,19–21] This may be due to 5-HT_{1A} receptors upregulating activity in dopaminergic reward systems relevant for sexual desire,[22,23] or action on the postsynaptic 5-HT_{1A} autoreceptor[24] downregulating serotonergic tone in neural regions that contribute to sexual inhibition and blockade of orgasmic reflexes.[25] Thus, from a mechanistic viewpoint, 5-HT_{1A} agonism may be less likely to cause sexual side effects or exacerbate or maintain existing sexual dysfunction.

Clinical Points

- Antidepressant sexual side effects are a significant clinical concern, contributing to low treatment adherence and poor quality of life.
- Gepirone-ER, a novel antidepressant recently approved for treatment for major depressive disorder (MDD), may have a lower burden of negative sexual effects and in some cases may improve existing sexual dysfunction in patients with MDD.
- Across 5 placebo controlled randomized clinical trials, gepirone-ER was associated with significantly lower rates of treatment-emergent sexual dysfunction than selective serotonin reuptake inhibitors (SSRIs), and no difference from placebo.

Gepirone extended-release (ER) is the first selective 5-HT_{1A} partial agonist to be FDA-approved for the treatment of MDD. Data from the 17 pivotal efficacy trials submitted to the FDA indicated that a lower percentage of patients randomized to gepirone-ER spontaneously reported sexual adverse events (2%) than those randomized to either placebo (3%) or any of the other antidepressants (10% fluoxetine, 17% paroxetine, and 14% imipramine). However, relying on spontaneously reported adverse events underestimates iatrogenic sexual effects by 4-fold,[26] as many patients are hesitant to report on their sexual functioning without direct prompting.[27,28] Thus, we here present a comprehensive analysis from prospectively collected sexual function measures from placebo- and active treatment-controlled clinical studies of gepirone-ER in MDD.

METHODS

Study Design and Participants

We examined data from the 5 randomized, double-blind, placebo-controlled trials of gepirone-ER for MDD in which sexual functioning was prospectively assessed using validated patient-reported sexual functioning scales. All 5 trials included an initial short-term (8-week) placebo controlled study phase (study numbers 134001, 134002, 134004, 134006, and 134017). Patients completing studies 134004, 134006, or 134017 could continue to receive double-blind study medication in their respective long-term extension studies: 134502 (44 weeks), 134503 (20 weeks), and 134506 (16 weeks). In study 134502, patients had the option to continue their assigned treatment or switch therapy in the extension study. All studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki, and all participants provided informed consent. Protocols were approved by the Independent Review Board of each participating trial site. Trials were conducted from June 1999 to January 2004, predating the requirements for trial registration. Trials were funded by Organon & Co and Fabre-Kramer Pharmaceuticals.

All 1,767 patients (ages 18–69 years) met MDD criteria as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*[29]). All participants were free of antidepressants and other medications that could interfere with sexual function with at least 2 weeks off antidepressants other than fluoxetine, which required a minimum washout of 4 weeks. Also, in study 134017, the protocol required eligible participants to be sexually active and have normal sexual functioning prior to enrollment.

Detailed data on trial design and the effectiveness of gepirone-ER in treatment of MDD symptoms are presented elsewhere[30–33] and summarized in Supplementary Tables 1 and 2. In sum, gepirone showed efficacy in treatment of MDD in adult patients as well as efficacy in relapse prevention in adult patients whose MDD had remitted with treatment. Also see supplementary materials for gender breakdown across studies (Supplementary Table 2), schedule of sexual function assessments during the treatment period of each study (Supplementary Table 3), and patient disposition across studies (Supplementary Table 4).

Randomization and Masking

Permuted block randomization allocated patients to treatment with gepirone-ER, placebo, or an SSRI (fluoxetine or paroxetine). Randomized double-blind, double-dummy techniques were used from randomization until study completion and data unblinding, with placebo administered in identically appearing over-encapsulated tablets, packaging, and instructions for use. Patients in the medication switching trial (134004) were able to continue their assigned treatment or switch during the extension phase; however, patients remained blinded to study condition.

Drug Administration

Each study started gepirone-ER doses at 20 mg/day and increased to 40 mg/day after 4–7 days; depending on clinical response and tolerability, doses were further titrated to 60 mg/day at day 7 and 80 mg/day at day 14. Active control drugs (fluoxetine, studies 134004 and 134017; paroxetine, study 134006) were given at levels within the approved dose range (fluoxetine 20–40 mg/day or paroxetine 20–60 mg/day).

Assessment of Sexual Function

There were 3 separate types of sexual function assessment: spontaneous report of adverse events, clinical

diagnosis, and patient-reported outcomes. Each provided parallel, but distinct forms of evidence of sexual effects of trial antidepressants, allowing evaluation of convergence of findings across assessment type.

Adverse event reporting. Adverse events (AEs) were collected at each study visit and coded using an established dictionary (MedDRA[34]). The following codes were used to define sexual dysfunction AE: sexual function and fertility disorders, orgasmic disorders and disturbances, sexual arousal disorders, and sexual desire disorders.

Diagnosis. Investigators interviewed patients to determine whether they met *DSM-IV* diagnostic criteria for the following disorders: sexual desire disorders (*DSM-IV* codes 302.71 or 302.79), sexual arousal disorder (*DSM-IV* code 302.72), orgasmic disorder (*DSM-IV* codes 302.73 and 302.74), and premature ejaculation (men only; *DSM-IV* code 302.75). Diagnostic interviews occurred at baseline; weeks 2, 4, and 8; and approximately every 4 weeks during the extension period of each study.

Rating scales. Across all 5 studies, validated clinical rating scales gave additional information on both overall sexual function and individual domains.

Derogatis Interview for Sexual Functioning (DISF) and Derogatis Interview for Sexual Functioning Self-Report (DISF-SR). Four studies (134001, 134002, 134004, and 134006) and their extensions used the DISF or DISF-SR. The DISF/DISF-SR[35] are brief instruments with 25 items that assess sexual functioning across 5 domains: sexual cognition/fantasy, sexual arousal, sexual behavior/experience, orgasm, and sexual drive/relationship. In validation studies, reliabilities of the total scale and subscales were good to excellent (Cronbach $\alpha = 0.70–0.80$) and inter-rater reliability of the interview version was similarly excellent (IRR = 0.84–0.92).[36] Gender-specific male and female versions were used in the present analyses. Items are rated on either a 0–4 Likert scale (8 items) or a 0–8 Likert scale (17 items), for a total score that ranges from 0 to 168. Higher scores denote better sexual function, and a change of 3–5 points in total score is considered clinically meaningful (i.e., a more rigorous metric than statistical significance alone).

Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14). Sexual function in one study (134017) and its extension was assessed using the CSFQ.[37] The CSFQ-14 is a self-report instrument with 14 items that capture sexual functioning in 5 domains: sexual pleasure, sexual desire/frequency, sexual desire/interest, sexual arousal, and orgasm. Items are scored on a 1–5 Likert scale, for a total score ranging from 14–70. Higher scores denote better sexual function, with thresholds indicating sexual dysfunction for total scores ≤41 for women and ≤47 for men.[37] A 2–3 point change/difference in total score is considered clinically meaningful. In validation studies, reliability of the measure was good to excellent (Cronbach $\alpha = 0.64–0.8$).[36,38,39]

Analytic Plan

All analyses were conducted in SAS version 9.4.

Data pooling and treatment of missingness. The individual studies were powered to detect a treatment effect for changes in depression symptoms, not for changes in sexual functioning. For this reason, studies of similar design that used the same assessment tool were pooled to improve power. All treated participants with at least one post-baseline assessment of sexual function were used for analysis. Out of all 1,767 participants receiving treatment in these 5 studies, a total of 1,520 participants (86%) had at least one post-baseline evaluation of sexual function (Supplementary Table 4). The percentage of participants providing sexual function data was relatively high in each of the treatment groups: gepirone (82%), placebo (84%), fluoxetine (96%), and paroxetine (91%). The missingness of individual items across measures was low (average = 9.6%) and not related to effects of interest (e.g., due to clerical error) and thus was addressed using imputation from the average of nonmissing items within the subscale and with use of mixed-effects models robust to missingness.

Primary analyses. Descriptive statistics present the incidence of sexual AEs and diagnoses coded for each study, alongside binomial tests evaluating differences in proportions between each pair of treatment groups.

Treatment effects on sexual function scale scores were evaluated using mixed models for repeated measures, with change from baseline score as the dependent variable. The models included fixed effects for treatment, center (or study for pooled analyses), visit, and treatment-by-visit interaction, with visit as the repeating factor and patient as a random effect, and baseline score as a covariate. An unstructured covariance matrix was specified for repeated measures (i.e., within-participant correlations). The scores on the relevant rating scale (DISF or CSFQ) obtained prior to the first dose of study drug served as each patient's baseline value.

We evaluated 2 paradigms: evidence of no negative effect of medication, and evidence of superiority relative to active control. To establish no effect on sexual functioning, data had to show medication did not increase sexual dysfunction compared to placebo in a study with an active control that *did* show a significantly negative effect on sexual function, demonstrating assay sensitivity.[28] Assay sensitivity was declared if the active control was associated with significantly more sexual dysfunction than placebo, with $P \leq .05$. If this test was positive, gepirone-ER's effect on sexual function was interpreted based on the 2-sided 95% CI for the difference (gepirone-ER vs placebo). In Tables 1 and 2, we highlight instances where the lower limit of the CI exceeds −1, indicating the drug is not inferior to placebo; this 1-point margin is greater than the change deemed clinically meaningful for either scale (2–3 points for CSFQ and 3–5 points for DISF). Superiority of gepirone-ER was

Table 1.

Change in DISF Total Scores From Baseline at Each Visit (Pooled Studies 134004 and 134006)

DISF total score	Gepirone (N = 257)[a]	Placebo (N = 267)	SSRI (N = 261)	Treatment difference		
				Gepirone—placebo	SSRI—placebo	SSRI—gepirone
All participants						
Week 2						
n	230	251	244			
Mean[b]	3.1	0.1	−6.0	3.0	−6.1	−9.1
95% CI				−0.06, 6.12	−9.14, −3.05	−12.24, −6.01
P value				.0546	**<.0001**	**<.0001**
Week 4						
n	209	236	228			
Mean	6.1	2.8	−4.7	3.3	−7.4	−10.8
95% CI				−0.32, 6.97	−11.02, −3.88	−14.44, −7.10
P value				.0734	**<.0001**	**<.0001**
Week 8						
n	187	213	208			
Mean	7.2	3.8	−0.4	3.4	−4.2	−7.6
95% CI				−0.88, 7.63	−8.37, −0.06	−11.87, −3.31
P value				.1197	**.0469**	**.0005**
Overall[c]						
n	234	256	261			
Mean	6.3	3.0	−2.4	3.3	−5.4	−8.7
95% CI				−0.16, 6.78	−8.81, −2.00	−12.22, −5.22
P value				.0617	**.0019**	**<.0001**
Women						
Week 2						
n	156	176	175			
Mean	2.4	−2.6	−8.7	5.0	−6.0	−11.0
95% CI				1.17, 8.82	−9.72, −2.30	−14.84, −7.18
P value				**.0105**	**.0015**	**<.0001**
Week 4						
n	141	164	169			
Mean	5.9	1.3	−6.1	4.6	−7.4	−12.0
95% CI				0.22, 9.02	−11.62, −3.19	−16.40, −7.65
P value				**.0395**	**.0006**	**<.0001**
Week 8						
n	124	145	154			
Mean	6.7	2.1	−1.6	4.5	−3.7	−8.2
95% CI				−0.84, 9.91	−8.82, 1.42	−13.56, −2.92
P value				.0977	.1559	**.0025**
Overall						
n	158	178	179			
Mean	5.8	1.2	−3.9	4.6	−5.1	−9.7
95% CI				0.30, 8.95	−9.23, −0.95	−14.01, −5.42
P value				**.0361**	**.0161**	**<.0001**
Men						
Week 2						
n	74	75	69			
Mean	0.2	1.5	−3.8	−1.4	−5.4	-4.0
95% CI				−6.46, 3.74	−10.60, −0.10	−9.26, 1.27
P value				.6009	**.0458**	.1359
Week 4						
n	68	72	59			
Mean	2.1	1.1	−5.9	1.0	−7.0	−8.0
95% CI				−5.57, 7.47	−13.82, −0.27	−14.82, −1.16
P value				.7739	**.0416**	**.0220**
Week 8						
n	63	68	54			
Mean	3.6	2.5	−2.6	1.2	−5.0	−6.2
95% CI				−5.64, 7.97	−12.09, 2.08	−13.34, 0.99
P value				.7354	.1653	.0910

(continued)

Table 1 (continued).

DISF total score	Gepirone (N = 257)[a]	Placebo (N = 267)	SSRI (N = 261)	Treatment difference		
				Gepirone—placebo	SSRI—placebo	SSRI—gepirone
Overall						
n	76	78	69			
Mean	2.7	1.9	−3.7	0.7	−5.6	−6.4
95% CI				−5.02, 6.51	−11.63, 0.35	−12.42, −0.34
P value				.7989	.0650	**.0384**

[a]N = participants with DISF total scores at baseline and at least one post-baseline visit.
[b]Least-squares means and *P* values from a mixed model with fixed effects for treatment, study, week, gender (for all participants analysis), and treatment-by-week interaction term, with week as the repeating factor, patient as a random effect, and baseline score as a covariate. Positive mean change (blue font) denotes improvement in sexual function from baseline; negative mean change (red font) denotes worsening. Cells are highlighted in blue if the lower limit of the 95% CI is above −1.0, indicating that gepirone's effect is noninferior to placebo. *P* values ≤ .05 (2-sided) are in **boldface**.
[c]Overall tests based on contrasts of the least-squares means weighted across weeks for each treatment pair.
Abbreviation: DISF = Derogatis Interview of Sexual Functioning.

indicated when pairwise treatment comparisons (gepirone-ER vs SSRI and gepirone-ER vs placebo) of total scores on rating scales favored gepirone-ER with $P \leq .05$. Sub-domains of the sexual function scores were evaluated in a similar manner.

Subgroup analyses. Sexual function scores were analyzed by gender and by presence or absence of pretreatment sexual dysfunction as determined by established cutoffs for DISF and CSFQ total scores.[32,37,40] As patients were medication free at baseline, these analyses examined changes in preexisting sexual dysfunction, potentially associated with the major depressive episode.

RESULTS

Participant Demographics and Clinical Characteristics

Participants were predominantly White (81%) and women (67%), with an average age of 39 years. For roughly half of participants, the duration of the current depressive episode was less than 1 year; the average age at first episode was 25 years. Treatment groups were comparable with respect to baseline age, gender, racial distribution, depression severity, and prevalence of sexual dysfunction. Pretreatment sexual function scores were comparable among treatment groups, but higher in men than women in each study. See Supplementary Tables 5 and 6 for detailed demographic data and mean pretreatment sexual functioning data at baseline for all participants.

Sexual AEs

Figure 1 illustrates pooled safety data from the 5 short-term studies, showing the overall incidence of sex-related AEs was lower during treatment with gepirone-ER (3%) compared to placebo (5%) and each of the SSRI comparators: fluoxetine (15%) and paroxetine (28%). SSRI treatment was associated with a 4-fold higher risk of sex-related AE vs placebo (RR = 4.21, $P < .0001$), whereas patients treated with gepirone-ER had a 40% lower risk of experiencing a sex-related AE than patients treated with placebo (RR = 0.60, $P = .0805$).

Diagnosis of Sexual Dysfunction

TESD was defined as a newly diagnosed sexual disorder (by *DSM-IV* criteria) that was not present at baseline. Among patients without a sexual disorder at baseline (72%–87% of the population in each study), the incidence of TESD for gepirone-ER (9%) was comparable to placebo (10%) and significantly less than in the SSRI group (27%). Disorders related to sexual desire and orgasm were significantly more common with use of SSRIs than either gepirone-ER or placebo (Supplementary Table 7). See Supplementary Materials for detailed data on incidence of TESD across different domains of sexual function (Supplementary Table 7) and by gender (Supplementary Table 8).

Rating Scales

Overall effects of treatment on sexual functioning scores. Table 1 summarizes results from analysis of DISF total scores and each of the 5 DISF domains. Patients treated with SSRIs demonstrated statistically significant reductions in total DISF scores compared to placebo and gepirone-ER at all visits. The mean change in DISF scores from baseline was numerically (although not always significantly) better for gepirone-ER than placebo at every visit. Likewise, the lower 95% confidence limit on the difference between mean scores (gepirone-ER vs placebo) exceeded −1 in many instances, providing evidence that gepirone-ER's effect on sexual function was no worse than placebo. The direction of treatment effects was similar across genders, with greater effects in women. Likewise, similar patterns were observed across all 5 subdomains (Supplementary Table 9). Gepirone-ER treatment was associated with better function in every domain relative to placebo; the lower limit of the 95% CI

Table 2.

Changes in CSFQ Total Scores From Baseline at Each Visit in Patients With Normal Baseline Sexual Function (Study 134017)

CSFQ total score	Gepirone (N = 155)[a]	Placebo (N = 155)	SSRI (N = 159)	Treatment difference: Gepirone—placebo	Treatment difference: SSRI—placebo	Treatment difference: SSRI—gepirone
Week 2						
n	100	118	108			
Mean[b]	0.2	−0.0	−1.8	**0.3**	**−1.8**	**−2.1**
95% CI				−1.04, 1.59	−3.09, −0.52	−3.42, −0.73
P value				0.6812	**0.0062**	**0.0025**
Week 4						
n	86	113	103			
Mean	1.5	−0.6	−2.1	2.1	−1.5	−3.6
95% CI				0.36, 3.86	−3.21, 0.14	−5.43, −1.86
P value				**0.0180**	0.0717	**<0.0001**
Week 8						
n	79	105	90			
Mean	1.7	0.3	−2.2	1.4	−2.5	−3.9
95% CI				−0.42, 3.26	−4.25, −0.71	−5.79, −2.01
P value				.1290	**.0062**	**<.0001**
Overall[c]						
n	101	122	109			
Mean	1.4	−0.0	−2.1	1.5	−2.1	−3.6
95% CI				−0.03, 2.94	−3.54, −0.68	−5.09, −2.05
P value				.0547	**.0039**	**<.0001**

[a]N = Participants with CSFQ total scores at baseline and at least one post-baseline visit.
[b]Least-squares means and *P* values from a mixed model with fixed effects for treatment, center, week, gender, and treatment by week interaction term, with week as the repeating factor, patient as a random effect, and baseline score as a covariate. Positive mean change (blue font) denotes improvement in sexual function from baseline; negative mean change (red font) denotes worsening. Cells are highlighted in blue if the lower limit of the 95% CI is above −1.0, indicating that gepirone's effect is noninferior to placebo. *P* values ≤ .05 (two-sided) are in **bold font**.
[c]Overall tests based on contrasts of the least-squares means weighted across weeks for each treatment pair.
Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire.

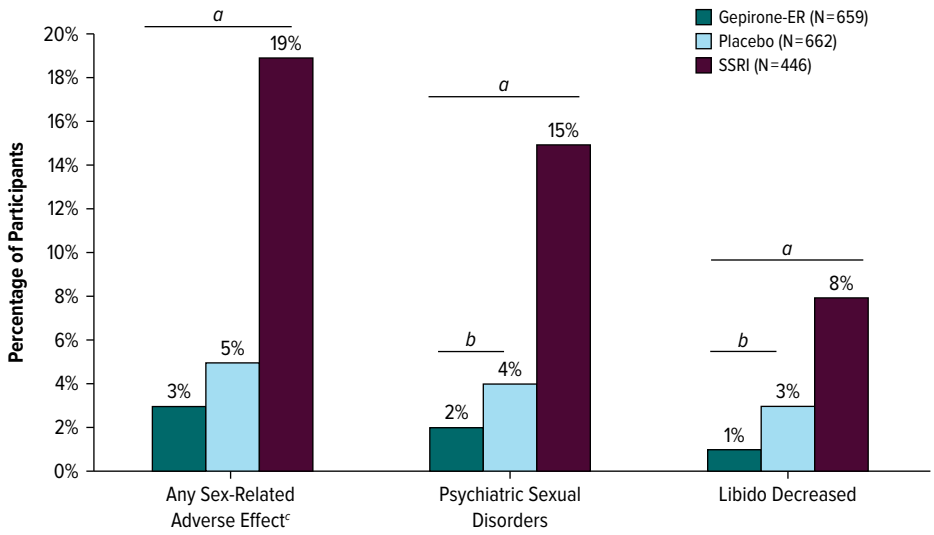
(gepirone-ER vs placebo) exceeded −1.0 in all but 2 instances and never fell below −1.11.

Effects of treatment on sexual functioning in patients without sexual dysfunction at baseline. In 1 study (134017), the protocol required participants to be sexually active prior to enrollment and excluded participants with sexual arousal disorder, anorgasmia, premature ejaculation, erectile dysfunction, dyspareunia, or vaginismus. In this group with normal sexual function at baseline, CSFQ scores showed a sharp and significant decline during fluoxetine treatment, significant improvement with gepirone-ER, and no change in the placebo group (Figure 2; Table 2). At week 8 (study end point), patients treated with fluoxetine had a mean reduction in CSFQ total score of −2.2 ± 0.68, which was statistically significant compared to increase in CSFQ total score observed on placebo (+0.3 ± 0.64, $P = .006$) and gepirone-ER (+1.7 ± 0.73, $P < .001$). Of note, the mean improvement in CSFQ scores at week 4 on gepirone-ER was also statistically significant and clinically meaningful (i.e., differences of 2 points or more) when compared to placebo (2.1, 95% CI, 0.4–3.9, $P = .018$) and fluoxetine (3.6, 95% CI, 1.9–5.4, $P < .0001$).

These results are supported by pooled analysis of data from participants without sexual dysfunction at baseline in the 2 active comparator studies that used the DISF scale (Figure 3). The reduction in DISF total score averaged across all study weeks was statistically significant in the SSRI group (−15.1 ± 2.3) compared to placebo (−5.4 ± 2.0, $P = .002$) and gepirone-ER (−1.7 ± 2.2, $P < .001$) based on a mixed model analysis. On average, patients on gepirone-ER showed less reduction in DISF scores than placebo (+3.7, 95% CI, −2.2 to +9.6).

Switching from SSRI to Gepirone-ER. Participants who completed the 8-week study 134004 had the option to continue their assigned treatment or switch therapy in the 44-week extension study 134502. Supplementary Figure 1 shows the change in DISF scores in participants who finished 8 weeks of treatment with fluoxetine in the acute study and either switched to gepirone-ER (n = 54) or continued fluoxetine (n = 39) during the extension study. Those who switched to gepirone-ER experienced greater improvement in sexual function than those who continued the SSRI. This effect was mainly driven by women who made up the majority of participants in this cohort (65%; Supplementary Figures 2 and 3). It should be noted that depressive symptoms (as measured by the Hamilton Depression Rating Scale) also improved in participants who switched treatments in this study, with improvement in participants who switched from

Figure 1.
Incidence of Sexual Dysfunction Adverse Events (Pooled Studies)



[a]SSRI significantly higher than placebo ($P < .0001$) and gepirone-*ER* ($P < .0001$).
[b]Gepirone-ER significantly lower than placebo ($P < .05$).
[c]Adverse effects included MedDRA high-level group terms: sexual function and fertility disorders, orgasmic disorders and disturbances, sexual arousal disorders, and sexual desire disorders.
Abbreviations: ER = extended-release, SSRI = selective serotonin reuptake inhibitor.

fluoxetine to gepirone-ER as well as those who switched from gepirone-ER to fluoxetine.

DISCUSSION

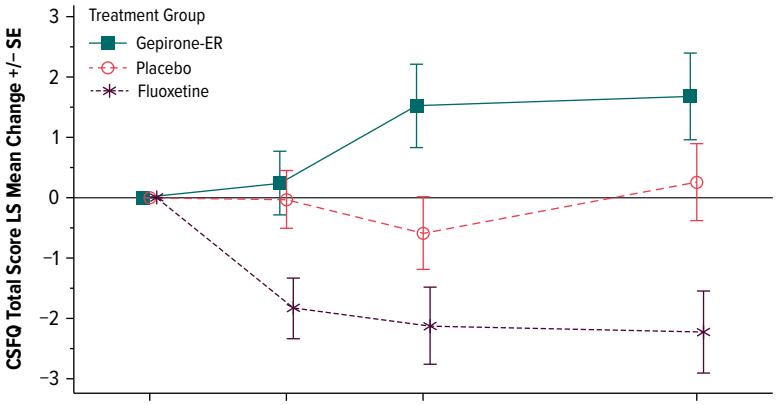
Data from 5 randomized, double-blinded controlled clinical trials suggest that gepirone-ER does not adversely affect sexual function in depressed patients and, in some cases, may improve sexual dysfunction. Patients without sexual dysfunction at baseline were less likely to meet diagnostic criteria for TESD and showed less decline in scores on validated patient-reported sexual functioning measures with gepirone-ER than those assigned to either placebo or SSRIs. Among patients who reported sexual dysfunction prior to randomization, treatment with gepirone-ER was associated with significantly greater improvement in sexual function than either placebo or SSRI. Finally, patients who had previously experienced sexual side effects of SSRIs showed significant improvement of sexual function after switching to gepirone-ER. Collectively, these results point to a favorable sexual functioning profile for gepirone-ER in patients with MDD. Other azapirones (such as buspirone)[19] and serotonin reuptake inhibitors with 5-HT_{1A} receptor agonism as an additional mechanism (such as vilazodone)[41] also have lower rates of sexual side effects than SSRIs, pointing to 5-HT_{1A} receptor agonism as a mechanism that preserves, and in some cases improves, sexual function in patients with MDD. These data support the inclusion of gepirone-ER in the clinician's toolkit of novel-mechanism antidepressants lacking negative effect on sexual function.

When evaluating antidepressant effects on sexual dysfunction, two kinds of clinical questions must be addressed[28]: how the agent compares against existing (iatrogenic) treatments and how the agent compares to placebo. Both must be answered with evidence from designs that use well-validated instruments with prospective assessment of sexual function prior to initiating treatment, both because sexual dysfunction is a common presenting symptom of MDD[42,43] and because fewer than 20% of patients who experience sexual side effects will report them unless specifically prompted to do so.[27,44] All 5 of the trials reported here met these rigorous criteria: all used doses sufficient to generate significant improvements on MDD symptoms, all conducted measurement of sexual function at baseline and end of study (with 3 studies conducting measurement periodically during the study), and all used scales highlighted by expert consensus for their validity and utility in capturing changes in sexual functioning.[28,45,46]

To assess if a medication causes no more sexual dysfunction than placebo, supporting evidence must include *both* placebo and active control conditions to verify that the trial was truly able to detect sexual dysfunction. If both the placebo and the experimental drug show no effect on sexual function, this could be a true null effect, or could reflect a design that is unable to

Figure 2.

Change in Sexual Functioning Among Participants With No Sexual Dysfunction at Baseline (Study 134017)



	Baseline	wk 2	wk 4	wk 8
Gepirone-ER	108	100	86	79
Placebo	125	118	113	105
Fluoxetine	114	108	103	90

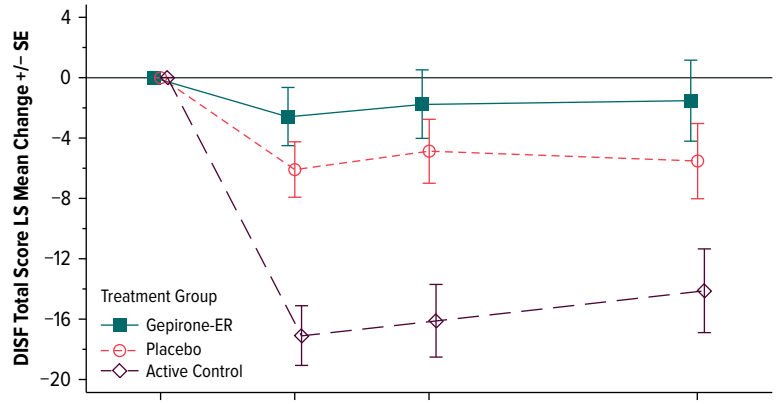
Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire, ER = extended-release, LS = least squares.

detect any changes in sexual function. Thus, establishing true lack of effect must be made with data showing a negative effect of an active control drug, establishing assay sensitivity. The data presented here meet that criterion, with 2 separate trials demonstrating no decline in sexual function for gepirone-ER and placebo conditions but a significant decline for SSRIs.

When assessing comparative superiority to existing treatments, evidence should include trials with patients who have experienced sexual dysfunction on the active comparator, as one of the strongest predictors of sexual side effects with a new medication is prior experience of sexual side effects, even when subsequent treatment is from a different medication class.[47] The data presented

Figure 3.

Change in Sexual Functioning Among Participants With No Sexual Dysfunction at Baseline (Pooled Studies 134004 and 134006).



	Baseline	wk 2	wk 4	wk 8
Gepirone-ER	96	89	76	69
Placebo	102	99	93	81
Active Control	90	85	73	69

Abbreviations: DISF = Derogatis Interview for Sexual Functioning, ER = extended-release, LS = least squares.

here also meet this criterion, showing that not only is gepirone-ER significantly less likely to cause TESD relative to SSRIs but it also is associated with significant benefits to sexual function in patients switching *from* SSRIs. Given the limited number of empirically supported treatments that address SSRI-induced sexual dysfunction[19,48]—particularly in women[49]—these data are promising.

Although the relative superiority of gepirone-ER was observed well into the maintenance phase (more than 6 months), the distinctions between gepirone-ER and SSRIs are particularly noteworthy in the acute adjustment phase within the first few weeks of treatment initiation. The first 4 weeks of treatment are a critical period for treatment success, as patients start to experience side effects but not depressive symptom reduction.[6,7] Patients who experience sexual side effects within the first 4 weeks of antidepressant therapy are significantly more likely to discontinue treatment prior to remission[6,8,12] and report significantly worsened quality of life.[13] These data thus provide evidence that gepirone-ER is associated with significantly fewer distressing side effects during a particularly critical treatment period.

There were some limitations that must be considered. As is common in active-control antidepressant trials,[50] attrition prevented the estimation of treatment effects in all patients randomized to treatment. While the rate of attrition was not higher than typical for depression treatment studies (25%–30%) and our analyses used statistical methods robust to missingness, it cannot be ruled out that participants who experienced worsening of sexual function were more likely to drop out. However, there is no reason to expect that dropout due to sexual side effects differed by treatment arm, and, thus, comparisons across treatments are likely sound. No data are available on the relationship status of participants in these trials, which may contribute to error in sexual functioning measures.[51] However, this limitation is partially mitigated in one study (134017) by use of the CSFQ, which incorporates direct assessment of sexual (in)activity into scoring. Across studies, there was a gender imbalance with more women than men participating. While this disparity is representative of population-level gender differences in MDD[52] and in clinical trials for MDD, and the sample of men was sufficiently large to power stratified analyses, the higher proportion of women in these data should be taken into account when interpreting overall effects. The samples were predominantly White and non-Hispanic, which limits generalizability. It is unknown how racial disparities in mental health care access and bias[53] may influence the effects reported here. Despite these limitations, there were also considerable strengths in multiple converging lines of evidence using well-controlled trials with prospective, validated measures of sexual functioning.

CONCLUSION

Across studies, gepirone-ER demonstrated equivalence to placebo and superiority to SSRIs on sexual functioning outcomes, in patients both with and without existing sexual dysfunction at baseline. Results were similar across genders and phases of sexual function. Importantly, patients randomized to gepirone-ER did not experience the precipitous decline in sexual function during the first 2–4 weeks of treatment that is characteristic of SSRIs, suggesting that gepirone-ER may be better tolerated during this critical window. Moreover, these differences were observed well into longer term follow-up, suggesting the persistence of both the negative effects of SSRIs and null or beneficial effects of gepirone-ER on sexual function. In sum, these findings suggest that gepirone-ER is not associated with sexual dysfunction in patients diagnosed with MDD and in some cases is associated with improvements in sexual functioning.

Article Information

Published Online: October 21, 2024. https://doi.org/10.4088/JCP.24m15357

Submitted: March 29, 2024; accepted July 23, 2024.

To Cite: Lorenz TK, Johnson MF, Clayton AH. Effects of gepirone-ER on sexual function in patients with major depressive disorder. *J Clin Psychiatry.* 2024;85(4):24m15357.

Author Affiliations: Center for Brain, Biology and Behavior, University of Nebraska-Lincoln, Lincoln, Nebraska (Lorenz); Department of Psychology, University of Nebraska – Lincoln, Lincoln, Nebraska (Lorenz); MJbiostat, LLC, Spring Lake, New Jersey (Johnson); Department of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, Virginia (Clayton).

Corresponding Author: Tierney K. Lorenz, PhD, Center for Brain, Biology and Behavior, University of Nebraska-Lincoln, C69 East Stadium, Lincoln, NE 68588 (tierney.lorenz@unl.edu).

Relevant Financial Relationships: No authors received renumeration for the writing or editing of this paper. **Dr Lorenz** has received grant/research support from the Sexual Health and Wellness Institute and the National Institutes of Health. **Dr Clayton** serves on the advisory board or as a consultant of AbbVie, Inc, Biogen, Brii Biosciences, Fabre-Kramer, Initiator Pharma, Janssen Research & Development, LLC, Seaport Therapeutics (formerly PureTech Health), Reunion Neuroscience, Inc, S1 Biopharma, Sertsei Pharmaceuticals, Inc and Vella Bioscience, Inc; and has received grant/research support from Autobahn, Daré Bioscience, Janssen, Neumora Therapeutics, Otsuka, and Relmada Therapeutics, Inc. **Dr Clayton** also reports royalties/copyright with Ballantine Books/Random House, the Changes in Sexual Functioning Questionnaire; and Guilford Publications; and has shares with Mediflix LLC and restricted stock units with S1 Biopharm. **Dr Johnson** reports no relevant financial relationships.

Funding/Support: The data used for this analysis were provided by Organon and Fabre-Kramer Pharmaceuticals, who conducted all study trials reported here. Fabre-Kramer Pharmaceuticals provided funding to cover the publication of the supplementary materials accompanying this article.

Role of the Funders/Sponsors: Organon and Fabre-Kramer Pharmaceuticals conducted all study trials and supplied the data for this analysis. The first author, who has no past or present affiliation with either company, completed an independent review of the data and analysis and was responsible for interpretation of the evidence. Although staff at Fabre-Kramer Pharmaceuticals reviewed the manuscript for factual content, final approval for the decision to submit the manuscript was the sole decision of the authors.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the University of Nebraska.

Acknowledgments: The first author is supported by the National Institute of General Medical Sciences of the National Institutes of Health (P20GM130461) and the Rural Drug Addiction Research Center at the University of Nebraska-Lincoln.

Additional Information: The original data for these analyses are available upon request from the senior author.

ORCID: Tierney K. Lorenz: https://orcid.org/0000-0002-4999-1584; Anita Clayton: https://orcid.org/0000-0003-4372-0879

Supplementary Material: Available at Psychiatrist.com.

References

1. Kearns B, Cooper K, Orr M, et al. The incidence and costs of adverse events associated with antidepressants: results from a systematic review, network meta-analysis and multi-country economic model. *Neuropsychiatr Dis Treat*. 2022;18:1133–1143.
2. Tarchi L, Merola GP, Baccaredda-Boy O, et al. Selective serotonin reuptake inhibitors, post-treatment sexual dysfunction and persistent genital arousal disorder: a systematic review. *Pharmacoepidemiol Drug Saf*. 2023;32(10):1053–1067.
3. Trinchieri M, Trinchieri M, Perletti G, et al. Erectile and ejaculatory dysfunction associated with use of psychotropic drugs: a systematic review. *J Sex Med*. 2021;18(8):1354–1363.
4. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol*. 2009;29(3):259–266.
5. Stephenson JJ, Touya M, Chrones L, et al. Antidepressant use and treatment-emergent sexual dysfunction among patients with major depressive disorder: results from an internet-based survey study. *J Affect Disord Rep*. 2024;16(11):100750.
6. Braund TA, Tillman G, Palmer DM, et al. Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: an iSPOT-D report. *Transl Psychiatry*. 2021;11(1):417.
7. Dunn JA, Arakawa R, Greist JH, et al. Assessing the onset of antidepressant-induced sexual dysfunction using interactive voice response technology. *J Clin Psychiatry*. 2007;68(4):525–532.
8. Golder S, Medaglio D, O'Connor K, et al. Reasons for discontinuation or change of selective serotonin reuptake inhibitors in online drug reviews. *JAMA Netw Open*. 2023;6(7):e2323746.
9. Khalifian CE, Knopp K, Wilks CR, et al. The association between sexual functioning and suicide risk in US Military veteran couples seeking treatment for post-traumatic stress disorder. *Arch Sex Behav*. 2020;49(5):1601–1613.
10. Blais RK, Xu B, Hoyt T, et al. Sexual compulsivity, erectile dysfunction, and suicidality among male survivors of military sexual violence. *J Trauma Stress*. 2022;35(6):1709–1720.
11. Hieronymus F, Lisinski A, Eriksson E, et al. Do side effects of antidepressants impact efficacy estimates based on the Hamilton Depression Rating Scale? A pooled patient-level analysis. *Transl Psychiatry*. 2021;11(1):249.
12. Jacobsen PL, Thorley EM, Curran C. Real-world patient experience with sexual dysfunction and antidepressant use in patients with self-reported depression: a cross-sectional survey study. *Neurol Psychiatry Brain Res*. 2020;36:57–64.
13. Garcia-Marin LM, Mulcahy A, Byrne EM, et al. Discontinuation of antidepressant treatment: a retrospective cohort study on more than 20,000 participants. *Ann Gen Psychiatry*. 2023;22(1):49.
14. Winter J, Curtis K, Hu B, et al. Sexual dysfunction with major depressive disorder and antidepressant treatments: impact, assessment, and management. *Expert Opin Drug Saf*. 2022;21(7):913–930.
15. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord*. 1998;51(3):215–235.
16. Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. *Postgrad Med*. 2014;126(2):91–99.
17. Lasker GF, Halis F, Gokce A. Selective serotonin reuptake inhibitors for premature ejaculation: review of erectile and ejaculatory side effects. *Curr Drug Saf*. 2014;9(2):118–126.
18. Bijlsma EY, Chan JSW, Olivier B, et al. Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? *Pharmacol Biochem Behav*. 2014;121:88–101.
19. Luft MJ, Dobson ET, Levine A, et al. Pharmacologic interventions for antidepressant-induced sexual dysfunction: a systematic review and network meta-analysis of trials using the Arizona sexual experience scale. *CNS Spectr*. 2022;27(4):496–505.
20. Olivier JDA, Esquivel-Franco DC, Waldinger MD, et al. Serotonin and sexual behavior. In: Tricklebank MD, Daly E, eds. *The Serotonin System: History, Neuropharmacology, and Pathology*. Elsevier; 2019:117–132.
21. Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. *Drug Saf*. 2014;37(1):19–31.
22. Croft HA. Understanding the role of serotonin in female hypoactive sexual desire disorder and treatment options. *J Sex Med*. 2017;14(12):1575–1584.
23. Stahl SM. Mechanism of action of flibanserin, a multifunctional serotonin agonist and antagonist (MSAA), in hypoactive sexual desire disorder. *CNS Spectr*. 2015;20(1):1–6.
24. Smith ALW, Harmer CJ, Cowen PJ, et al. The serotonin 1A (5-HT_{1A}) receptor as a pharmacological target in depression. *CNS Drugs*. 2023;37(7):571–585.
25. Snoeren EMS, Veening JG, Olivier B, et al. Serotonin 1A receptors and sexual behavior in male rats: a review. *Pharmacol Biochem Behav*. 2014;121:102–114.
26. Montejo A, Llorca G, Izquierdo J, et al. [Sexual dysfunction secondary to SSRIs. A comparative analysis in 308 patients]. *Actas Luso Esp Neurol Psiquiatr Cienc Afines*. 1996;24(6):311–321.
27. Moreira ED, Glasser DB, Nicolosi A, et al; GSSAB Investigators' Group. Sexual problems and help-seeking behaviour in adults in the United Kingdom and continental Europe. *BJU Int*. 2008;101(8):1005–1011.
28. Khin NA, Kronstein PD, Yang P, et al. Regulatory and scientific issues in studies to evaluate sexual dysfunction in antidepressant drug trials. *J Clin Psychiatry*. 2015;76(8):1060–1063.
29. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. American Psychiatric Publishing, Inc; 1994.
30. Fabre LF, Smith LC. The effect of major depression on sexual function in women. *J Sex Med*. 2012;9(1):231–239.
31. Fabre LF, Brown CS, Smith LC, et al. Gepirone-ER treatment of hypoactive sexual desire disorder (HSDD) associated with depression in women. *J Sex Med*. 2011;8(5):1411–1419.
32. Fabre LF, Clayton AH, Smith LC, et al. Association of major depression with sexual dysfunction in men. *J Neuropsychiatry Clin Neurosci*. 2013;25(4):308–318.
33. Keam SJ. Gepirone extended-release: first approval. *Drugs*. 2023;83(18):1723–1728.
34. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109–117.
35. Derogatis LR. The Derogatis Interview for Sexual Functioning (DISF/DISF-SR): an introductory report. *J Sex Marital Ther*. 1997;23(4):291–304.
36. Meston CM, Derogatis LR. Validated instruments for assessing female sexual function. *J Sex Marital Ther*. 2002;28(suppl 1):155–164.
37. Keller A, McGarvey EL, Clayton AH. Reliability and construct validity of the Changes in Sexual Functioning Questionnaire short-form (CSFQ-14). *J Sex Marital Ther*. 2006;32(1):43–52.
38. Clayton AH, McGarvey EL, Clavet GJ, et al. Comparison of sexual functioning in clinical and nonclinical populations using the Changes in Sexual Functioning Questionnaire (CSFQ). *Psychopharmacol Bull*. 1997;33(4):747–753.
39. Clayton AH, McGarvey EL, Clavet GJ. The changes in sexual functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull*. 1997;33(4):731–745.
40. Jacobsen PL, Mahableshwarkar AR, Chen Y, et al. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *J Sex Med*. 2015;12(10):2036–2048.
41. Chauhan M, Parry R, Bobo WV. Vilazodone for major depression in adults: pharmacological profile and an updated review for clinical practice. *Neuropsychiatr Dis Treat*. 2022;18:1175–1193.
42. Gonçalves WS, Gherman BR, Abdo CHN, et al. Prevalence of sexual dysfunction in depressive and persistent depressive disorders: a systematic review and meta-analysis. *Int J Impot Res*. 2023;35(4):340–349.
43. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. *J Sex Med*. 2012;9(6):1497–1507.
44. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther*. 1997;23(3):176–194.
45. Kronstein PD, Ishida E, Khin NA, et al. Summary of findings from the FDA regulatory science forum on measuring sexual dysfunction in depression trials. *J Clin Psychiatry*. 2015;76(8):1050–1059.
46. Dodd S, Mitchell PB, Bauer M, et al. Monitoring for antidepressant-associated adverse events in the treatment of patients with major depressive disorder: an international consensus statement. *World J Biol Psychiatry*. 2018;19(5):330–348.
47. Katz AJ, Dusetzina SB, Farley JF, et al. Distressing adverse events after antidepressant switch in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial: influence of adverse events during initial treatment with citalopram on development of subsequent adverse events with an alternative antidepressant. *J Hum Pharmacol Drug Ther*. 2012;32(3):234–243.
48. Montejo AL, Prieto N, de Alarcón R, et al. Management strategies for antidepressant-related sexual dysfunction: a clinical approach. *J Clin Med*. 2019;8(10):1640.
49. Lorenz T, Rullo J, Faubion S. Antidepressant-induced female sexual dysfunction. *Mayo Clin Proc*. 2016;91(9):1280–1286.
50. Sharma T, Guski LS, Freund N, et al. Drop-out rates in placebo-controlled trials of antidepressant drugs: a systematic review and meta-analysis based on clinical study reports. *Int J Risk Saf Med*. 2019;30(4):217–232.
51. Meyer-Bahlburg HFL, Dolezal C. The female sexual function index: a methodological critique and suggestions for improvement. *J Sex Marital Ther*. 2007;33(3):217–224.
52. Hyde JS, Mezulis AH. Gender differences in depression: biological, affective, cognitive, and sociocultural factors. *Harv Rev Psychiatry*. 2020;28(1):4–13.
53. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol*. 2003;3:28.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Effects of Gepirone-ER on Sexual Function in Patients with Major Depressive Disorder

Authors: Tierney K. Lorenz, PhD; Mary F. Johnson, PhD; and Anita H. Clayton, MD

DOI Number: 10.4088/JCP.24m15357

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Trial design details.

Study No.	Design Overview	Control Drug (s)	Duration	Dose Regimen and Route	Trial Center Locations
134001	8-week randomized, double-blind, placebo-controlled, parallel group trial in subjects with moderate-severe MDD	Placebo	Acute (8 weeks)	Oral tablets taken once each morning with food. After an initial dose of 20 mg/day, patients were titrated to 40 mg/day on Day 4 of treatment. Dose could be increased to 60 mg/day after 7 days, and to 80 mg/day after 14 days.	Newport Beach, CA; Wheat Ridge, CO; New York, NY; Portland, OR; King of Prussia, PA
134002	8-week randomized, double-blind, placebo-controlled, parallel group trial in subjects with moderate-severe MDD	Placebo	Acute (8 weeks)	Oral tablets taken once each morning with food. Flexible-dose design with one forced titration from 20 to 40 mg/day on Day 4. Minimum dose 40 mg/day.	Newport Beach, CA; Wheat Ridge, CO; New York, NY; Portland, OR; King of Prussia, PA
134004	3-arm, double-blind, randomized, placebo- and active-controlled study in subjects with moderate-severe MDD with atypical features	Placebo and Fluoxetine	Acute (8 weeks)	Oral tablets taken once each morning with food. Dose range 20-80 mg/day with a forced titration to 40 mg/day during the first week of treatment. For fluoxetine, dose 20 mg for the first 4 weeks which could be titrated to 40 mg.	Berkeley, CA; Beverley Hills, CA; Denver, CO; Atlanta, GA; Belmont, MA; Clementon, NJ; New York; NY; Philadelphia, PA; Dallas, TX; Salt Lake City, UT
134502	Extension of 134004; Double-blind, placebo-and active-controlled, parallel group study in subjects with moderate-severe MDD with atypical features	Placebo and Fluoxetine	Extension (44 weeks) for patients completing 134004	Subjects continued into the extension with the same treatment used in the short-term trial or switched; switchers followed a similar titration schedule as in 134004.	Beverley Hills, CA; San Diego, CA; Denver, CO; Atlanta, GA; Belmont, MA; Clementon, NJ; New York, NY; Philadelphia, PA; Dallas, TX; Salt Lake City, UT
134006	8-week randomized, double-blind, placebo-and active-controlled, parallel group trial in subjects with moderate-severe MDD with atypical features	Placebo and Paroxetine	Acute (8 weeks)	Subjects took one 20 mg tablet of gepirone-ER once each morning with food on Days 1-3. Day 4, there was a mandatory increase in dose to 40 mg/day. Dose could be increased to 60 mg after 7 days and to 80 mg after 14 days. Dose could be titrated between 40 mg and 80 mg. Subjects in the paroxetine group received 10 to 40 mg based on tolerability.	San Diego, CA; Boca Raton, FL; Atlanta, GA; Libertyville, IL; Boston MA; Farmington Hills, MI; Chapel Hill, NC; Durham, NC; New York, NY; Toronto, ON; Philadelphia PA; Seattle, WA; West Allis, WI
134503	Extension of 134006; Double-blind, placebo-and active-controlled, parallel group study in subjects with moderate-severe MDD with atypical features	Placebo and Paroxetine	Extension (16 weeks) for patients completing 134006	Subjects continued with their treatment and dosing regimen as used in the short-term treatment. During the extension, dose could be adjusted to improve tolerability.	San Diego, CA; Boca Raton, FL; Atlanta, GA; Libertyville, IL; Boston MA; Farmington Hills, MI; Chapel Hill, NC; Durham, NC; New York, NY; Toronto, ON; Philadelphia PA; Seattle, WA; West Allis, WI
134017	8-week randomized, double-blind, placebo-and active-controlled, parallel group trial in subjects with moderate-severe MDD	Placebo and Fluoxetine	Acute (8 weeks)	Subjects in the gepirone-ER group received 20 to 40 mg/day from Days 1 through 7 and 40 to 80 mg from Day 8 until discontinuation or the end of treatment. Subjects in the fluoxetine group received 20 mg/day from Days 1 through 27 and between 20 to 40 mg/day from Day 28 until discontinuation or the end of treatment.	Burbank, CA; Upland, CA; Atlanta; GA; Edwardsville, IL; Okemos, MI; Conshohocken, PA; Portland, OR; Charleston, SC; Seattle WA
134506	Extension of 134017; Double-blind, placebo-and active-controlled, parallel group study in subjects with moderate-severe MDD	Placebo and Fluoxetine	Extension (16 weeks) for patients completing 134017	Subjects continued with their treatment and dosing regimen as used in the short-term treatment. During the extension, dose could be adjusted to improve tolerability. Minimum doses were 40 mg gepirone or 20 mg fluoxetine; maximum doses were 80 mg gepirone or 40 mg fluoxetine.	Perioa, AZ; Glendale, CA; San Diego, CA; Wheat Ridge, CO; Smyrna, GA; Clementon, NJ; Brooklyn, NY; Cleveland, OH; Bellevue, WA

Supplementary Table 2: Controlled gepirone-ER studies prospectively measuring sexual function

Study Identifier	Intervention(s)	Number of Participants*		
		Total	Women	Men
134001	Placebo Gepirone ER (20-80 mg)	208	126	82
134002	Placebo Gepirone ER (20-80 mg)	218	135	83
134004	Placebo Gepirone ER (20-80 mg) Fluoxetine (20-40 mg)	409	269	140
134006	Placebo Gepirone ER (20-80 mg) Paroxetine (10-40 mg)	437	331	106
134017	Placebo Gepirone ER (20-80 mg) Fluoxetine (20-40 mg)	495	315	180
	Total	1,767	1,176	591
Extension				
134502	Non-switchers: Final dosing in the last week of study 134004	114	73	41
	Switchers: Gepirone ER (20-80 mg) Fluoxetine (20-40 mg)	155	98	57
134503	Final dosing in the last week of study 134006 adjusted, Gepirone ER (40-80 mg) Paroxetine (20-40 mg)	197	154	43
134506	Final dosing in the last week of study 134017 adjusted, Gepirone ER (40-80 mg) Fluoxetine (20-40 mg)	208	142	66
	Total	674	467	207

Supplementary Table 3: Schedule of sexual function assessments in controlled gepirone-ER studies

Study/ Extension	Control(s)	Sexual Function Measure	Weeks [a]														
			----Short-term---				----------Extension Phase----------										
			B	2	4	8	12	16	20	21	24	26	28	36	40	44	52
134001	Placebo	DISF-SR	X			**ET**											
134002	Placebo	DISF-SR	X			**ET**											
134004/ 134502	Fluoxetine Placebo	DISF	X	X	X	**ET**	X	X	X				X	X		X	**ET**
134006/ 134503	Paroxetine Placebo	DISF	X	X	X	**ET**	X	X	X		X		**ET**				
134017/ 134506	Fluoxetine Placebo	CSFQ	X	X	X	**ET**	X	X	X		**ET**						

[a] Weeks are defined relative to the start of double-blind treatment
Abbreviations: B=Baseline; ET=End of Treatment Assessment

Supplementary Table 4: Participant disposition

Status	Gepirone - ER	Placebo	Fluoxetine	Paroxetine	Total [a]
Participants Randomized	660	665	304	144	1773
Participants Treated	659	662	304	142	1767
Full Analysis Set [b]	542 (82%)	558 (84%)	291 (96%)	129 (91%)	1520 (86%)
Participants Discontinued	210 (32%)	156 (24%)	65 (21%)	41 (29%)	472 (27%)
Adverse Event	67 (10%)	19 (3%)	12 (4%)	8 (6%)	106 (6%)
Lack of Efficacy	30 (5%)	25 (4%)	8 (3%)	4 (3%)	67 (4%)
Other Reason	113 (17%)	112 (17%)	45 (15%)	29 (20%)	299 (17%)

[a] *Percentage is calculated using the number of participants randomized and treated as the denominator.*
[b] *Participants with at least one post-baseline sexual function assessment.*

Supplementary Table 5: Demographic and baseline characteristics of participants with sexual function data in 5 pooled studies, grouped by treatment

Variable Statistic/Category	Treatment Groups – Full Analysis Set [a]		
	Gepirone - ER (N = 542)	Placebo (N = 558)	SSRI [b] (N = 420)
Age (years)			
n	542	558	420
Mean	39.0	38.7	39.0
Standard Deviation	11.47	11.35	11.42
Median	38.0	38.0	39.0
Range	18, 69	18, 69	18, 65
Gender (n, %)			
Men	177 (32.7)	192 (34.4)	137 (32.6)
Women	365 (67.3)	366 (65.6)	283 (67.4)
Race (n, %)			
White	449 (82.8)	455 (81.5)	339 (80.7)
Black	51 (9.4)	59 (10.6)	39 (9.3)
Asian	7 (1.3)	9 (1.6)	11 (2.6)
Other	35 (6.5)	35 (6.3)	31 (7.4)
Baseline Level of Depression (n, %)			
Mild	112 (20.7)	123 (22.0)	128 (30.5)
Moderate	224 (41.3)	221 (39.6)	137 (32.6)
Severe / Extreme	206 (38.0)	214 (38.4)	155 (36.9)
Age at first episode (years)			
n	334	350	280
Mean	25.0	24.5	24.8
Standard Deviation	11.49	10.96	12.10
Median	23.0	22.0	22
Range	4, 60	4, 60	4, 58
Duration of present episode < 1 year (n, %)			
Yes	272 (50.2)	291 (52.2)	210 (50.0)
No	270 (49.8)	267 (47.8)	210 (50.0)
Baseline HAMD-17 Total Score			
N	542	558	420
Mean	21.36	21.34	20.95
Standard Deviation	3.693	3.912	3.986
Median	22.00	22.00	22
Range	10.0, 31.0	9.0, 33.0	10.0, 32.0

[a] *All treated participants with at least one post-baseline assessment of sexual function.*
[b] *Fluoxetine (N=291) and Paroxetine (N=129).*

Supplementary Table 6: Sexual function (mean total score) at baseline

Study/ Scale	Participants	N	Gepirone-ER	Placebo	SSRI [a]
134001 DISF-SR	All	148	42.4	44.9	--
	Women	94	42.5	36.7	--
	Men	54	42.4	56.6	--
134002 DISF-SR	All	93	49.2	44.4	--
	Women	62	42.7	31.7	--
	Men	31	62.0	70.0	--
134004 DISF	All	372	56.3	54.9	53.9
	Women	241	45.3	46.6	47.0
	Men	131	74.8	71.9	66.4
134006 DISF	All	403	50.4	53.7	50.0
	Women	304	42.7	44.5	45.2
	Men	99	73.5	77.8	68.2
134017 CSFQ	All	456	48.3	50.6	48.7
	Women	290	45.4	47.4	45.7
	Men	166	54.2	56.1	53.1
4 Pooled Studies (DISF/DISF-SR) [b]	All	1016	50.6	51.2	52.0
	Women	701	43.4	42.3	46.0
	Men	315	66.7	69.5	67.1

[a] *Active Control = Fluoxetine in studies 134004 and 134017, Paroxetine in study 134006.*
[b] *Higher scores denote better sexual function*

Abbreviations: CSFQ: Changes in Sexual Function Questionnaire; DISF: Derogatis Interview for Sexual Functioning; SR: Self Report

Supplementary Table 7: Incidence of treatment-emergent sexual dysfunction (per DSM-IV criteria) in participants without sexual dysfunction at baseline [Pooled studies 134004, 134006, and 134017]

DSM-IV Diagnosis Incidence [a]	Gepirone-ER (N [b]=331-389)	Placebo (N=346-405)	SSRI (N=347-404)
Any Sexual Dysfunction	9%	10%	27%**
Sexual Desire Disorder	7%	8%	16%**
Sexual Arousal Disorder	2%	2%	4%
Orgasmic Disorder	4%	5%	18%**

[a] Incidence = Number of patients with sexual dysfunction during the study, as a percentage of those without sexual dysfunction at baseline. Sexual dysfunction was diagnosed by the investigator according to established DSM-IV criteria.

[b] N = Number of patients without sexual dysfunction at baseline; specific Ns for each diagnosis vary as shown.
***Statistically significantly higher than Placebo (p<0.001) and Gepirone-ER (p<0.001)*

Supplementary Table 8: Incidence of Treatment Emergent Sexual Dysfunction (per DSM-IV criteria), by Gender [Pooled Studies 134004, 134006, and 134017]

Incidence by Gender [a]	Gepirone-ER N=218:113 [b]	Placebo N=227:119	SSRI N=232:115
Women	11%	8%	26%**
Men	5%*	15%	30%**

[a] Incidence = Number of patients with sexual dysfunction during study, as a percentage of those without sexual dysfunction at baseline.
[b] Size for group is the number of patients (women: men) without sexual dysfunction at baseline.
**Statistically significantly lower than Placebo (p<0.05).*
***Statistically significantly higher than Placebo (p<0.01) and Gepirone-ER (p<0.001).*

Supplementary Table 9: Change in DISF domain scores from baseline at each visit (Pooled studies 134004 and 134006)

DISF Domain		Gepirone - ER (N [a]=257)	Placebo (N=267)	SSRI (N=261)	Treatment Difference		
					Gepirone - Placebo	SSRI - Placebo	SSRI - Gepirone
Arousal							
Week 2	**n**	230	250	244			
	Mean [b]	0.6	0.1	-1.1	**0.5**	**-1.2**	**-1.6**
	95% CI				-0.37, 1.27 [c]	-2.00, -0.39	-2.47, -0.82
	p-value [b]				0.2789	**0.0038** [d]	**<0.0001**
Week 4	**n**	207	234	227			
	Mean	1.2	0.8	-0.9	**0.4**	**-1.7**	**-2.1**
	95% CI				-0.54, 1.37	-2.66, -0.78	-3.10, -1.17
	p-value				0.3940	**0.0003**	**<0.0001**
Week 8	**n**	185	212	208			
	Mean	1.3	1.1	-0.0	**0.2**	**-1.1**	**-1.3**
	95% CI				-0.84, 1.30	-2.12, -0.04	-2.39, -0.24
	p-value				0.6693	**0.0418**	**0.0166**
Overall*	**n**	234	256	248			
	Mean	1.2	0.8	-0.4	0.3	-1.3	-1.6
	95% CI				-0.56, 1.19	-2.14, -0.42	-2.48, -0.71
	p-value				0.4800	**0.0036**	**0.0004**
Behavior							
Week 2	**n**	228	249	244			
	Mean	0.4	-0.2	-1.0	**0.6**	**-0.8**	**-1.4**
	95% CI				-0.08, 1.34	-1.47, -0.07	-2.12, -0.68
	p-value				**0.0817**	**0.0313**	**0.0001**
Week 4	**n**	208	235	227			
	Mean	0.8	0.1	-0.3	**0.7**	**-0.4**	**-1.1**
	95% CI				-0.16, 1.49	-1.24, 0.37	-1.93, -0.27
	p-value				0.1128	0.2863	**0.0093**
Week 8	**n**	183	212	209			
	Mean	1.0	0.4	0.4	**0.7**	**0.0**	**-0.6**
	95% CI				-0.28, 1.62	-0.90, 0.95	-1.61, 0.31
	p-value				0.1684	0.9616	0.1858
Overall*	**n**	233	256	248			
	Mean	0.9	0.2	-0.0	**0.7**	**-0.2**	**-0.9**
	95% CI				-0.10, 1.43	-0.97, 0.53	-1.66, -0.11
	p-value				**0.0895**	0.5602	**0.0246**
Sexual Desire							
Week 2	**n**	229	253	244			
	Mean	0.9	-0.2	-1.2	**1.1**	**-0.9**	**-2.0**
	95% CI				-0.15, 2.35	-2.17, 0.28	-3.30, -0.79
	p-value				**0.0833**	0.1313	**0.0015**
Week 4	**n**	208	237	228			
	Mean	1.5	-0.2	-1.0	**1.8**	**-0.8**	**-2.5**
	95% CI				0.36, 3.17	-2.16, 0.59	-3.96, -1.12
	p-value				**0.0140**	0.2653	**0.0005**
Week 8	**n**	186	215	210			
	Mean	1.8	-0.0	0.7	**1.9**	**0.7**	**-1.1**
	95% CI				0.29, 3.42	-0.78, 2.26	-2.69, 0.46

DISF Domain		Gepirone - ER (N [a]=257)	Placebo (N=267)	SSRI (N=261)	Treatment Difference		
					Gepirone - Placebo	SSRI - Placebo	SSRI - Gepirone
	p-value				**0.0200**	0.3413	0.1637
Overall*	**n**	233	258	248			
	Mean	1.6	-0.1	-0.1	**1.7**	**0.1**	**-1.7**
	95% CI				0.46, 2.99	-1.17, 1.30	-2.94, -0.38
	p-value				**0.0078**	0.9193	**0.0111**
Orgasm							
Week 2	**n**	225	239	231			
	Mean	0.6	0.4	-2.0	**0.2**	**-2.4**	**-2.6**
	95% CI				-0.69, 1.15	-3.30, -1.47	-3.55, -1.68
	p-value				0.6264	**<0.0001**	**<0.0001**
Week 4	**n**	204	222	216			
	Mean	1.2	1.2	-2.1	**-0.1**	**-3.3**	**-3.3**
	95% CI				-1.10, 0.95	-4.35, -2.32	-4.29, -2.23
	p-value				0.8872	**<0.0001**	**<0.0001**
Week 8	**n**	181	199	197			
	Mean	1.5	1.5	-1.5	**0.0**	**-3.0**	**-3.0**
	95% CI				-1.11, 1.17	-4.08, -1.84	-4.14, -1.85
	p-value				0.9547	**<0.0001**	**<0.0001**
Overall*	**n**	230	244	238			
	Mean	1.3	1.2	-1.7	**0.0**	**-3.0**	**-3.0**
	95% CI				-0.89, 0.95	-3.89, -2.08	-3.94, -2.10
	p-value				0.9481	**<0.0001**	**<0.0001**
Drive							
Week 2	**n**	227	247	240			
	Mean	1.0	0.5	-0.5	**0.5**	**-1.0**	**-1.5**
	95% CI				-0.10, 1.05	-1.55, -0.42	-2.04, -0.89
	p-value				0.1023	**0.0006**	**<0.0001**
Week 4	**n**	207	231	223			
	Mean	1.6	1.2	-0.3	**0.4**	**-1.5**	**-1.9**
	95% CI				-0.22, 1.01	-2.12, -0.91	-2.54, -1.29
	p-value				0.2076	**<0.0001**	**<0.0001**
Week 8	**n**	186	207	204			
	Mean	1.8	1.4	0.2	**0.4**	**-1.1**	**-1.6**
	95% CI				-0.28, 1.17	-1.84, -0.42	-2.31, -0.85
	p-value				0.2277	**0.0018**	**<0.0001**
Overall*	**n**	232	252	245			
	Mean	1.6	1.2	-0.0	**0.4**	**-1.2**	**-1.7**
	95% CI				-0.15, 1.02	-1.80, -0.65	-2.25, -1.07
	p-value				0.1437	**<0.0001**	**<0.0001**

[a] N = Participants with DISF total scores at baseline and at least one post-baseline visit; N for other domains may vary.

[b] Least square means and p-values from a mixed model with fixed effects for treatment, study, gender, and treatment by week interaction term, with week as the repeating factor, patient as a random effect, and baseline score as a covariate. Positive mean change denotes improvement in sexual function.

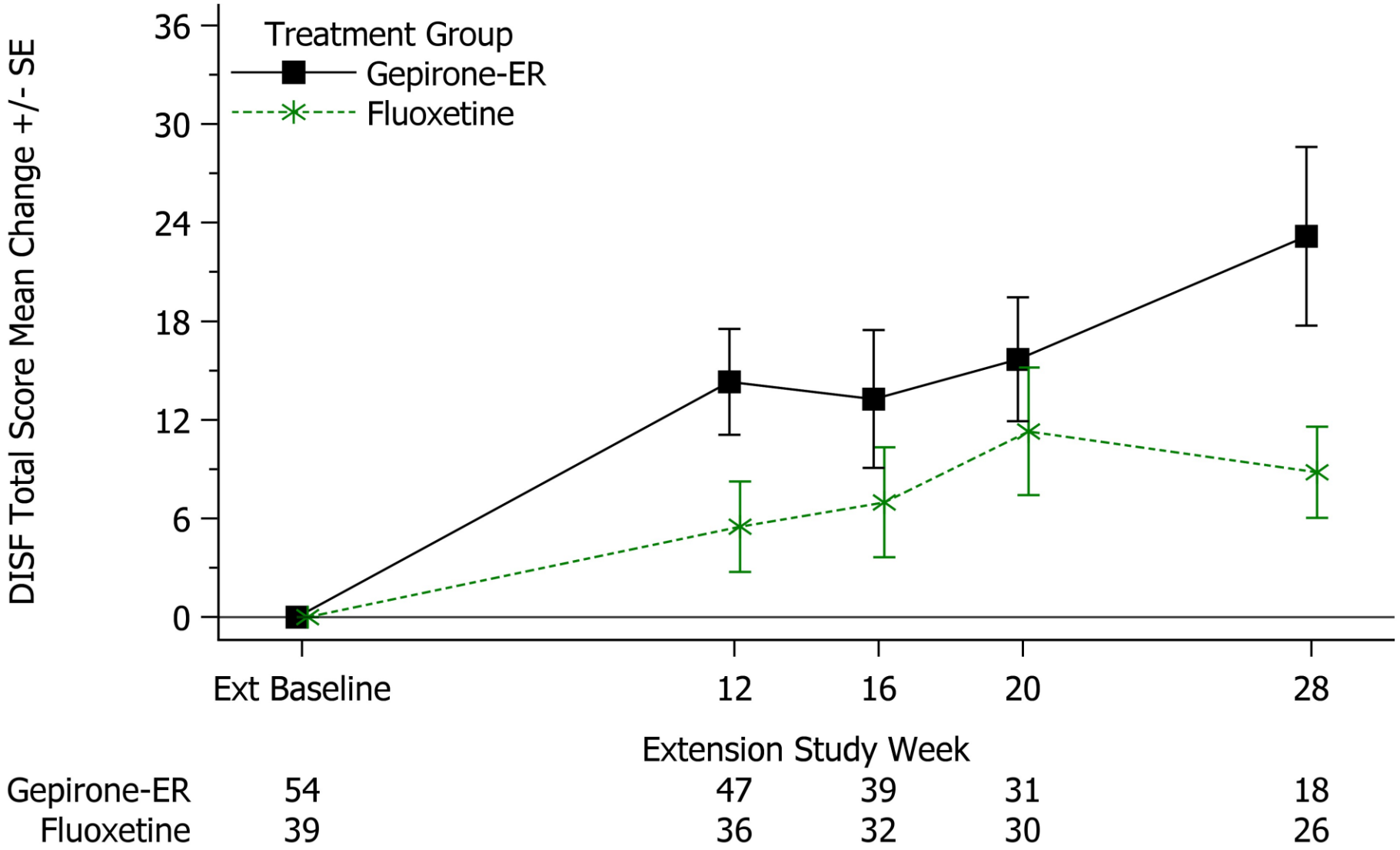
[c] Yellow highlighted cells indicate that the lower limit of the 95% CI is above -1.0.

[d] *P-values ≤ 0.10 (two-sided) are in bold font.*

**Based on contrasts of the least squares means weighted across weeks for each treatment pair.*

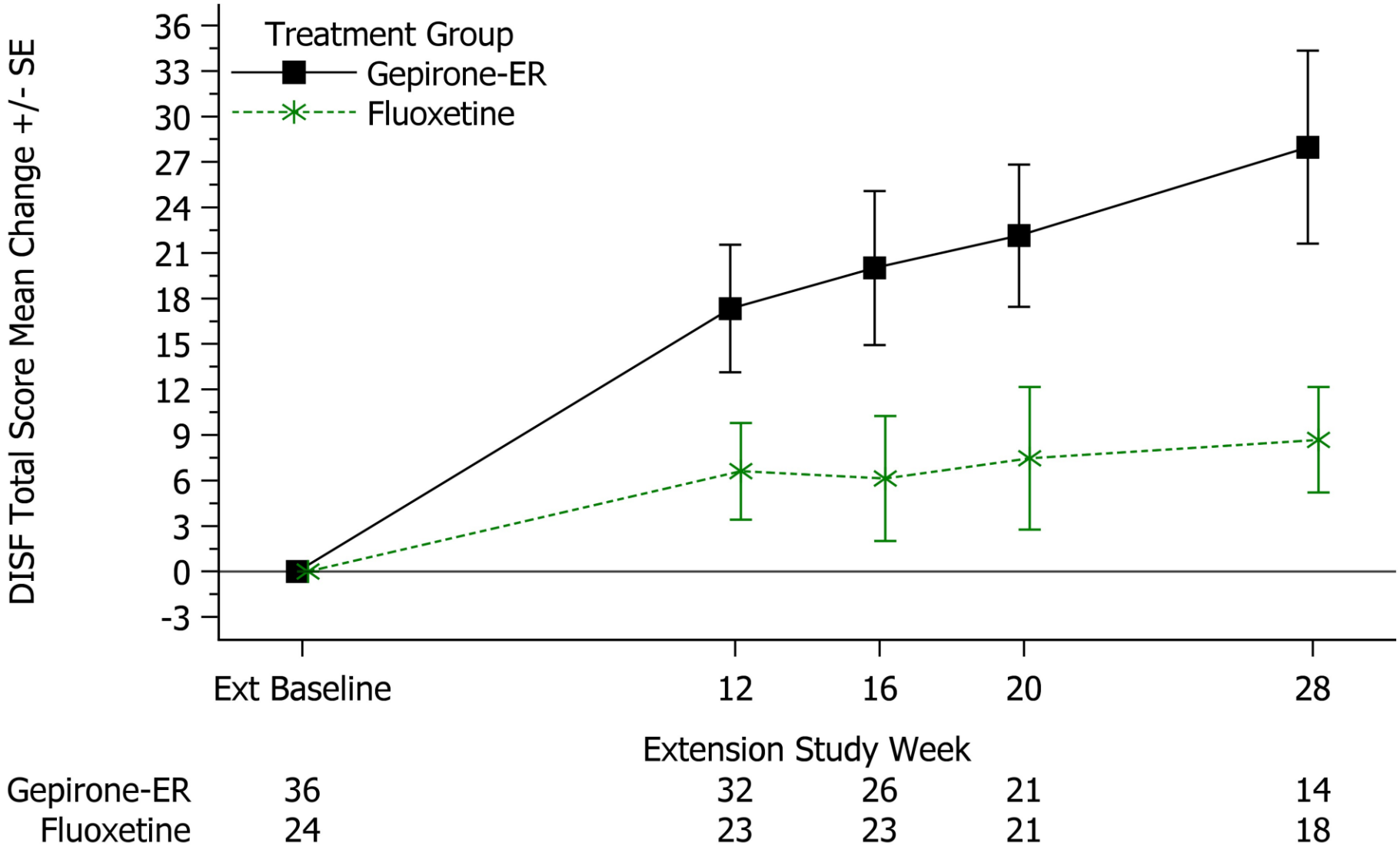
Abbreviations: CI=confidence interval; Derogatis Interview for Sexual Functioning; LS=least squares

Supplementary Figure 1: Change in sexual functioning among participants on SSRI in prior study (Study 134502 data only)



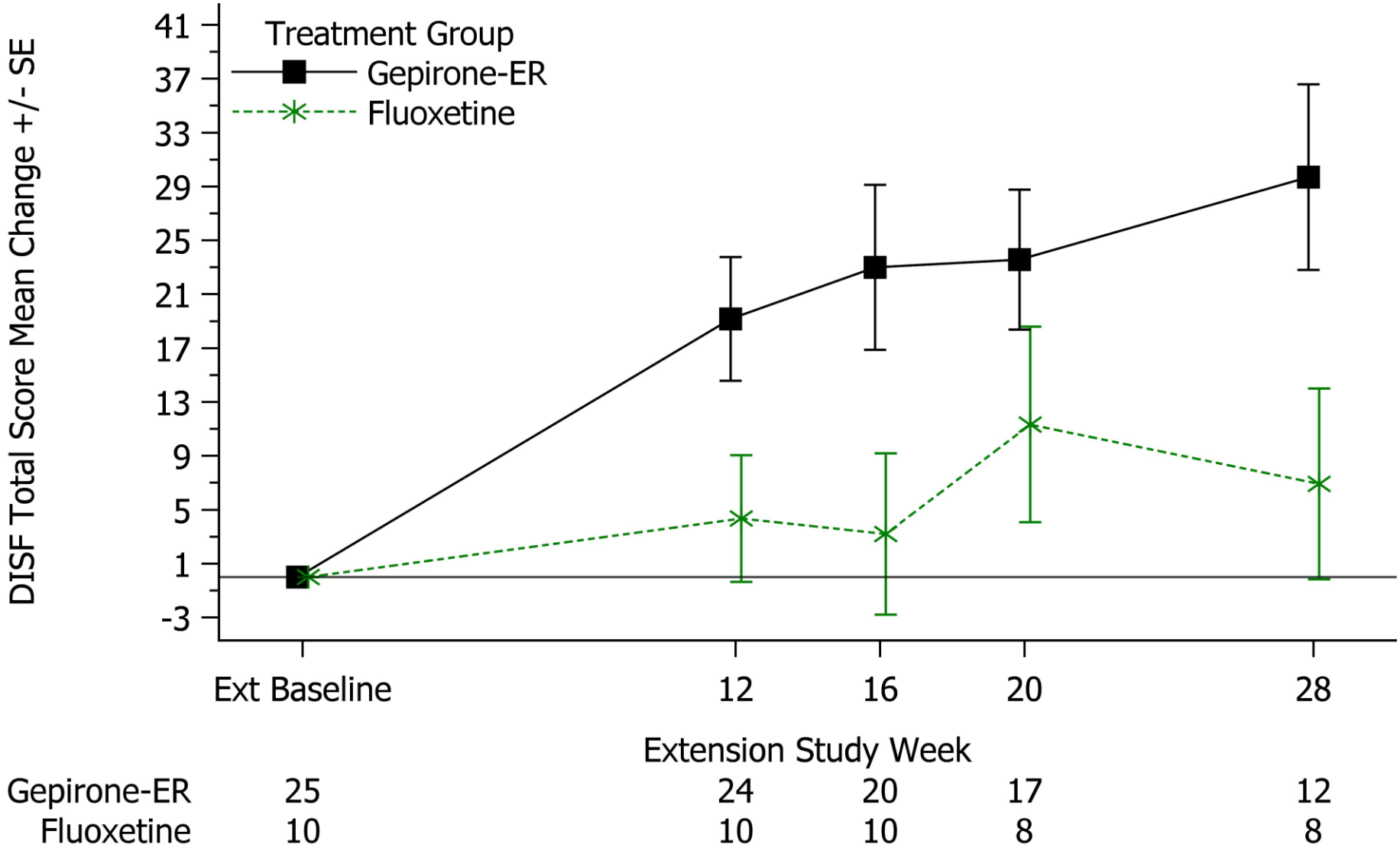
Abbreviations: Derogatis Interview for Sexual Functioning; ER: Extended Release; SE: Standard Error

Supplementary Figure 2: Average change in sexual functioning from baseline among women on SSRI in prior study (Study 134502 data only)



Abbreviations: Derogatis Interview for Sexual Functioning; ER: Extended Release; SE: Standard Error

Supplementary Figure 3: Average change in sexual functioning from baseline among women with treatment-emergent sexual dysfunction in prior study (Study 134502 data only)



Abbreviations: DISF: Derogatis Interview for Sexual Functioning; ER: Extended Release; SE: Standard Error