Sexual Functioning in Long-term Treatment of MDD: Duloxetine, Escitalopram, and Placebo

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ABSTRACT

Background: Depression and antidepressant therapy have been associated with sexual dysfunction in short term and point-prevalence trials. This report describes effects on sexual functioning during long-term treatment for Major Depressive Disorder (MDD).
Methods: This 8-month, double-blind, placebo-controlled study of duloxetine and escitalopram had 2 phases: a) an 8-week acute phase, fixed-dose, comparison of duloxetine 60 mg/d (n=273), escitalopram 10 mg/d (n=274), and placebo (n=137); and b) a 6-month, flexible dose extension phase (duloxetine, 60, 90, or 120 mg/d; escitalopram, 10 or 20 mg/d; placebo rescue to active drug) based on pre-defined criteria. The 14-item, self-report Changes in Sexual Functioning Questionnaire (CSFQ) was used to assess sexual function.
Results: Statistically significant worsening of sexual functioning as measured by the CSFQ was observed for escitalopram versus placebo at 4 and 8 Weeks ($p \leq .01$), while duloxetine was not statistically different from placebo at anytime. There was a statistically significant difference for duloxetine versus escitalopram at 12 and 20 Weeks ($p \leq .05$). Furthermore, the Quality of Life Enjoyment and Satisfaction Questionnaire-SF demonstrated an advantage during the 8-month study for duloxetine over escitalopram in satisfaction with sexual drive, interest, and /or performance (p=.013). At 8 weeks categorical changes in sexual function (same, better or worse) on the CSFQ differed significantly for duloxetine versus escitalopram (p=.019) in male patients, with no significant difference between active drugs in females. At 8 months there were no statistically significant differences observed between duloxetine and escitalopram in categorical changes on the CSFQ for male or female patients. Discontinuation rates for sexual side effects did not differ for duloxetine (n=2) versus escitalopram (n=7, p=.07).
Conclusions: Short-term treatment demonstrated worsening of sexual functioning with escitalopram compared to placebo, while duloxetine was not significantly different from placebo at anytime during the 8-month study.

INTRODUCTION

- Depression and antidepressant therapy have been associated with sexual dysfunction in short term and point-prevalence trials.[1,2]
- Sexual dysfunction is common among patients with depression, with a reported incidence as high as 47 percent.[3] Sexual dysfunction is also a common side effect associated with antidepressant medications,[4] affecting up to 73 % of depressed patients treated with selective serotonin reuptake inhibitors (SSRIs).[5]
- The incidence of sexual dysfunction secondary to antidepressant treatment is an important contributor to treatment nonadherence and discontinuation. [6]
- This report describes effects of duloxetine (a dual reuptake inhibitor of serotonin and norepinephrine)[7] and escitalopram (a selective serotonin reuptake inhibitor)[8] on sexual functioning during long-term treatment for depression.

METHODS

Study Design

- Randomized, multicenter, double-blind, placebo-controlled, 8-week clinical trial
- This study incorporated a double-blind, variable-duration placebo lead-in period
- Patients were randomized in a 2:2:1 ratio to fixed doses of duloxetine (60 mg/day), escitalopram (10 mg/day), or placebo
- A 6-month, double-blind, flexible dose extension phase followed the 8-week acute treatment. Dose escalations and placebo rescue occurred based on pre-defined blinded criteria. The duloxetine dose could be increased from 60 to 90 to 120 mg/d; and escitalopram from 10 to 20 mg/d.
- Study protocol reviewed and approved by the ethical review board at each center. All patients provided written informed consent.

Study Patients

- Outpatients 18 years of age or older, met DSM-IV criteria for MDD, and had a Montgomery-Asberg Depression Rating Scale (MADRS) total score $\geq$22 and a Clinical Global Impression of Severity (CGI-S) score $\geq$4 at the screening and second study visits
- Exclusion criteria included: a current and primary Axis I disorder other than MDD; an Axis II disorder which could interfere with protocol compliance; lack of response of the current depressive episode to 2 or more adequate courses of antidepressant therapy; serious medical illness; a serious risk of suicide; a history of substance dependence within the last 6 months, or a positive urine drug screen
- Concomitant medications with primarily central nervous system activity were not permitted.

Assessment of Sexual Functioning

The following measures were used to assess sexual functioning:

- 14-item self-report Changes in Sexual Functioning Questionnaire (CSFQ)[9]
- Quality of Life Enjoyment and Satisfaction Questionnaire-short form (Q-LES-Q-SF)[10]
- Spontaneously reported sexual side effects
- Discontinuation due to sexual side effects

Statistical Analyses

- All patients with a baseline and at least one post-baseline observation were included in the analyses
- Longitudinal mean changes were assessed using a likelihood-based, mixed-effects model repeated measures (MMRM) approach. Models for mean changes included treatment, investigator, visit, treatment-by-visit interaction, and baseline value
- Changes in sexual functioning were assessed by analyzing the proportion of patients within each treatment group who experienced categorical changes (improvement, no change or worsening) in CSFQ total score between baseline and endpoint.
- Treatment comparisons for demographic categorical variables were made using the chi-square test
- Fisher's exact test was used for comparisons of treatment-emergent adverse events
- Placebo-treated patients were included in the analyses until the timepoint at which they were rescued to active drug

RESULTS

Baseline Patient Demographics

Demographic	Duloxetine 60 mg QD (N=273)	Escitalopram 10 mg QD (N=274)	Placebo (N=137)
*Mean Age, y (SD)	41.1 (11.6)	43.3 (13.0)	42.5 (12.3)
Ethnicity, n (%)			
Caucasian	206 (75.5)	212 (77.4)	113 (82.5)
Hispanic	22 (8.1)	26 (9.5)	8 (5.8)
African Descent	35 (12.8)	28 (10.2)	14 (10.2)
Asian	2 (0.7)	3 (1.1)	0 (0)
Other	5 (1.8)	4 (1.5)	2 (1.5)
Gender, n (%)			
Female	173 (63.4)	186 (67.9)	87 (63.5)
Male	100 (36.6)	88 (32.1)	50 (36.5)
Baseline Psychiatric Profile, Mean (SD)			
$HAMD_{17}$ Total	17.6 (4.8)	17.8 (5.1)	17.7 (5.2)
CGI-Severity	4.2 (0.7)	4.2 (0.7)	4.2 (0.7)
HAMA	14.1 (5.2)	14.6 (5.2)	14.4 (5.1)

*The mean age of patients in the duloxetine treatment group was statistically significantly lower than that in the escitalopram group (41.1 years vs. 43.3 years; p=.036). There were no other significant between-group differences in baseline demographics or psychiatric profile.

PATIENT ATTRITION

The number of patients in the placebo arm significantly decreased after 8 weeks, and only 15 placebo-treated patients contributed data at the final study visit (8-month timepoint).

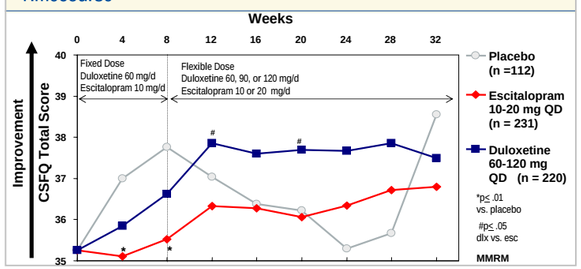
Therefore, comparisons of drug to placebo after the 8-week timepoint should be interpreted with the understanding that power to detect a difference was significantly decreased.

	Baseline (N)	Week 1 (N)	Week 8 (N)	Week 12 (N)	Week 16 (N)	Week 24 (N)	Week 32 (N)
Placebo	137	135	100	56	39	20	15
Duloxetine	273	262	195	180	158	123	105
Escitalopram	274	267	216	195	169	139	124

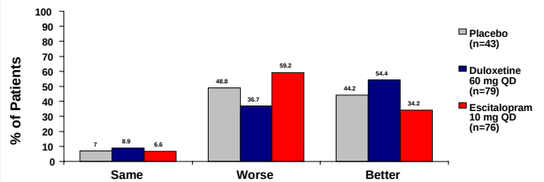
STUDY DRUG DOSAGE

- Flexible dosing was allowed after the initial 8 weeks of fixed dosing (duloxetine 60 mg/d and escitalopram 10 mg/d).
- For Patients continuing in the study after 8 weeks:
  - Last dose for duloxetine patients was 60 mg/d (55%), 90 mg/d (23%), or 120 mg/d (22%).
  - Last dose for escitalopram treated patients was 10 mg/d (47%) or 20 mg/d (53%).

CSFQ Total Score 14-Item Clinical Version (All Patients): 8-Month Timecourse

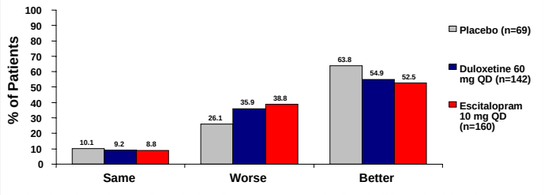


Changes in Sexual Functioning Questionnaire: *Overall Score in Male Patients (8 weeks)*



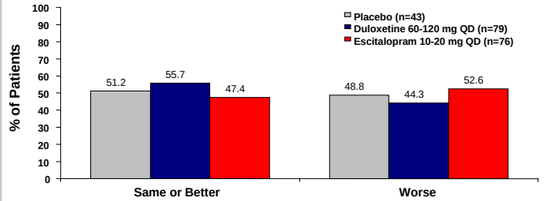
- In male patients, the overall distribution of outcomes was not significantly different for duloxetine vs. placebo (p=.428).
- In male patients, the overall distribution of outcomes was significantly different for duloxetine vs. escitalopram (p=.019).

Changes in Sexual Functioning Questionnaire: *Overall Score in Female Patients (8 months)*



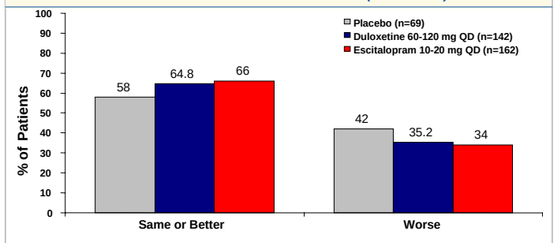
- In female patients, the overall distribution of outcomes was not significantly different for duloxetine vs. placebo (p=.359).
- In female patients, the overall distribution of outcomes was not significantly different for duloxetine vs. escitalopram (p=.879).

Changes in Sexual Functioning Questionnaire: *Overall Score in Male Patients (8 months)*



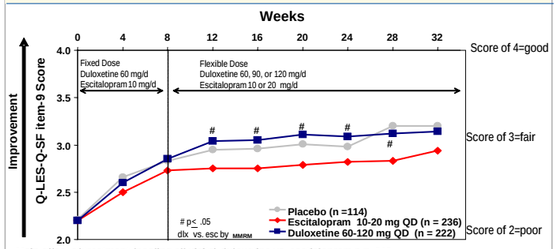
- In male patients, the distribution of outcomes was not significantly different for duloxetine vs. placebo (p=.631).
- In male patients, the distribution of outcomes was not significantly different for duloxetine vs. escitalopram (p=.300).

Changes in Sexual Functioning Questionnaire: *Overall Score in Female Patients (8 months)*



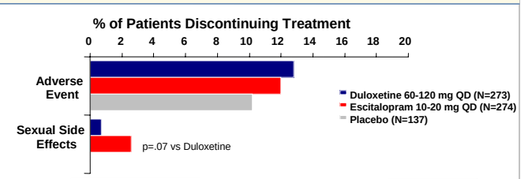
- In female patients, the distribution of outcomes was not significantly different for duloxetine vs. placebo (p=.337).
- In female patients, the overall distribution of outcomes was not significantly different for duloxetine vs. escitalopram (p=.818).

Quality of Life Enjoyment and Satisfaction Questionnaire Short Form: Satisfaction with Sexual Drive, Interest and/or Performance (Item-9)



Main effect of treatment (pooling all visits) duloxetine vs. esctialopram p = .013

Adverse Events Causing Patient Discontinuation (8 months)



Sexual Side Effect	Discontinued Duloxetine (n)	Discontinued Escitalopram (n)	Discontinued Placebo (n)
Erectile Dysfunction	2	2	0
Decreased Libido	0	2 (female)	0
Orgasmic Dysfunction Anorgasmia	0	1 (female)	0
Ejaculation Delay	0	2	0

Anorgasmia was the only treatment emergent sexual side effect reported statistically more frequently for duloxetine or escitalopram vs. placebo during the course of the study (4.8%, 4.0%, and 0% for duloxetine, escitalopram, and placebo respectively; p< .05 for both active drugs vs. placebo).

Summary of Results

- Statistically significant worsening of sexual functioning as measured by the CSFQ was observed for escitalopram versus placebo at 4 and 8 Weeks ($p \leq .01$), while duloxetine was not statistically different from placebo at anytime.
- The CSFQ showed a statistically significant difference for duloxetine versus escitalopram at 12 and 20 Weeks ($p \leq .05$). The Q-LES-Q-SF also demonstrated an advantage during the 8-month study for duloxetine over escitalopram in satisfaction with sexual drive, interest, and /or performance (p=.013 by main effect of treatment).
- At 8 Weeks, categorical changes in sexual function (same, better or worse) on the CSFQ differed significantly for duloxetine versus escitalopram (p=.019) in male patients, with no significant difference between active drugs in females.
- At 8 Months, there were no statistically significant differences observed between duloxetine and escitalopram in categorical changes on the CSFQ for male or female patients.
- Discontinuation rates for sexual side effects did not differ for duloxetine (n=2) versus escitalopram (n=7, p=.07).

Study Limitations

After 8 weeks, the power to detect a difference between the active treatments and placebo was significantly decreased due to attrition and placebo-rescue, and by endpoint (8 months) few patients (n=15) remained on placebo compared with duloxetine (n=105) or escitalopram (n=124).

CONCLUSION

Short-term treatment demonstrated worsening of sexual functioning with escitalopram as compared to placebo, while duloxetine was not significantly different from placebo at anytime during the 8-month study.

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