

Orgasm, Serotonin Reuptake Inhibition, and Plasma Oxytocin in Obsessive-Compulsive Disorder. Gleaning From a Distant Randomized Clinical Trial



Mats B. Humble, MD,^{1,2} and Susanne Bejerot, MD^{1,2}

ABSTRACT

Introduction: Serotonin reuptake inhibitors (SRIs) are widely used for the treatment of psychiatric disorders, including obsessive-compulsive disorder (OCD). SRIs commonly cause delayed orgasm, the mechanism of which is poorly understood. Oxytocin is involved in sexual function and is interconnected with serotonin within the brain. SRIs are reported to affect the oxytocin system, but possible relations between SRI-induced changes of sexual function and oxytocin are unexplored in humans. In a randomized, double-blinded, placebo-controlled trial of OCD, the anti-obsessive efficacy and adverse events of SRIs and oxytocin measurements were studied.

Aims: To identify possible correlates between oxytocin levels and sexual function; find out whether sexual side effects correlate with levels of oxytocin and/or paroxetine and clomipramine; and test whether changes in sexual functioning are related to an anti-obsessive response.

Methods: Reported sexual function and oxytocin plasma levels at rest were studied in 31 adults (15 men and 16 women) with OCD who participated in a randomized, double-blinded trial comparing the SRIs clomipramine and paroxetine with placebo. Sexual adverse effects were quantified by a clinician-administered semistructured interview. Anti-obsessive response was based on the Yale-Brown Obsessive-Compulsive Scale.

Main Outcome Measures: Ratings on the Sexual Symptom Checklist, plasma oxytocin, serum paroxetine and clomipramine levels, and Yale-Brown Obsessive-Compulsive Scale scores.

Results: Baseline oxytocin levels were positively correlated with baseline OCD severity, but not with sexual functioning. Impaired orgasm at week 6 was reported by 73% of SRI-treated and 20% of placebo-treated patients ($P = .03$). Impaired orgasm was related to higher oxytocin levels after 4 weeks of SRI treatment ($P < .01$) but not to SRI concentrations. In men, an association between impaired orgasm and anti-obsessive treatment response was found ($P = .028$).

Conclusion: This pilot study suggests that some collateral effects of SRIs, particularly delayed orgasm, might be influenced by changes within the oxytocinergic system and are related to anti-obsessive mechanisms. Early-onset delayed orgasm in SRI-treated patients could serve as a predictor for OCD treatment response.

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Key Words: Obsessive-Compulsive Disorder; Oxytocin/Plasma; Serotonin; Clomipramine; Paroxetine; Serotonin Uptake Inhibitors; Response Prediction; Adverse Effects; Randomized Controlled Trial; Sexual Physiology

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¹Örebro University, School of Medical Sciences, Örebro, Sweden;

²University Health Care Research Center, Örebro, Sweden

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INTRODUCTION

Antidepressant-Induced Sexual Dysfunction, Serotonergic, and Oxytocinergic Mechanisms

In clinical practice, treatment with potent serotonin reuptake inhibitors (SRIs; eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-noradrenaline reuptake inhibitors, and the tricyclic antidepressant clomipramine) is commonly associated

with sexual side effects. The frequency of these side effects has been debated, because in major depression (the most common indication for SRIs) sexual dysfunction constitutes a typical symptom of the disorder. However, in patients without sexual dysfunction at baseline, SRIs often induce decreased libido and delayed orgasm and/or ejaculation.^{1,2} The specificity of serotonergic mechanisms is evident, because serotonergic antidepressants cause a much higher rate of sexual dysfunction than noradrenergic drugs, especially concerning orgasmic function.^{2,3} Thus, SRIs seem to affect most specifically orgasmic function, which is further supported by the fact that SSRIs (eg, paroxetine and dapoxetine) currently constitute first-line pharmacologic treatment of premature ejaculation.⁴ Despite the usefulness of this side effect of SSRIs in andrology, in psychiatric practice, it is mainly viewed as an undesired adverse effect. In any case, further knowledge of the neurochemical mechanisms is warranted. Concerning the role of various serotonin (5-hydroxy-tryptamine [5-HT]) receptors, agonists on 5-HT_{1A} receptors have been found to facilitate, whereas 5-HT_{1B} agonists have been found to inhibit or delay, ejaculatory functions in rats.^{5–7} Not only direct effects of changed serotonergic transmission, but also indirect effects of serotonin, such as inhibited dopamine release,⁸ or increased prolactin levels⁹ have been mechanistically implicated. However, serotonin has increasingly been shown to interact with the hypothalamic-neurohypophyseal hormone oxytocin, which clearly is involved in sexual functions, although its role in human sexuality is insufficiently defined.^{10–12} Serotonin increases the hypothalamic mRNA expression of oxytocin by stimulating 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C} receptors¹³ and increases oxytocin release by 5-HT_{1A}, 5-HT_{2C} and 5-HT₄ receptors.¹⁴ Plasma oxytocin increases rapidly after SSRI administration in rats,¹⁵ and the therapeutic effect of SSRIs might be mediated by oxytocin.^{15,16} Conversely, oxytocin might modulate the release of serotonin in mice¹⁷ and humans.¹⁸ SSRI treatment leads to downregulation of 5-HT_{1A} receptors after approximately 1 week,^{19,20} thereby potentially decreasing oxytocin activity. Because 5-HT_{1A} receptor activation releases oxytocin and facilitates ejaculation in rats, de Jong et al²¹ suggested that SSRI-induced delayed orgasm might be related to downregulation of 5-HT_{1A} receptors and decreased oxytocin activity.

However, it should be noted that, with few exceptions,^{10,11,18} these studies were performed in rodents, and to our knowledge, no human studies relating oxytocin and serotonin measurements with sexual function are available. Two single cases of male sexual dysfunction (not caused by SSRIs) were reportedly improved by intranasal oxytocin^{22,23}; however, when intranasal oxytocin was administered to 10 male volunteers, a moderate but significant delay of ejaculation was recorded.¹¹

Serotonin and Oxytocin in Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a psychiatric disorder that frequently has a long-term course and does not include

sexual dysfunction among its typical symptoms. Some specific symptoms (eg, obsessions related to contamination, religion, or sexuality) can interfere with sexual function,²⁴ but sexual obsessions have been found in only 13% of adult patients with OCD.²⁵ In a direct comparison of sexual dysfunction, patients with OCD were more similar to healthy controls than to patients with a major depressive disorder.²⁶ Because of early findings that the potent SRI clomipramine has a specific anti-obsessive effect,²⁷ pathophysiologic research on OCD has focused on serotonin.^{28,29} Currently, SRIs are the main pharmacologic anti-obsessive treatment, but a clinical problem is the long delay of therapeutic response.³⁰ Interestingly, Ackerman et al^{31,32} found relations between sexual side effects of SRIs and the anti-obsessive clinical response, with early-onset sexual dysfunction being the side effect most consistently predicting a response to the SSRI fluoxetine.

Oxytocin also has been implicated in the pathophysiology of OCD.^{33,34} In a previous study, we investigated how SRIs change oxytocin levels in patients with OCD.³⁵ We found higher plasma oxytocin levels after 4 weeks of treatment in SRI responders compared with non-responders.

Accordingly, drug-induced sexual effects are common in SRI-treated patients, but the mechanisms of these effects are insufficiently studied. A putative role of oxytocin is unsubstantiated in humans, because, to our knowledge, oxytocinergic measurements in relation to sexual functions in SRI-treated humans have not been reported.

AIMS

While investigating SRI treatment of OCD, we had the opportunity to study oxytocin in relation to SRI-induced sexual side effects. Our aims were to:

1. Identify possible correlates between baseline oxytocin plasma levels and baseline sexual function;
2. Find out whether the degree of sexual side effects correlates with plasma levels of oxytocin, with changes of oxytocin induced by treatment, and/or with serum levels of paroxetine and clomipramine;
3. Test whether incident changes of sexual functioning have any relation to the anti-obsessive clinical response.

METHODS

Patients

In a 12-week, multicenter, randomized, double-blinded, parallel-group drug trial comparing flexible doses of the SRIs paroxetine (20–60 mg daily) and clomipramine (50–250 mg daily) and placebo for the treatment of OCD, our center included 43 patients with OCD.³⁶ Of these, 36 patients participated in a site-specific biochemical extension of the trial,^{35,37} including plasma levels of oxytocin (at baseline and 1 and 4 weeks after treatment) and serum concentration of the

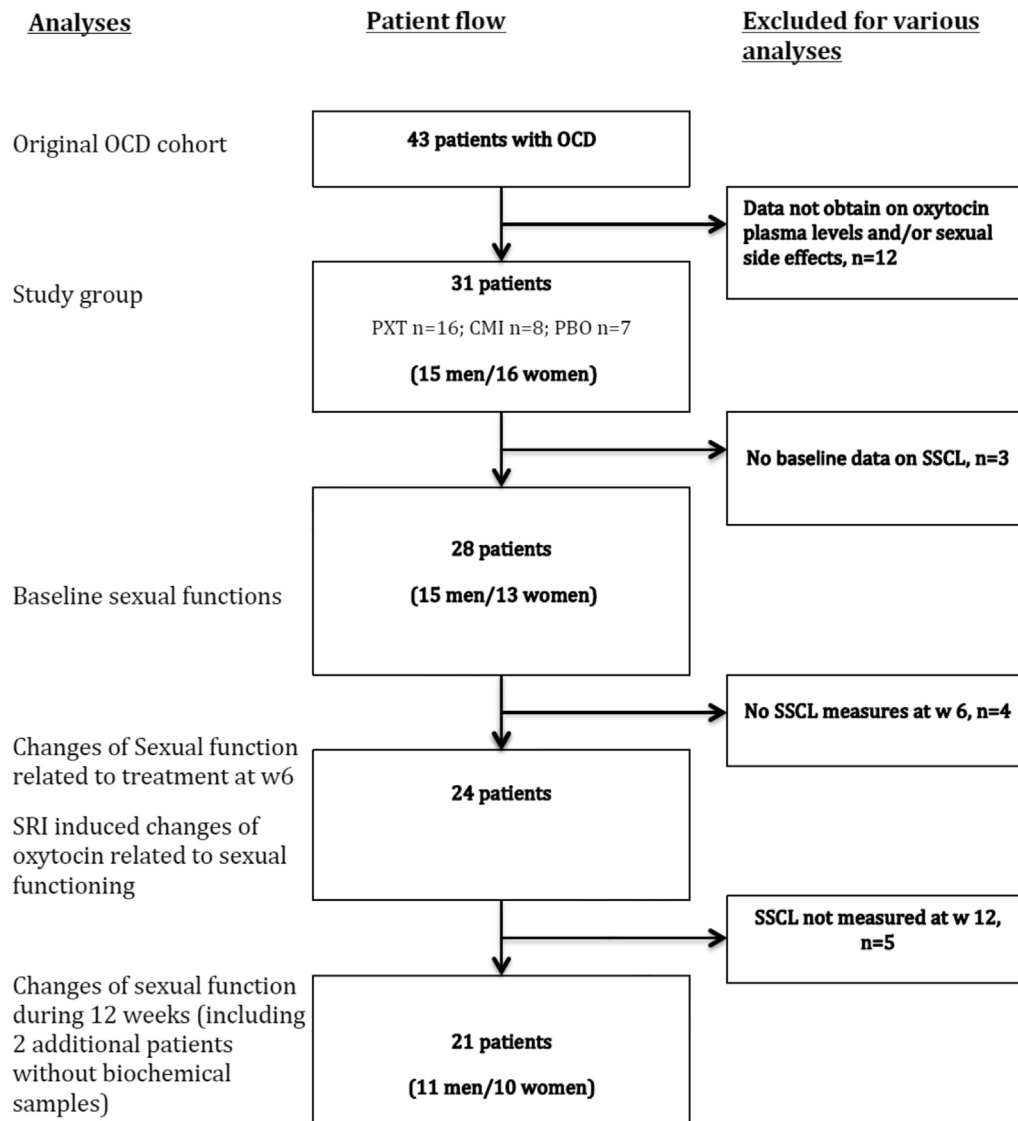


Figure 1. Flowchart. CMI = clomipramine treated; OCD = obsessive-compulsive disorder; PBO = placebo treated; PXT = paroxetine treated; SRI = serotonin reuptake inhibitor; SSCL = Sexual Symptom Checklist; w = week.

drugs (after 4 weeks). Information on sexual function ratings for at least one time point was available for 35 of these 43 patients and oxytocin levels were available in 36. Oxytocin levels and sexual function were available in 31 patients (15 men and 16 women). Of these, 17 were single and 14 were cohabiters. Mean age was 40.8 years (SD = 11.1 years, minimum = 18.1 years, maximum = 57.2 years). Mean age at onset of OCD was 13.9 years (SD = 6.7 years). Mean duration of OCD was 26.9 years (SD = 13.0 years). Twenty-one patients (68%) were SRI naive, and none had been taking antidepressant agents during the preceding 3 months. Their mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)³⁸ score was 25.1 (SD = 5.7) at baseline and their mean Montgomery-Åsberg Depression Rating Scale (MADRS)³⁹ score was 11.9 (SD = 7.8). [Figure 1](#) shows a flowchart of subject selection. Details on the criteria for inclusion and exclusion of patients have been published elsewhere.^{35–37}

MAIN OUTCOME MEASURES

Measurements of Sexual Function and Side Effects and the Sexual Symptom Checklist

Using a semistructured interview, the Limited Symptom Checklist, administered by the clinician, anticipated adverse effects were quantified. Eight of the 14 items on this checklist concern sexual function, closely following the items reported in an early study of clomipramine-induced anorgasmia.⁴⁰ These items are (i) interest in sex, (ii) sleepiness interfering with sexual function, (iii) frequency of sex or masturbation, (iv) erection (men) or lubrication (women), (v) sexual sensation, (vi) intensity of orgasm, (vii) difficulty or increased time to reach orgasm, and (viii) intensity of pain at orgasm. Each item was graded “none,” “low,” “medium” or “high.” The clinician was instructed to perform this interview at baseline and at each visit during the 12-week trial. For the present study, the sleepiness and pain

Table 1. Mean scores on each item from the SSCL in 32 patients with obsessive-compulsive disorder between men and women and score changes after 6 weeks of double-blinded treatment between treatments*

SSCL items graded 0–3		Pretreatment ratings (n = 32)				Score changes after 6 wk of treatment (n = 27)			
		Men (n = 18)	Women (n = 14)	MW-U	P value	SRI (n = 21)	Placebo (n = 6)	MW-U	P value
1	Sexual interest	1.9	1.6	90.5	.18	–0.05	0.17	50.0	.48
2	Sexual frequency	1.7	1.2	73.5	.045	–0.05	0.00	58.5	.80
3 (men)	Erection	1.9				.08 (n = 12)	0.00 (n = 3)	16.5	.84
3 (women)	Lubrication		1.6			–0.11 (n = 9)	0.33 (n = 3)	8.5	.37
4	Sexual sensation	1.8	1.6	113	.64	0.00	0.50	42.0	.24
5	Orgasm intensity	1.9	1.5	95.5	.25	–0.38	0.33	36.0	.12
6	Orgasm difficulty or delay—R [†]	2.8	2.0	59.0	.01	–1.81	0.00	18.5	.007
SSCL total score (0–18)		12.1	9.6	62.5	.014	–2.29	1.17	14.0	.003

MW-U = Mann-Whitney U-test; SRIs = serotonin reuptake inhibitors; SSCL = Sexual Symptom Checklist.

*Higher scores denote less sexual dysfunction. Mann-Whitney U-test was used for group comparisons. Means are presented because the small number of alternative scores for each item made medians and quartiles uninformative. SDs varied from 0.4 to 1.0 for the separate items; also see Table 2.

[†]The scoring of this item is reversed to comply with the other items (ie, higher scores denote less orgasm difficulty).

items (items ii and viii) were excluded, because of questionable relevance and low endorsement rate, respectively. The six remaining items, constituting the Sexual Symptom Checklist (SSCL) in the present study, are strikingly similar to the Arizona Sexual Experience Scale (ASEX),⁴¹ commonly used in psychopharmacology studies. Each item of the SSCL was graded from 0 to 3 and included in our analyses as Likert-type items (Table 1 presents item content). The item “difficulty or increased time to reach orgasm” was reversed, because higher points for all other items denote improved or increased sexual function. Then, the six items could be summed to a SSCL total score, approximating general sexual functioning.

Simulation of ASEX Scores

The Limited Symptom Checklist was an “ad hoc” scale for the multicenter study that had not been validated, and to our knowledge, the results at the multicenter level from this scale were never published.³⁶ Therefore, to support the use of the SSCL, we mathematically transformed our SSCL scores to simulate the differently scored but otherwise similar ASEX (five items scored 1–6). For this purpose, grade 0 (very poor function) in the SSCL was replaced by grade 6, grade 3 (optimal function) was replaced by grade 1, and the other grades correspondingly in between (with the reversed item fitted accordingly). Of the five ASEX items, two (“penile erection or vaginal lubrication” and “ability to reach orgasm”) are almost exactly equivalent to two items in the SSCL; “satisfaction from orgasm” in the ASEX corresponds well to “intensity of orgasm” in the SSCL. Of the remaining SSCL items, “interest in sex” and “frequency of sex” can reasonably substitute for “arousal” and “drive,” respectively, on the ASEX, making the last SSCL item, “sexual sensation,” superfluous. With transformation, our scores could be directly compared with ASEX scores from two published studies,^{26,42} in which patients with OCD were compared

with other psychiatric subjects and healthy controls concerning their sexual functions (Table 2).

In addition, the utility of the SSCL was probed by its ability to detect differences between men and women, as reported by the ASEX⁴¹ and changes induced by SRI treatment^{1,3} (Table 1).

To categorize the level of sexual side effects, we created two indices from the SSCL: “markedly decreased sexual interest” (items 1–4) and “markedly impaired orgasm” (items 5 and 6). For each index, items were added, and a worsening from baseline of at least two points was required for endorsement.

Measurements of OCD and Response to Treatment

Ratings of OCD symptom severity and depression were assessed with the Y-BOCS³⁸ and the MADRS, respectively.³⁹ In addition, possible adverse effects were elicited by open questioning.

Response to treatment was defined as a score decrease of at least 25% on the Y-BOCS and a rating of 1 or 2 (“very much improved” or “much improved,” respectively) on the Patients’ Global Evaluation (a self-rating version of the Clinical Global Impression improvement scale)⁴³ after 12 weeks of treatment.

Measurements of Plasma Oxytocin and Serum Antidepressant Concentrations

After an overnight fast, blood samples for analyses were taken from 8:00 AM to 9:00 AM after a 10-minute rest in a calm room, at baseline, and after 1 and 4 weeks of double-blinded treatment. All samples were frozen and analyzed in the same assay. For oxytocin, plasma was stored, samples were extracted before assay, and the concentration of oxytocin was measured with a specific radioimmunoassay; for details, see Humble et al.³⁵

Regarding antidepressant concentrations, serum samples were considered as reasonable steady-state trough values. Paroxetine and clomipramine serum concentrations were analyzed after

Table 2. Simulated ASEX scores compared with genuine ASEX scores across three studies and between women and men*

N	HCS [†]	MDD [†]	SAD [†]	OCD [†]	OCD [‡]	OCD-F [§]	OCD-F [¶]	OCD-M [¶]	OCD-M [§]
n	50	50	26	31	50	32	28	22	18
ASEX									
Sex drive or frequency	2.94 (0.9)	4.42 (1.4)	3.50 (1.2)	3.97 (1.5)	3.54 (1.4)	3.55 (1.0)	3.91 (1.4)	3.25 (1.4)	3.22 (1.0)
Arousal or interest	2.60 (1.0)	4.08 (1.3)	3.00 (1.1)	3.45 (1.3)	3.26 (1.4)	2.98 (0.8)	3.68 (1.4)	2.93 (1.4)	2.76 (0.7)
Erection or lubrication	2.86 (1.1)	3.86 (1.4)	2.88 (1.2)	3.26 (1.4)	3.26 (1.4)	3.03 (0.9)	3.64 (1.4)	2.96 (1.3)	2.85 (0.8)
Ability to reach orgasm	2.42 (1.2)	3.74 (1.5)	2.73 (1.4)	3.77 (1.4)	3.98 (1.4)	1.89 (1.4)	3.50 (1.6)	4.42 (1.2)	1.28 (0.9)
Orgasm satisfaction	3.02 (1.3)	4.04 (1.3)	3.27 (1.4)	3.90 (1.3)	3.38 (1.4)	3.08 (1.2)	3.59 (1.6)	3.21 (1.3)	2.76 (0.7)
Total score	14.3 (4.6)	20.3 (6.1)	16.0	18.4	17.7 (6.6)	14.5 (3.9)	18.7 (7.1)	17.1 (5.9)	12.9 (2.5)

ASEX = Arizona Sexual Experience Scale; F = female; HCS = healthy control subjects; M = male; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; SAD = social anxiety disorder.
 *Data are presented as mean (SD). Higher scores denote more sexual dysfunction.

[†]Kendurkar and Kaur.²⁶

[‡]Fontenelle et al.⁴²

[§]Present study.

[¶]Simulated ASEX scores.

extraction with high-performance liquid chromatography with UV detection as previously described.⁴⁴ When patients with depression were treated with paroxetine 40 mg/day, their median level was 125 nmol/L, (quartile 1 = 105 nmol/L, quartile 3 = 400 nmol/L). To enable statistical calculations of the two drugs together, Z scores were generated and used in combined analyses.

Ethics

The study was approved by the research ethical committee of the Karolinska Institutet (Stockholm, Sweden), and informed consent was obtained from all participants.

Statistics

Because items in the SSCL and oxytocin levels were non-normally distributed, non-parametric tests (Mann-Whitney U-test with two-by-one-sided exact P values and Spearman rank order correlation) were applied. However, means are presented for clarity in Table 1, and means and SDs are presented in Table 2 to facilitate comparisons with other research. Otherwise, medians and quartiles were used. Statistica 12 (StatSoft, Inc, Tulsa, OK, USA) was used. Probabilities less than .05 were considered significant.

RESULTS

Baseline Sexual Functions

Thirty-two patients (18 men and 14 women) responded reliably to all six items from the SSCL at baseline (Table 1). For 27 patients, complete ratings from baseline and 6 weeks were available, and for 19 patients we had access to complete SSCL ratings from all three time points and oxytocin concentrations at baseline and week 4. Men reported higher scores than women on sexual frequency, and women reported more difficulties reaching orgasm. There were no differences at baseline between single and cohabiting subjects or among randomized treatment groups (paroxetine, clomipramine, and placebo) for any of the SSCL items.

Simulation of ASEX Scores

As presented in Table 2, our SSCL score transformations produced sums that were somewhat lower than published reports of genuine ASEX scores from other patients with OCD^{26,42} (P = .02). However, except for orgasm ability, for which the Swedish men reported substantially less dysfunction compared with the men in the study by Kendurkar and Kaur²⁶ (P < .0001), no differences were found among women or men regarding scores on all remaining items (including orgasm ability in women).

Oxytocin Plasma Levels and Sexual Functions at Baseline

In 28 of the 32 patients, plasma oxytocin and SSCL ratings at baseline before treatment were available. Median baseline levels of oxytocin were 35.6 pg/mL (28.2–39.6 pg/mL) and 28.5

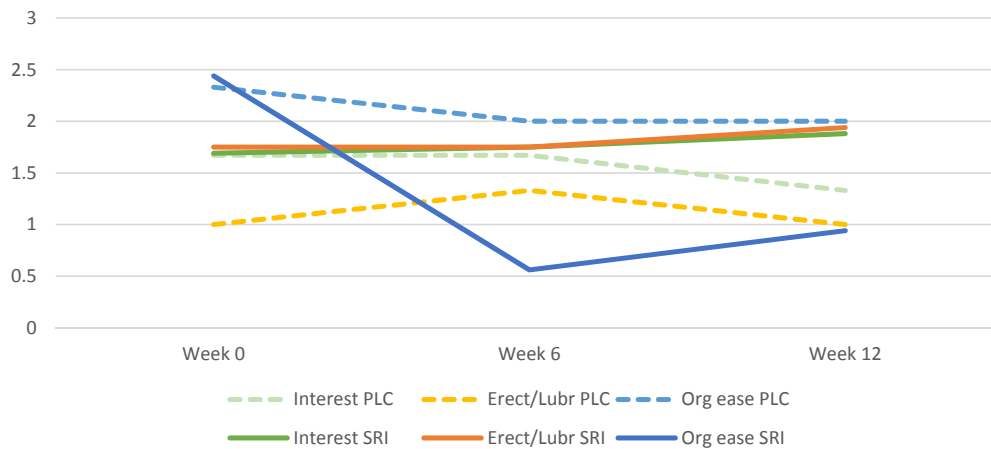


Figure 2. Sexual functioning in paroxetine-, clomipramine-, and placebo-treated patients with obsessive-compulsive disorder for 12 weeks. Mean levels over time of three items from the Sexual Symptom Checklist (sexual interest, erection or lubrication, and difficulty to reach orgasm) are shown. Only completers of all three time points were included (SRI group, $n = 17$; placebo group, $n = 4$). Significant differences between groups were found only for difficulty to reach orgasm at week 6 ($t_{19} = 3.5$, $P = .002$) and at week 12 ($t_{19} = 2.2$, $P = .043$). Erect = erection; Lubr = lubrication; PLC = placebo; SRI = serotonin reuptake inhibitor.

pg/mL (22.6–37.1 pg/mL) in men and women, respectively (Mann-Whitney U-test = 71.5, $P = .24$). Oxytocin at baseline was not related to any of the SSCL items, MADRS scores, age, or duration of OCD, but was related to baseline OCD severity (Y-BOCS scores, $n = 28$, Spearman $r_s = 0.39$, $P = .04$).

Treatment-Induced Changes of Sexual Functions

After 6 weeks of double-blinded treatment, the SRI-treated patients reported delayed orgasm, whereas other individual items in the SSCL did not differ among groups (Table 1).

The index “markedly decreased sexual interest” after 6 weeks of treatment was endorsed by 6 of 19 SRI-treated patients (32%) and by 0 of 5 placebo-treated patients (0%; $n = 24$, missing data = 7, $\chi^2_1 = 2.1$, $P = .15$). The index “markedly impaired orgasm” at week 6 was endorsed by 16 of 22 SRI-treated patients (73%) and by 1 of 5 placebo-treated patients (20%; $n = 27$, missing data = 4, $\chi^2_1 = 4.9$, $P = .028$). No differences were found between paroxetine- and clomipramine-treated patients on any item. For 21 patients, we had ratings from baseline, 6 weeks, and 12 weeks. For these patients, the evolution over time of three items from SSCL is shown in Figure 2. From all comparisons among treatment groups, the only consistent effect of SRI treatment was delayed orgasm. Three women who refrained from responding to the SSCL at baseline because of low interest or no sexual activity responded after 6 and 12 weeks, apparently because their sexual activity had increased. All three were treated with paroxetine.

Sexual Side Effects and Treatment Response in Relation to Plasma Oxytocin

Significantly higher oxytocin levels at week 4 were associated with “markedly impaired orgasm” at week 6 of SRI treatment ($P = .005$, Cohen $d = 1.06$). In these patients, oxytocin plasma

level increased by 17% from baseline to week 4, whereas those without impaired orgasm function had a 2% decrease of their oxytocin levels during the same period (not significant; Table 3). No association between “markedly decreased sexual interest” and levels of SRIs or oxytocin was found, and there was no association between serum levels of SRIs and “markedly impaired orgasm.”

When oxytocin levels at week 4 were split by the median into a high and a low group in the SRI-treated patients, 11 of 11 (100%) in the high group vs 5 of 10 (50%) in the low group reported orgasmic delay ($\chi^2_1 = 7.22$, $P = .007$). Using the same median split to compare anti-obsessive treatment response, the high oxytocin group was significantly more likely to respond to treatment than the low oxytocin group ($\chi^2_1 = 4.31$, $P = .038$).

Serum Levels of SRI

Serum concentrations of paroxetine ($n = 13$, mean = 116 nmol/L, SD = 72 nmol/L) and clomipramine ($n = 5$, mean = 230 nmol/L, SD = 102 nmol/L) were available in all but one patient treated with clomipramine. However, one paroxetine-treated patient (a non-responder with markedly delayed orgasm function) had no measurable concentration of paroxetine at week 4, suggesting he had taken a drug holiday. Therefore, he was removed from the analysis presented in Table 3. The SRI concentrations did not differ according to adverse sexual effects, decreased interest, or delayed orgasm (Table 3).

Anti-Obsessive Response and Sexual Functions

Of the 16 SRI-treated patients reporting markedly impaired orgasm at week 6, 12 (75%) were classified as responders on OCD ratings after 12 weeks of SRI treatment. Three of the six patients (50%) without impaired orgasm responded to SRI treatment (not significant). Of the five placebo-treated patients

Table 3. Oxytocin in plasma and paroxetine and clomipramine in serum in relation to incident changes of sexual function during the first 6 weeks of treatment*

	Normal or increased sexual interest (n = 14)	Markedly decreased sexual interest (n = 6)	Mann-Whitney test			Normal orgasm function (n = 5)	Markedly impaired orgasm (n = 15)	Mann-Whitney test		
			U	Z	P value			U	Z	P value
			Oxytocin level (pg/mL) at baseline	34.1 (28.2, 50.9)	32.8 (23.1, 39.5)			35.5	0.49	.62
Oxytocin level (pg/mL) at week 4	37.3 (28.6, 44.7)	40.0 (31.4, 53.4)	40.0	-0.12	.90	27.6 (26.5, 31.5)	42.7 (36.7, 54.1)	7.5	2.57	.005
Z score for SRI serum level at week 4†	0.14 (-0.37, 0.57)	0.07 (-0.95, 1.44)	39.0	0.04	.97	-0.34 (-0.89, 0.57)	0.20 (-0.39, 0.61)	30.0	0.42	.69
Paroxetine serum level (nmol/L) at week 4 (n = 14)	129 (94, 161) (n = 11)	155 (54, 260) (n = 3)	13.0	-0.47	.64	77 (50, 158) (n = 4)	140 (104, 161) (n = 10)	12.0	1.06	.29
Clomipramine serum concentration (nmol/L) at week 4 (n = 5)†	232 (175, 288) (n = 2)	190 (119, 376) (n = 3)	3.0	-0.29	.77	288 (n = 1)	183 (147, 283) (n = 4)	0	0	.00

SRI = serotonin reuptake inhibitor.
 *Data are present as median (quartiles 1, 3). Sexual function was assessed with the Sexual Symptom Checklist. Only the 20 patients treated with an SRI and with available plasma oxytocin levels at week 4 are included (data for placebo-treated patients not presented).
 †Missing data on serum concentration from one patient treated with clomipramine.

with at least two SSCL ratings, the one responder reported no orgasm impairment.

When subjects were divided according to sex, 12 men were treated with an SRI. Ten reported impaired orgasm, 8 of these were responders compared with none of the 2 without orgasm impairment ($\chi^2_1 = 4.8, P = .028$). Among the 10 SRI-treated women, 6 reported impaired orgasm and 4 of these were responders (67%). Of the four women without orgasm impairment, three (75%) were responders (not significant).

DISCUSSION

In this study, we found a relation between higher oxytocin levels after 4 weeks of SRI treatment and treatment-induced delayed orgasm in patients with OCD. We also found that delayed orgasm in men was related to an anti-obsessive treatment response with SRIs. Furthermore, our results suggested that oxytocin levels have greater impact on orgasmic function than the concentration of the SRI drugs per se. In fact, clomipramine serum levels were numerically lower in patients with delayed orgasm than in those without.

Approximately 70% of patients treated with paroxetine for depression have reported sexual dysfunction when carefully investigated,⁴⁵ in accordance with our findings in OCD. Interestingly, three paroxetine-treated women in the present study reported increased libido and sexual function, and this was not linked to significant changes of depression ratings. This could represent a “forme fruste” of previously reported hypersexual states during SRI treatment.⁴⁶ As opposed to decreased libido, delayed orgasm is not related to depression and could constitute the most specific SRI-induced sexual effect. Indeed, one SRI drug (dapoxetine) is specifically marketed for the treatment of premature ejaculation.

The exact mechanisms by which SRIs cause delayed orgasm are not known, although central serotonergic transmission is certainly involved.^{2,7,45} The main endocrine candidates related to orgasmic function are prolactin and oxytocin,⁴⁷ but only prolactin has been investigated previously in clinical samples. SRI drugs increase prolactin,⁴⁸ and in a study of consecutive men consulting an andrology clinic for sexual dysfunction, prolactin levels were indeed higher in men treated with SRIs,⁹ even if no associations between prolactin and sexual effects were presented. In line with this, it was hypothesized that sexual function could be improved in patients treated by an SRI for depression by adjunctive treatment with aripiprazole (predictably decreasing prolactin levels). However, no correlation between orgasm function and change in prolactin levels emerged⁴⁸; accordingly, increased prolactin is less likely to cause SRI-induced orgasmic dysfunction. Oxytocin involvement in SRI-induced delayed orgasm has not been explored in humans, but our findings suggest an influence of the oxytocin system. However, they are at variance with the hypothesis by de Jong et al²¹ suggesting that SRI-induced orgasm delay is related to a decrease of oxytocin; our results suggest the reverse. Consistent with our findings, a

drug trial with an oxytocin antagonist for treating premature ejaculation showed no clinically or statistically significant effect on the condition.⁴⁹ Also supporting our finding are the sexual effects of 3,4-methylenedioxy-methamphetamine (“Ecstasy”), an indirect serotonin agonist and a powerful oxytocin releaser.⁵⁰ Despite enhanced sexual desire, 80% of men and 40% of women using the drug have reported delayed orgasm.⁵¹ A hypothetical explanation of the discrepancy between animal studies and the present study might be related to the temporal patterns of oxytocin during orgasm. Plausibly, a rapid rise of oxytocin could determine the orgasm mechanism.⁵² If so, then an SRI-induced elevated baseline could decrease the amplitude of this surge, thus impairing orgasmic liability. Most likely, these processes are located within the hypothalamic neuronal network, and our plasma measurements could represent only a reflection of these processes.

In this study, we found a significant relation between incident orgasmic dysfunction and anti-obsessive response in SRI-treated men but not in women. The fact that women had significantly lower points on orgasmic function at baseline might have precluded an identification of any such association among women with our sample size. Because both delayed orgasm and anti-obsessive response³⁵ seem related to increased plasma oxytocin, the relation between sexual side effects and an anti-obsessive response as reported by Ackerman et al^{31,32} might not merely reflect compliance to drug treatment. Together, these results support an involvement of oxytocin in OCD pathophysiology and in the anti-obsessive and orgasm-delaying mechanisms of SRIs.

Patients with OCD respond slowly to SRI treatment compared with patients with other SRI-responsive disorders, such as major depression or premenstrual dysphoric disorder. A period of 12 weeks is recommended for an anti-obsessive effect, and higher doses are often required.³⁰ If orgasm delay is an early sign predicting treatment outcome (as suggested by our findings), then termination after 4 weeks could spare the patient troublesome and ineffective treatment.

Limitations

This study has several limitations that should be addressed, and the most serious limitation is the small sample. For example, we could not show that an increase in oxytocin levels from baseline to week 4 was significantly higher between those with orgasm delay and those without. However, the difference between the two groups was substantial (+17% vs -2% in oxytocin levels) and could represent a type II error.

The SSCL was not validated, but at the time of our study, no suitable scale had been published. However, results presented in [Tables 1 and 2](#) support a reasonable sensitivity to change and to differences among groups. In psychopharmacology studies, the ASEX is commonly used, and our simulation supports a similar utility. Our lower scores for orgasm ability could be explained by the reversed formulation of this item in the SSCL. Another likely

explanation is that patients in the compared studies might have used SSRIs, which likely affected this particular item. Such use was carefully excluded at baseline in our study but was acknowledged in a comparison study.⁴² Indeed, compared with the other samples, the sexual function of our patients appears more similar to healthy controls than to patients with major depression. Nevertheless, the generalizability of our findings is limited by the fact that only patients with OCD were studied.

Oxytocin in plasma has a short half-life and can change rapidly, but we did not collect serial plasma samples. However, our single samples were taken in a standardized way, and the associations with sexual function and treatment response indicate that plasma oxytocin levels do reflect some relevant aspect of central oxytocin mechanisms.³⁵

At the end of the trial, some measurements of sexual function seemed to show subtle improvement. This could indicate that the trial was of insufficient duration to determine the persistence of sexual side effects. Long-term studies are necessary to resolve this issue.

When interpreting our findings, it should be considered that our study population had OCD. Although sexual dysfunction is consistently reported in SRI-treated patients, irrespective of diagnosis, the relation between oxytocin and sexual dysfunction could be specific to OCD.

This study presents data at least 20 years old. Because of a binding agreement between the pharmaceutical company funding the study and the researchers, there was no legal possibility to publish these data sooner. The company was aware of the extensive sexual side effects of the drugs because the SSCL items were included in the study protocol; however, they refrained from publishing them. What they did publish and carefully categorize were the spontaneous reports of adverse events that subjects were asked for at each visit.³⁶ Presumably, the patients and the clinicians tended to avoid double reporting of sexual adverse events. In consequence, in almost 300 participants treated with SRIs, no sexual adverse events (but a number of others) were communicated. Our cohort represents 11% of the participants in the multicenter trial, a large proportion was drug naive, and we had only one placebo responder. In the early 1990s, there was an unawareness of sexual adverse events from SRIs,^{53,54} decreasing the likelihood that these were “nocebo” effects. This has the effect of increasing the validity of this study’s results.

CONCLUSION

This pilot study lends some support to the notion that some collateral effects of SRIs, particularly delayed orgasm, might be exerted through changes within the oxytocinergic system and are related to anti-obsessive mechanisms. Early signs of delayed orgasm in SRI-treated patients with OCD could serve as a clinical predictor for treatment response. Future studies should

explore the utility of this finding in other patient groups treated with SRIs.

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Corresponding Author: Mats B. Humble, MD, Örebro University, School of Medical Sciences, SE-701 82 Örebro, Sweden; E-mail: mats.humble@oru.se

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Mats B. Humble; Susanne Bejerot

(b) Acquisition of Data

Susanne Bejerot

(c) Analysis and Interpretation of Data

Mats B. Humble; Susanne Bejerot

Category 2

(a) Drafting the Article

Mats B. Humble; Susanne Bejerot

(b) Revising It for Intellectual Content

Mats B. Humble; Susanne Bejerot

Category 3

(a) Final Approval of the Completed Article

Mats B. Humble; Susanne Bejerot

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