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Original Papers

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Resolution of sexual dysfunction during double-blind treatment of major depression with reboxetine or paroxetine

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Abstract

The selective noradrenaline re-uptake inhibitor reboxetine may have advantages over the selective serotonin re-uptake inhibitors fluoxetine and citalopram, in effects on sexual function and satisfaction. The effects of reboxetine and paroxetine on sexual function were compared by examining data from the UK centres in an international double-blind flexible-dose parallel-group multi-centre randomized controlled trial of acute treatment of patients with DSM-IV major depression.

Patients were randomly assigned to receive reboxetine (4 mg *b.d.*) or paroxetine (20 mg *mane*) using a double-dummy technique to preserve the blind. The dosage could be increased at day 28 (to reboxetine 4 mg *mane*, 6 mg *nocte*; or paroxetine 20 mg *b.d.*). Antidepressant efficacy was assessed by the 21-item Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impression Scale for Severity (CGI-S) at all study visits, and the Clinical Global Impression of Improvement (CGI-I) at each visit after randomization. Sexual function and satisfaction was assessed by visual analogue scale (VAS) items of the Rush Sexual Inventory completed at baseline and days 28 and 56.

There were no significant differences between groups in demographic or clinical features at baseline. There was a gradual reduction in severity of depressive symptoms (reboxetine, −14.3; paroxetine, −12.0: observed case analysis), with no significant differences between groups. There were significant differences ($p < 0.05$), with advantages for reboxetine, at Week 4 and Week 8 on the VAS item assessing ability to become sexually excited, and non-significant trends with advantages for reboxetine, in frequency of sexual thoughts at Week 4 ($p = 0.05$) and Week 8 ($p = 0.08$); and in desire to initiate sexual activity at Week 4 ($p = 0.09$). Exclusion of patients who had ever experienced sexual dysfunction with any medication prior to participation in this study ($n = 10$) reduced the statistical significance of the findings, although there were still numerical advantages for reboxetine.

Sexual function and satisfaction in depressed patients improves during double-blind acute treatment with reboxetine or paroxetine, but this improvement is greater and more rapid with reboxetine.

Keywords
reboxetine, paroxetine, sexual dysfunction, randomized controlled trial

Introduction

Reboxetine is a selective noradrenaline re-uptake inhibitor, with little effect on serotonin (5-hydroxytryptamine, 5-HT) or dopamine re-uptake; it does not inhibit monoamine oxidase activity, and has low affinity for α-adrenergic and muscarinic receptors (Baldwin and Carabal, 1999). It is efficacious in the acute and continuation phases of treatment of depression, with similar efficacy to desipramine and the SSRI fluoxetine, and has possible advantages over fluoxetine in improving social function in remitted patients (Dubini *et al.*, 1997; Massana *et al.*, 1999).

Although case reports suggest reboxetine treatment can affect sexual function adversely (O'Flynn and Michael, 2000; Haberfellner, 2002), it may be associated with a lower burden of sexual dysfunction than that seen with SSRIs. A randomized placebo-controlled trial indicates that reboxetine and fluoxetine differ in effects on sexual function: using the Rush Sexual Inventory (RSI) (Zajecka *et al.*, 1997), reboxetine treatment was associated with significantly greater improvements in sexual satisfaction than with fluoxetine, whereas sexual function was significantly worse with fluoxetine than with placebo (Clayton *et al.*, 2003). This finding is supported by the results of a randomized double-blind controlled

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trial comparing reboxetine and the SSRI citalopram (Bodlund *et al.*, 2003), in which reboxetine was associated with fewer adverse effects on sexual function.

The SSRI paroxetine is efficacious in the acute treatment of major depression, panic disorder, social phobia, obsessive-compulsive disorder and post-traumatic stress disorder. The aim of this study was to compare the effects of double-blind acute treatment with reboxetine or paroxetine on measures of sexual function and satisfaction in patients with major depression. The study hypotheses were that reboxetine would have significant advantages over paroxetine in effects on sexual function as assessed by item 14 of the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) and by the visual analogue items of the RSI, the null hypothesis being tested was there would be no significant differences between treatments on these measures.

Method

The patient sample described here was recruited in the United Kingdom centres of an international multi-centre double-blind parallel-group flexible-dose randomized controlled trial, comparing reboxetine and paroxetine in the acute treatment of patients with major depressive episodes. The findings of the overall study have not yet been presented.

Participating patients underwent a 4–28 day washout period (dependent upon previous antidepressant treatment) prior to randomization, and 8 weeks of double-blind treatment. Assessment visits occurred at baseline and at weekly intervals during double-blind treatment. Patients were randomly assigned to receive reboxetine (4 mg *b.d.*) or paroxetine (20 mg *mane*) using a double-dummy technique. The dosage of double-blind treatment could be increased at day 28, to a reboxetine dosage of 4 mg *mane*, 6 mg *nocte*, and paroxetine dosage of 20 mg *b.d.*

Antidepressant efficacy was assessed by the HAM-D (total score on the first 17 items of the 21-item version) at all study visits. In addition, the Clinical Global Impression Scale for Severity (Guy, 1976) (CGI-S) was used at each visit, and the Clinical Global Impression of Improvement (CGI-I) at each visit after randomization. As in a previously reported study (Clayton *et al.*, 2003), sexual function and satisfaction were assessed by the Visual Analogue Scale (VAS) items of the RSI, completed at baseline and days 28 and 56. It was considered inappropriate to subject all items of the RSI to detailed analysis, due to the size of the sample. As in a double-blind comparison of nefazodone and paroxetine (Feiger *et al.*, 1996), the mean score on item 14 of the HAM-D (genital symptoms) was also examined, as another (but rather limited) measure of sexual function.

Statistical analysis involved calculation of the mean score (and standard deviation) on the HAMD, item 14, CGI-I and VAS items

Table 1 Demographic and clinical characteristics at baseline

	Reboxetine	Paroxetine	Total
Number	34	36	70
Gender			
Male, n (%)	20 (58.8)	20 (55.6)	40 (57.1)
Female, n (%)	14 (41.2)	16 (44.4)	30 (42.9)
Mean age, years (SD)	38.0 (10.5)	45.3 (11.9)	41.7 (11.8)
Age range, years	21–60	23–63	21–63
17-item HAM-D score, mean (SD)	24.0 (3.8)	23.7 (4.0)	23.8 (3.9)
Previous sexual dysfunction with any medication			
No, n (%)	25 (89.3)	20 (74.1)	45 (81.8)
Yes, n (%)	3 (10.7)	7 (25.9)	10 (18.2)
Genitourinary surgical or medical procedure			
No, n (%)	21 (72.4)	21 (75.0)	42 (73.7)
Yes, n (%)	8 (27.6)	7 (25.0)	15 (26.3)
Non-routine investigation of reproductive organs			
No, n (%)	25 (86.2)	27 (96.4)	52 (91.2)
Yes, n (%)	4 (13.8)	1 (3.6)	5 (8.8)
Evaluated for sexual dysfunction			
No, n (%)	28 (96.6)	26 (92.9)	54 (94.7)
Yes, n (%)	1 (3.4)	2 (7.1)	3 (5.3)
Treated for sexual dysfunction			
No, n (%)	29 (100.0)	27 (96.4)	56 (98.3)
Yes, n (%)	0 (0.0)	1 (3.6)	1 (1.7)

SD, standard deviation.
Not all patients provided responses on all RSI items at baseline.

of the RSI for each visit; and calculation of the difference between treatment groups in mean scores (together with standard error and 95% confidence intervals), significance values being estimated by two-tailed t-tests. The statistical package STATA 7.0 (StataCorp, 2001) was used throughout.

The overall treatment study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. The study was approved by the local or regional research ethics committees, either for each study centre or each country, according to local legal requirements.

Results

Study sample

The age and gender distributions were similar in the two treatment groups, as were the mean 17-item HAM-D total scores at baseline (Table 1). More patients in the reboxetine treatment group had previously experienced sexual dysfunction whilst taking other medication; similar proportions had undergone genitourinary surgical or medical procedures; but more patients in the reboxetine treatment group had undergone non-routine investigation of their reproductive organs.

Efficacy of double-blind treatment

There was a gradual reduction in severity of depressive symptoms in both treatment groups, measured by the mean total 17-item HAM-D score at each visit, using an observed case analysis (Table 2). The mean CGI-I score declined from Week 1 in both treatment groups, reflecting an improvement in overall clinical condition. The overall change in score was similar (−1.49 with reboxetine, −1.32 with paroxetine). There were no significant differences between treatment groups in HAMD, CGI-S or CGI-I scores at any assessment.

Change in genital symptoms (item 14 of the HAM-D)

In both groups, the severity of genital symptoms first increased, and then subsequently reduced over the course of the study, although the pattern of change was different. There were no significant differences in mean values between treatment groups, although there were non-significant trends with advantages for reboxetine at Week 7 ($p = 0.097$) and Week 8 ($p = 0.06$). The magnitude of the difference in mean score was small (0.38 at Week 7, 0.43 at Week 8).

Change in RSI visual analogue item scores

Not all patients completed the RSI at the baseline assessment, and the number of observations at subsequent assessments declined during double-blind treatment. The visual analogue items are not gender-specific and data from male and female patients are combined. Table 3 gives the mean scores on these items at baseline, and after 4 and 8 weeks of double-blind treatment. Items are all rated 0–100, higher scores indicating greater satisfaction.

The pattern of change in individual items shows marked differences between treatment groups. The mean score on the item assessing frequency of pleasurable sexual thoughts increased steadily with reboxetine treatment, but with paroxetine an initial decrease was followed by a much smaller increase. The item measuring ability to become sexually excited showed increases in mean score in both treatment groups, although the change with paroxetine was slight (7.1% increase, compared to 66.5% with reboxetine) (Fig. 1).

The mean score on the item assessing frequency of desires to initiate sexual activity increased in both groups, but the change was much less with paroxetine than with reboxetine (10.2% increase, compared to 64.4%). The mean score on the item assessing frequency of initiation of sexual activity increased in both groups, with a greater increase with reboxetine (61.9%, compared to 20.1% with paroxetine). The mean score on the item assessing

Table 2 Mean 17-item HAM-D total scores (observed case analysis)

	Reboxetine			Paroxetine		
Time	*n*	Mean	SD	*n*	mean	SD
Baseline	34	24.03	3.81	36	23.67	3.96
Week 1	33	21.97	5.13	36	21.06	5.14
Week 2	29	20.31	4.94	34	18.68	6.12
Week 3	28	18.25	6.40	32	15.90	6.20
Week 4	26	14.50	7.14	31	14.51	5.54
Week 5	24	14.08	7.19	31	14.87	6.26
Week 6	21	13.05	6.67	29	13.86	6.81
Week 7	20	12.35	5.91	30	13.60	6.97
Week 8	21	9.90	6.20	30	11.67	6.22

SD, standard deviation.

All scores given to two decimal places.

Table 3 Mean RSI visual analogue item scores (observed case analysis, all patients)

	Reboxetine			Paroxetine			Difference between treatments				
Item	*n*	mean	SD	*n*	mean	SD	Diff mean	SE (n)	95% CI lower, upper		*p*-value
Sexual thoughts											
Baseline	26	34.38	30.04	28	31.64	32.18	2.74	8.49	−14.29	19.77	0.75
Week 4	19	48.94	31.17	23	29.87	30.20	19.08	9.50	−0.12	38.27	0.05
Week 8	10	60.80	24.44	16	38.75	32.3	22.05	12.00	−2.71	46.81	0.08
Sexual excitement											
Baseline	27	41.44	25.72	28	35.82	31.64	5.62	7.79	−10.01	21.25	0.47
Week 4	20	56.45	30.46	22	35.00	34.56	21.45	10.09	1.05	41.85	0.04
Week 8	10	69.00	36.04	16	38.38	35.85	30.63	14.48	0.74	60.51	<0.05#
Sexual desire											
Baseline	27	32.48	28.91	28	31.32	30.96	1.16	8.08	−15.06	17.38	0.88
Week 4	19	51.52	30.19	22	33.73	34.39	17.80	10.19	−2.80	38.40	0.09
Week 8	10	53.40	30.91	15	34.53	36.79	18.87	14.12	−10.36	48.09	0.19
Initiate sex											
Baseline	26	23.65	22.93	28	18.04	22.49	5.62	6.18	−6.79	18.02	0.37
Week 4	18	35.28	33.62	22	21.00	26.95	14.28	9.57	−5.10	33.65	0.14
Week 8	10	38.30	31.57	16	22.31	27.01	15.99	11.61	−7.98	39.96	0.18
Sexual satisfaction											
Baseline	26	32.00	29.44	27	29.96	32.75	2.04	8.57	−15.16	19.23	0.81
Week 4	18	46.44	38.33	21	29.43	32.94	17.02	11.41	−6.10	40.13	0.14
Week 8	10	50.10	36.58	16	32.44	30.30	17.66	13.22	−9.63	44.95	0.19

SD, standard deviation; SE, standard error; CI, confidence intervals; $p = 0.045$.
All scores given to two decimal places.

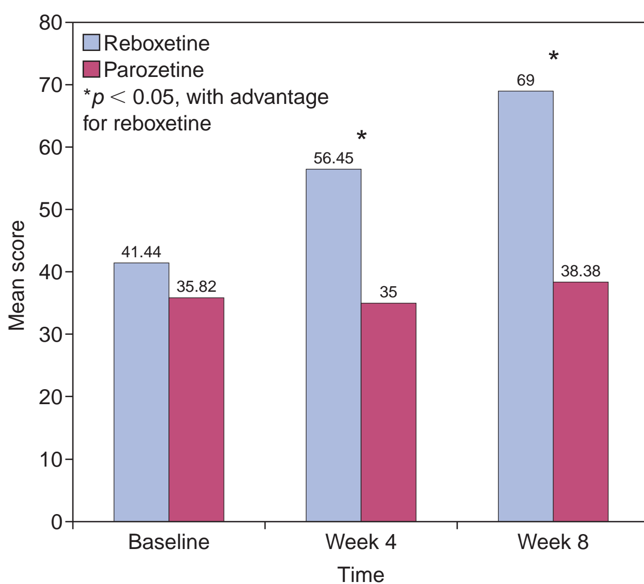

Figure 1 Change in RSI sexual excitement visual analogue scale (observed case analysis, all patients)

overall degree of sexual satisfaction increased steadily with reboxetine, but declined with paroxetine.

At baseline assessment, ten patients (three allocated to reboxetine and seven to paroxetine) reported having experienced sexual dysfunction during previous treatment with a medication. Exclusion of these patients from the study sample did not result in any significant differences between the remaining patient groups on the VAS items at baseline assessment. In the smaller group, there were still numerical advantages for reboxetine over paroxetine, but the difference between treatments on the sexual excitement VAS declined in significance (day 28, $p = 0.06$; day 56, $p = 0.09$): by contrast, the difference between treatments on the sexual thoughts VAS became more marked ($p = 0.01$) (Table 4).

Adverse events associated with treatment

Twelve patients (six in each group) reported a total of 13 adverse events relating to sexual function. Reboxetine treatment appeared associated with problems in sexual desire and arousal, paroxetine with problems in orgasm (inhibited ejaculation in men or anorgasmia in women).

Table 4 Mean RSI visual analogue item scores (observed case analysis, excluding patients with previous sexual dysfunction whilst taking any medication)

	Reboxetine			Paroxetine			Difference between treatments				
Item	*n*	mean	SD	*n*	mean	SD	Diff mean	SE (n)	95%	CI lower, upper	*p*-value
Sexual thoughts											
Baseline	23	33.91	31.15	21	34.29	33.82	0.37	9.79	−20.14	19.39	0.97
Week 4	16	51.38	30.81	18	31.17	30.73	20.21	10.57	−1.33	41.74	0.06
Week 8	9	63.44	24.37	12	32.00	27.51	31.44	11.57	7.23	55.66	0.01
Sexual excitement											
Baseline	24	42.96	25.86	21	35.10	31.79	7.86	8.60	−9.48	25.20	0.37
Week 4	17	56.88	30.86	17	34.47	35.12	22.41	11.34	−0.69	45.51	0.06
Week 8	9	65.56	36.44	12	36.50	37.01	29.06	16.22	−4.89	62.99	0.09
Sexual desire											
Baseline	24	35.00	29.49	21	32.76	31.98	2.23	9.17	−16.25	20.72	0.81
Week 4	16	52.81	31.37	17	34.94	35.65	17.87	11.72	−6.03	41.77	0.14
Week 8	9	54.56	32.55	11	35.36	37.76	19.19	15.97	−14.37	52.75	0.25
Initiate sex											
Baseline	23	24.65	23.28	21	16.43	19.76	8.22	6.54	−4.98	21.43	0.22
Week 4	15	34.40	34.44	17	19.82	25.41	14.58	10.61	−7.10	36.25	0.18
Week 8	9	39.44	33.27	12	19.33	22.82	20.11	12.21	−5.46	45.68	0.11
Sexual satisfaction											
Baseline	23	34.35	30.02	20	32.20	33.15	2.15	9.63	−17.31	21.61	0.82
Week 4	15	50.73	38.05	16	29.69	33.19	21.05	12.80	−5.14	47.23	0.11
Week 8	9	49.89	38.79	12	29.75	25.74	20.14	14.06	−9.30	49.57	0.16

SD, standard deviation; SE, standard error; CI, confidence intervals.
All scores given to two decimal places.

Conclusions

Although sexual function and satisfaction improved in both treatment groups as the severity of depressive symptoms declined, this study provides further evidence to support the contention (Baldwin, 2004) that antidepressants of similar efficacy can differ in their effects on sexual function. There were significant differences between groups, with advantages for reboxetine, at Weeks 4 and 8 on the item assessing ability to become sexually excited; and non-significant trends with advantages for reboxetine in frequency of sexual thoughts at Weeks 4 and 8, and in desire to initiate sexual activity at Week 4 ($p = 0.09$). The null hypothesis, that there would be no differences between treatments in effects on sexual function, can be rejected. In patients describing a lifetime history of sexual dysfunction during treatment with any medication, there were still numerical advantages for reboxetine, and some trends towards significance.

The investigation has a number of weaknesses. First is the absence of a placebo control. Second is the small size of the sample, which represents a sub-group from the total population recruited in the overall treatment study. A third is the decline in patient numbers during the course of the investigation, which reduces the confidence that can be placed in the findings. Only 51 patients (72.9% of the original sample) provided data on item 14 of the HAM-D at study end-point; 54 patients (77.1%) provided data on the RSI visual analogue items at baseline, but only 26 patients (37.1%) did so at end-point. Finally, item 14 of the HAMD is a composite measure used to assess loss of libido, other aspects of sexual function, and menstrual cycle problems and therefore does not allow characterization of the type of any disturbance of sexual function that may be present.

However, if the findings are confirmed in the overall treatment study, and providing there is no difference in antidepressant efficacy and other measures of treatment tolerability, it could be argued that reboxetine is preferable to paroxetine in depressed patients concerned with sexual function. As in an earlier investigation (Clayton *et al.*, 2003), this study provides further evidence that scores on the VAS items of the RSI change during the course of antidepressant treatment, and thereby confirms that it is possible to use the RSI to distinguish the effects on sexual function of antidepressants with differing pharmacological properties.

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Declaration

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