

Short Onset of Action of a Serotonin Reuptake Inhibitor When Used to Reduce Premenstrual Irritability

Mikael Landén^{*1}, Helena Erlandsson², Finn Bengtsson³, Björn Andersch² and Elias Eriksson⁴

¹Department of Clinical Neuroscience, Section of Psychiatry S:t Görän, Karolinska Institutet, Stockholm, Sweden; ²Department of Gynaecology and Obstetrics, Göteborg University, Göteborg, Sweden; ³Department of Medicine and Care, Division of Clinical Pharmacology, Linköping University, Linköping, Sweden; ⁴Department of Pharmacology, Institute of Neuroscience and Physiology, Göteborg University, Göteborg, Sweden

Several studies suggest that serotonin reuptake inhibitors (SRIs) exert a more rapid effect when used for the treatment of symptoms such as anger and irritability than when used for depression, obsessive-compulsive disorder, or anxiety. In line with this, premenstrual irritability can be effectively dampened by intermittent administration of an SRI, from ovulation to menstruation, indicating an onset of action of 10 days or less. How fast this effect appears, in terms of hours or days, is of considerable theoretical interest, but has previously not been studied in detail. To explore this issue, 22 women with marked premenstrual irritability, who previously had responded to paroxetine, were given this compound during two menstrual cycles and placebo during one cycle in a double-blind, cross-over fashion. The women were asked to start medication in the midst of the luteal phase when irritability had been intense for 2 days. The paroxetine cycles differed significantly from the placebo cycle as early as 14 h after drug intake with respect to the number of subjects experiencing sustained reduction in irritability. When the different cycles were compared with respect to irritability-rating scores for each time of assessment, the difference was significant at day 3. The side effect nausea had an even more rapid onset (4 h), but usually disappeared within 4 days. To summarize, this controlled trial shows that an SRI reduces premenstrual irritability already within a few days after the onset of treatment.

Neuropsychopharmacology (2009) **34**, 585–592; doi:10.1038/npp.2008.86; published online 2 July 2008

Keywords: irritability; premenstrual syndrome; premenstrual dysphoric disorder; serotonin reuptake inhibitor; paroxetine; onset of action

INTRODUCTION

When used for depression, obsessive-compulsive disorder, and various anxiety disorders, serotonin reuptake inhibitors (SRIs) are characterized by a delayed onset of action. It thus usually takes several weeks until a marked symptom reduction is noted, and months before a maximal effect is achieved. This delay in onset of action has prompted many authors to suggest that SRIs must have been present in the brain at sufficient concentrations for at least 1–2 weeks to facilitate serotonergic activity (Artigas *et al*, 1996). Reports arguing against this view, however, suggest that SRIs may reduce irritability, anger, and hostility with a short onset of action in healthy controls (Knutson *et al*, 1998) as well as in patients with a variety of disparate diagnoses (Rubey *et al*, 1996; Davidson *et al*, 2002; Reist *et al*, 2003).

Irritability and anger are prominent symptoms of premenstrual syndrome (PMS) or premenstrual dysphoric

disorder (PMDD) (Steiner and Born, 2000; Eriksson *et al*, 2002; Freeman, 2003; Halbreich *et al*, 2003; Landén and Eriksson, 2003). In the first trials showing SRIs to be effective for PMS, continuous treatment throughout the cycle was applied (Eriksson *et al*, 1990; Stone *et al*, 1991; Sundblad *et al*, 1992; Steiner *et al*, 1995). Suggesting that the onset of action of SRIs in PMDD is relatively short, it however soon became evident that a marked symptom-reducing effect can be achieved also when the treatment is restricted to the interval during which symptoms are normally present. Such treatment, which starts at the time of ovulation, and stops shortly after the beginning of menses, is usually referred to as intermittent treatment (Sundblad *et al*, 1993; Halbreich and Smoller, 1997; Steiner *et al*, 1997, 2005; Jermain *et al*, 1999; Cohen *et al*, 2002; Freeman *et al*, 2004; Landén *et al*, 2006). It should however be noted that all premenstrual complaints are not equally inclined to respond to intermittent SRI administration. While symptoms such as irritability and affect lability are reduced as effectively by intermittent drug administration as by continuous treatment, other complaints, such as somatic symptoms, are thus more effectively reduced when the treatment is given throughout the cycle (Landén *et al*, 2006). Needless to say, irritability being one of the premenstrual symptoms most inclined to respond to

*Correspondence: Dr Mikael Landén, Department of Clinical Neuroscience, Section of Psychiatry S:t Görän, Karolinska Institutet, SE 112 81 Stockholm, Sweden, Tel: +46 (8) 672 23 71, Fax: +46 (8) 672 19 08, E-mail: mikael.landen@cns.ki.se
Received 10 December 2007; revised 27 April 2008; accepted 8 May 2008

intermittent treatment is well in line with the notion discussed above that SRIs seem to exert rapid effects on anger and related emotions in a variety of conditions.

The short onset of action for the irritability-reducing effect of SRIs, eg in PMS, is of considerable theoretical interest, since it indicates that SRIs do facilitate serotonin transmission shortly after the onset of treatment in anger-modulating pathways. However, in most studies exploring the possible efficacy of intermittent administration of SRIs for PMS, the treatment has started around ovulation, ie 10 days before the first day of the late luteal phase during which the assessment of drug effects is usually undertaken. It is therefore not known whether as much as 10 days are required to achieve a reduction in premenstrual irritability, or if the effect might appear even earlier. Our recent finding that estrous cycle-related aggression in rodents, a tentative animal model of premenstrual irritability (Ho *et al*, 2001), may be reduced by an intraperitoneal injection of an SRI only 2 h before the animals are being tested (H-P Ho *et al*, to be published), does support to the notion that the effect of SRIs in PMS may indeed be very rapid. The aim of this study was to pinpoint the actual time to response for the effect of an SRI on premenstrual irritability in women.

PATIENTS AND METHODS

Participants

A total of 22 women participated in the study, all of whom had previously completed a placebo-controlled trial assessing the effect of three cycles of treatment with paroxetine *vs* placebo (Landén *et al*, 2006). To be included in that study, they should have been ≥ 18 years of age, reporting regular menstrual cycles, and meeting diagnostic criteria A–C for PMDD in DSM-IV according to a structured interview. In addition, they should have displayed at least a 50% increase in irritability or depressed mood as assessed by a visual analogue scale (VAS) during the luteal phase (mean of 5 days) as compared to the follicular phase for two consecutive reference cycles. To be included in the present study, they must have displayed at least a 50% increase in irritability during the reference cycles preceding the previous trial; patients reporting depressed mood but not irritability were hence not included. In addition, they should, during the interview, confirm that irritability was a dominating symptom of their condition. Moreover, they should have received and responded to paroxetine in the previous trial, or have been treated with paroxetine openly afterwards, and then responded to the drug, response being defined as a global improvement corresponding to 1 or 2 on the Clinical Global Impression-Improvement (CGI-I) scale and including a marked reduction in irritability. Women meeting these criteria and volunteering for this study were asked to stop any possible ongoing treatment for their premenstrual complaints and to perform prospective daily rating of premenstrual symptoms during one menstrual cycle while being off medication. To be eligible, they should display at least a 50% increase in irritability during the luteal phase as compared to the follicular phase during this reference cycle. The mean (SEM) rating of irritability during the reference cycle for the 22 included subjects was 69 ± 5 mm.

Treatment

A computer-generated randomization list was used to assign participants to treatment with (a) placebo in the first cycle and paroxetine in the second and third cycles, (b) paroxetine in the first cycle, placebo in the second cycle, and paroxetine in the third cycle, or (c) paroxetine in the first and second cycles and placebo in the third cycle, in a 1:1:1 ratio. Medication was provided in capsules containing either placebo or paroxetine 20 mg, each patient receiving three blister packs labeled 'menstrual cycle 1', 'menstrual cycle 2', and 'menstrual cycle 3'. Treatment was not to be started until the subject was past the estimated time of ovulation and had experienced marked irritability for 2 days; on the day before drug intake, the mean (SEM) irritability rating hence was high: 60 ± 3 mm (based on all treatment cycles). Since the purpose of this study was to explore the onset of action for the effect of an SRI on irritability rather than on the entire premenstrual syndrome, the possible presence of other symptoms was not considered in this context.

From the first day of treatment and during the rest of the cycle, the patient should take one capsule, containing paroxetine 20 mg or placebo, at 0800 hours. The treatment should be discontinued at the third day of menstruation, not to be resumed until symptoms had reappeared in the following premenstrual phase.

Assessments

Self-rated irritability was assessed each evening using a VAS (1–100 mm) during the reference cycle and the three treatment cycles. On the first day of medication in each cycle, this assessment was undertaken not only in the evening, but also 2, 4, and 8 h after drug intake (Figure 1).

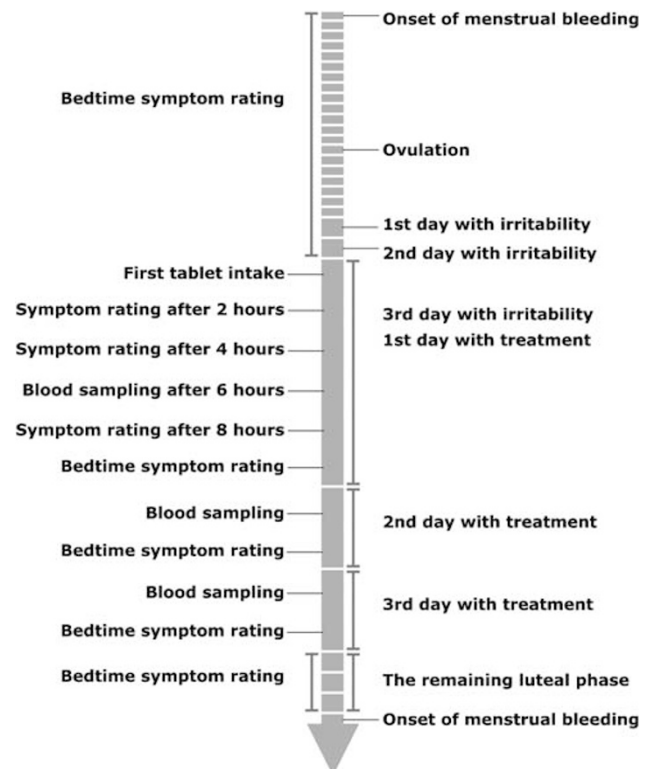


Figure 1 The assessment procedures.

At these time points on the first day of medication, as well as in the evening of all days when a capsule had been taken, the subjects were also to record if they experienced a common early side effect of SRIs, ie nausea (yes/no).

Although the purpose of this study was to assess the time course for the effect of paroxetine on one symptom only, ie self-rated irritability, six other symptoms often occurring in women with PMS were also rated at the same time points and using the same VAS form: depressed mood, affect lability, tension, bloating, breast tenderness, and change in appetite. In addition, at the end of each treatment cycle, the patients rated how they had felt during the past premenstrual period as compared to previous cycles with no treatment using patient-rated CGI-I.

Measurement of S-paroxetine

Blood samples for analysis of serum levels of paroxetine were drawn 6 ± 1 h after the intake of first, second, and third capsules. For practical reasons, it was not possible to obtain blood samples from all three occasions and all three treatment cycles from all subjects, but it was ensured that, for each subject, blood was obtained at least once during at least two of the three cycles.

Paroxetine was analyzed using high-performance liquid chromatography with UV-detection largely in accordance with a protocol previously described (Shin *et al*, 1998). Performance data for the method displayed an extraction recovery rate of 90%, a limit of quantitation of 15 nmol/l and an inter-day assay variation of 5.1% (at 175 nmol/l).

Mean serum levels of paroxetine were calculated for days 1, 2, and 3, respectively. Subjects from which blood samples had been obtained at the same time point for both paroxetine cycles were represented by the mean of these two measurements.

Possible relationships between serum levels of paroxetine and symptom improvement, as well as between paroxetine levels and the possible occurrence of nausea, were also addressed. For these analyses, subjects from whom blood samples had been obtained during two cycles were represented by the first of these cycles.

Calculations

Sign test was applied to compare the placebo cycle with the mean of the two paroxetine cycles at different points of assessments with respect to the number of subjects having reached sustained response. For this analysis, response was defined as the irritability rating being lower than 30 mm on the 1–100 mm VAS, and remaining lower than 30 mm for the rest of the cycle. To avoid transient responses to be erroneously defined as sustained response, patients failing to complete at least 3 days of rating after the onset of drug intake, due to onset of menses, were excluded from the test.

In addition, the two treatments were compared with respect to self-rated irritability at each assessment point using paired nonparametric statistics (Wilcoxon test). Also for this calculation, the mean of the ratings from the two paroxetine cycles was compared to the rating from the placebo cycle. For points of assessment where data could be obtained from one paroxetine cycle only, this rating was used.

To elucidate the onset of action of paroxetine-induced nausea, sign tests were performed for each point of assessment. Since previous studies have shown that the tolerance for SRI-induced nausea persists from one cycle to another, also when the drug is administered intermittently, only the first of the two treatment cycles was used for this analysis.

Sign test was used to compare each of the paroxetine cycles with the placebo cycle with regard to response on the CGI, subjects reporting themselves as 'very much improved' (1) or 'much improved' (2) being defined as responders.

Since the direction of the result was known *a priori*, ie paroxetine being superior to placebo to treat PMS, and more inclined to cause nausea, all tests undertaken were one-tailed. Since there was only one primary variable, ie self-rated irritability, no correction for multiple comparisons was undertaken. *P*-values < 0.05 were regarded as statistically significant.

Ethics

All patients provided written informed consent before entering the study. The ethic committee of Göteborg University approved the study protocol.

RESULTS

Participants

Of the 24 participants screened, 2 were excluded for failure to meet the inclusion criteria. Thus, a total of 22 patients were enrolled and randomized to one of the three treatment groups (Figure 2). The mean (SD) age of the participating women was 41 (6.0) years.

The mean (SEM) irritability rating on the day before the first day of capsule intake did not differ between the placebo cycle (58 ± 5 mm) and the two paroxetine cycles (60 ± 5 and 63 ± 5 mm, respectively).

One participant completed only two cycles of treatment, one on placebo and one on paroxetine. For the assessment of her response to paroxetine, data from her only paroxetine cycle were used. All other subjects completed all the three cycles.

Two subjects were excluded from the sign test because they failed to rate symptoms up to day 3 in the placebo cycle due to the onset of menses (see Patients and Methods). Subjects failing to rate symptoms up to day 3 in one of the paroxetine cycles were represented by the other paroxetine

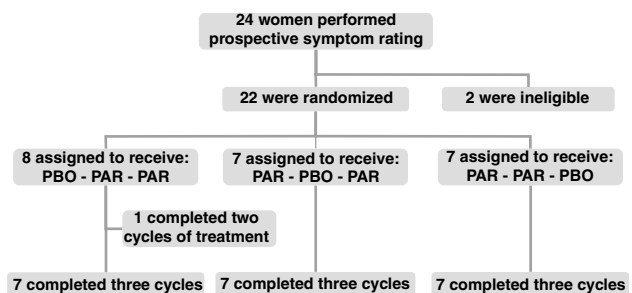


Figure 2 Trial flow diagram.

cycle for this analysis. No subject failed to rate symptoms up to day 3 in both paroxetine cycles. The median number of days between the first day of treatment and onset of menses was 6 (range: 1–15).

Outcome

The subjects were asked to start drug intake when ovulation had passed and marked irritability had been present for 2 days. As mentioned above, for some subjects this occurred shortly before the onset of menstruation, yielding only a few days of reliable symptom registration. For this reason, data from day 6 of treatment and onwards are difficult to interpret due to small numbers, and are hence not presented. This study thus yields reliable information only regarding the first 4–5 days of treatment. The number of subjects per day from which assessment could be done after onset of medication is accounted for in the legend of Figure 3. The number of subjects performing sufficient days of treatment after onset of drug intake to be included in the sign test is shown in Table 1.

Application of sign test revealed, as expected, a higher rate of sustained response—defined as the VAS rating of irritability being below 30 mm for the rest of the cycle—during treatment with paroxetine (mean of two cycles) than during treatment with placebo. The first point of assessment at which this difference reached statistical significance was at bedtime of the day treatment was initiated (Table 1).

Figure 3 shows the mean self-rated irritability at consecutive time points after the first intake of study drug. The difference between the paroxetine cycles and the placebo cycle was significant from day 3 and onwards.

As expected, irritability was the only symptom displayed by all subjects during the reference cycle and on the day medication started in all treatment cycles, confirming that this study was not useful to assess the time of onset for other symptoms. The mean (\pm SEM) sum ratings for all

Table 1 Differences Between the Placebo Cycle and the Paroxetine Cycles with Respect to Sustained Response in VAS-Rated Irritability (<30 mm) as Assessed Using One-Tailed Sign Test

	Placebo cycle	Paroxetine cycles	P-value
Sustained response	n (%)	n (%)	
2 h, first day	1 (5)	2 (10)	0.50
4 h, first day	2 (10)	4 (20)	0.34
8 h, first day	3 (15)	6 (30)	0.23
Bedtime, first day	4 (20)	11 (55)	0.046
Second day	5 (25)	11 (55)	0.073
Third day	5 (25)	12 (60)	0.033
Fourth day	5 (25)	13 (65)	0.019
Fifth day	5 (25)	14 (70)	0.011

N = 20 (see Results).

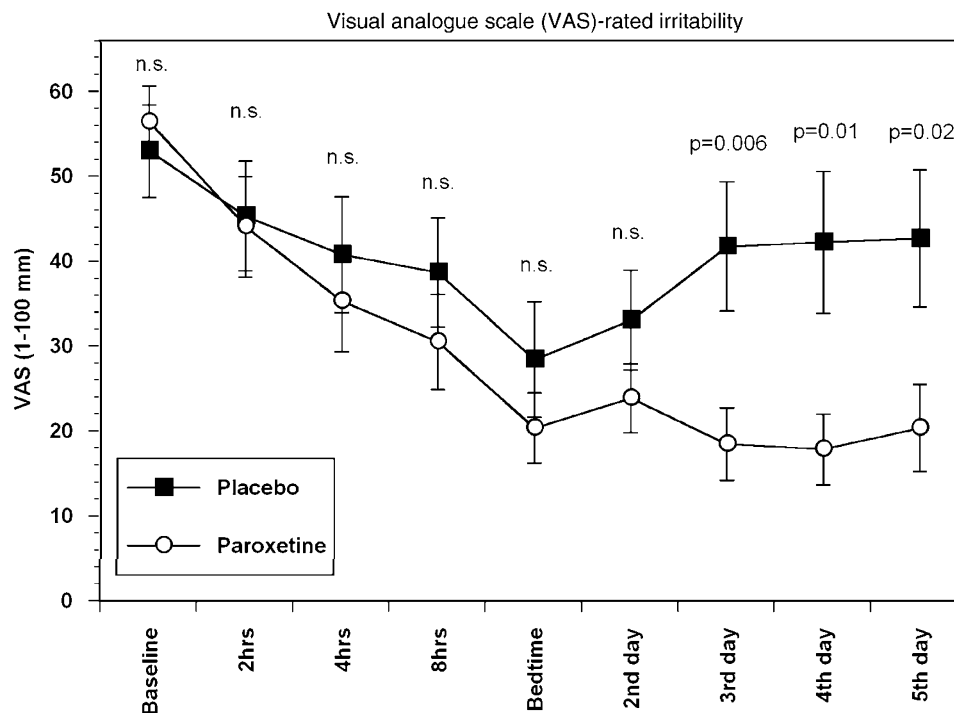


Figure 3 Shown are mean (SEM) of self-rated irritability (VAS 1–100 mm) at baseline (= mean of the 2 days preceding the first capsule intake) and during days 1–5 of treatment. On day 1, four assessments were made; on the following days, symptom assessment was conducted at bedtime only. P-values refer to differences in rating (placebo cycle vs mean of paroxetine cycles) as analyzed using the Wilcoxon test. N for the different points of assessment were baseline—placebo: 22, paroxetine: 22; 2 h—placebo: 22, paroxetine: 22; 4 h—placebo: 22, paroxetine: 22; 8 h—placebo: 22, paroxetine: 22; bedtime first day—placebo: 22, paroxetine: 22; second day—placebo: 21, paroxetine: 22; third day—placebo: 19, paroxetine: 22; fourth day—placebo: 19, paroxetine: 20; and fifth day—placebo: 18, paroxetine: 19.

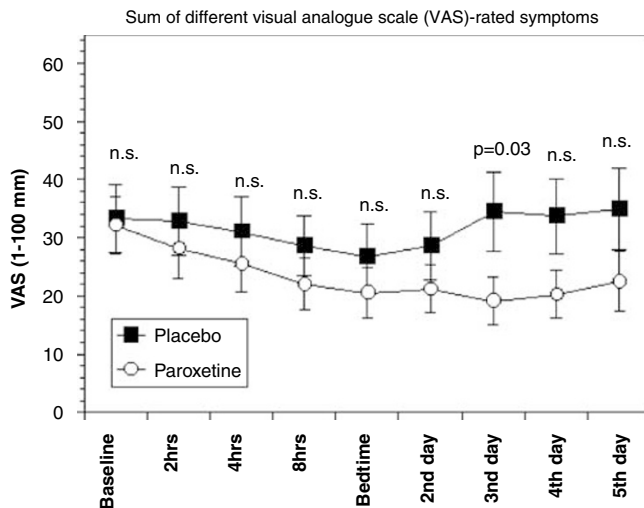


Figure 4 Mean (SEM) of the sum of six self-rated symptoms (depressed mood, affect lability, tension, bloating, breast tenderness, and change in appetite; VAS 1–100 mm) at baseline (=mean of the 2 days preceding the first capsule intake) and during days 1–5 of treatment. On day 1, four assessments were made; on the following days, symptom assessment was conducted at bedtime only. *P*-values refer to differences in rating (placebo cycle vs mean of paroxetine cycles) as analyzed using the Wilcoxon test. *N* for the different points of assessment: see Figure 3.

other symptoms, ie depressed mood, affect lability, tension, bloating, breast tenderness, and change in appetite are, however, shown in Figure 4.

All assessments revealed above are based on a comparison between the placebo cycle and the mean of the two paroxetine cycles. The general pattern of response was the same when each paroxetine cycle was separately compared with the placebo cycle; thus, for both paroxetine cycles 1 and 2, the comparison of groups at each assessment point using paired nonparametric statistics yielded a significant difference between groups at day 3 ($P=0.02$ for both cycle) but not before that (data not shown).

With respect to CGI, 5 out of 22 subjects reported themselves to be much improved or very much improved after the placebo cycle. The corresponding figures were 12 out of 22 ($P=0.03$ vs placebo) after the first paroxetine cycle and 14 out of 21 ($P=0.01$ vs placebo) after the second paroxetine cycle.

Nausea

In total, 15 out of 22 subjects reported nausea at least once during the first paroxetine cycle. The difference between active medication and placebo with respect to number of subjects experiencing nausea was statistically significant as early as 4 h after the first capsule was taken (Table 2).

Serum Levels of Paroxetine

The mean (\pm SEM) serum levels of paroxetine (nmol/l) during the paroxetine cycles were 6.5 ± 1.2 on day 1 ($N=18$), 12.2 ± 2.9 on day 2 ($N=10$), and 18.4 ± 4.3 on day 3 ($N=7$).

The differences in mean (\pm SEM) serum paroxetine levels between (i) participants who had reached sustained

Table 2 Differences Between Placebo Cycle and Paroxetine Cycles with Respect to Occurrence of Nausea (Present/Not Present) as Assessed Using One-Tailed Sign Test

	Placebo	First paroxetine cycle	<i>P</i> -value
Nausea (yes/no)	<i>n</i> (%)	<i>n</i> (%)	
Before taking the first capsule	0 (0)	2 (9.5)	0.25
2 h, first day	2 (9.5)	4 (18)	0.5
4 h, first day	1 (4.8)	9 (41)	0.020
8 h, first day	1 (4.5)	9 (41)	0.0039
Bedtime, first day	1 (4.5)	4 (18)	0.062
Second day	1 (4.8)	9 (41)	0.020
Third day	0 (0)	7 (32)	0.12
Fourth day	0 (0)	3 (17)	0.25
Fifth day	0 (0)	1 (7.7)	0.5

response and those who had not and (ii) participants who reported nausea and those who did not, did not reach statistical significance, as assessed using *t*-test (data not shown).

DISCUSSION

The purpose of this study was to assess the onset of the irritability-reducing effect of an SRI when administered to women with premenstrual dysphoria. While there was no difference between active drug and placebo 2 h after drug intake, the paroxetine curve and the placebo curve started to separate already after 4 h. With respect to sustained response, the difference between the paroxetine cycles and the placebo cycle was significant on the evening of the first day of drug intake, ie approximately 14 h after drug intake, close to significant at day 2, and significant from day 3 and onwards. When the paroxetine cycles were compared with the placebo cycle with respect to actual symptom rating at the different points of assessment, the difference between groups was significant from day 3 and onwards. When interpreting the effect of treatment, it should be considered that the assessments were made during the late luteal phase, when symptoms typically are increasing sharply day-by-day.

The short onset of action of an SRI on premenstrual irritability documented in this study contrasts to the delayed onset of action of these drugs when used for other conditions, including depression. The lag phase normally characterizing the symptom-reducing effects of SRIs has been suggested to imply that a downregulation of auto-receptors exerting negative feedback on serotonin release has to occur before the reuptake inhibition leads to a substantial increase in synaptic levels of serotonin (Artigas *et al*, 1996). Our present findings challenge this view, but are in line with *in vivo* microdialysis experiments in animals suggesting that SRIs do cause a prompt increase in extracellular serotonin (Rutter and Auerbach, 1993). They are also in agreement with the fact that SRIs cause an acute (and probably serotonin-mediated) increase in serum levels of prolactin and ACTH (Golden *et al*, 1989), as well as an

acute effect on ejaculation latency (Waldinger *et al*, 2004), in humans. Of interest in this context is also the observation that SRIs appear to reduce affect lability and emotional incontinence with a short onset of action (Sloan *et al*, 1992; Nahas *et al*, 1998; Burns *et al*, 1999; Muller *et al*, 1999; Landén *et al*, 2006).

Needless to say, it cannot be excluded that autoreceptor feedback plays a larger role in the serotonergic pathways mediating the delayed effect of SRIs in depression and anxiety disorders than in those mediating the effect on premenstrual irritability. Alternatively, a more modest increase in extracellular serotonin concentrations may be required to elicit an effect on premenstrual irritability than on other symptoms. However, there are previous observations strongly arguing against these possible explanations for the difference between depression and anxiety on the one hand, and premenstrual irritability on the other, with respect to onset of action on SRIs. Drugs such as fenfluramine and mCPP thus do not exert acute beneficial effects in depression (Kahn *et al*, 1988, Lichtenberg *et al*, 1992), obsessive-compulsive disorder (McBride *et al*, 1992, Gross-Isseroff *et al*, 2004), or panic disorder (Kahn *et al*, 1988; Targum and Marshall, 1989), notwithstanding the fact that they cause a much higher acute increase in extracellular concentrations of serotonin than do SRIs (Rothman and Baumann, 2002). Interestingly, however, these drugs do cause an immediate reduction in premenstrual dysphoria (Brzezinski *et al*, 1990, Su *et al*, 1997). The most likely interpretation of these findings, in conjunction with the results of the present trial, is that the main reason for the delay in the effect of SRIs in a number of indications is not an inability to rapidly enhance extracellular serotonin concentrations. Rather, it seems as if certain conditions, such as depression and anxiety disorders, but not others, such as premenstrual irritability, require weeks of serotonin facilitation before clinical improvement occurs. The reason for this remains to be disclosed, but one possibility would be that the effects of SRIs when used for depression and anxiety disorders may be mediated by a time-consuming influence on receptor responsiveness or nerve cell plasticity, and that such mechanisms might not be involved in the effects on anger and irritability.

The notion that SRIs indeed do facilitate serotonin transmission shortly after the start of medication in humans is supported also by the fact that nausea usually appears during the initial days of treatment. The early onset of this side effect is well established on the basis of clinical experience, as is the fact that it usually fades away after a few days or weeks of medication. To our knowledge, this is, however, the first study pinpointing, in terms of hours and days, the onset and decline of nausea after the initiation of per oral SRI medication. As shown in Table 2, a significant difference in nausea between the paroxetine cycles and the placebo cycle was observed as early as 4 h after intake of the first capsule. On the other hand, already on the fourth day of treatment, the number of subjects reporting nausea in the paroxetine group was low.

Serum levels of paroxetine were low (day 3: 18 nM) as compared with those observed at steady state when a dose of 20 mg per day is used for the treatment of depression (>50 nM; Reis *et al*, 2004), indicating that also low concentrations may exert a significant influence on

serotonin transporter function. Notably, there was a marked increase in serum levels from day 1 to day 2, and from day 2 to day 3. This finding emphasizes the importance of taking pharmacokinetic aspects into consideration when interpreting the fact that the reduction in irritability in this study, though significant, appeared less impressive as compared to when paroxetine is administered continuously or from ovulation. No association between serum levels and symptom reduction was however observed.

It may be argued that patients in this study, all of whom had previous experience of paroxetine, might have been able to separate active drug from placebo based on side effects, and that the reduction in self-rated irritability therefore is due to expectations of beneficial effects rather than on the pharmacodynamic effects of the drug. However, the observation that subjects reporting nausea did not report sustained response to a greater extent than those devoid of nausea (data not shown), as well as the apparent lack of a rapid effect on some of the measured symptoms (Figure 4; data not shown), argue against this notion.

For symptoms that usually fluctuate in intensity, such as premenstrual complaints, group means based on assessments made on specific time points, as in this trial, should be expected to display larger variation than group means based on the mean symptom rating during 5 consecutive days, which is the normal way of assessing premenstrual symptoms in PMS/PMDD drug trials. Since large variations within the groups were to be expected, and since the number of subjects in this study was relatively small, we deemed that the statistical power would be insufficient to assess the onset of action of paroxetine for the entire range of premenstrual symptoms. Many of these were thus expected to be absent for the entire luteal phase in several subjects (also when untreated or given placebo), and/or to be absent on the day medication started. On the other hand, we predicted that the statistical power would be sufficient to explore the effect on a symptom that, as a consequence of the study protocol, was present in all the studied subjects on the first day of medication, ie irritability. Although inspection of the data (Figure 4) seemed to confirm our previous assumption that some other premenstrual symptoms do not respond as rapidly as does irritability (Landén *et al*, 2006), the design of this study thus does not permit such a conclusion. For the same reason, no conclusion can be drawn regarding the feasibility of symptom-onset dosing in women suffering from premenstrual symptoms other than irritability. The CGI rating undertaken after each cycle suggests, as expected, paroxetine to be superior to placebo, but also indicates the number of nonresponders to be considerable. When interpreting this outcome, it should be considered that the CGI reflects the entire condition of the subjects, and not just the symptom irritability. Also, it should be taken into consideration that the patients were not allowed to start treatment until irritability had been marked for 2 days, which may have influenced their well-being during the forthcoming days.

Three studies with the aim of evaluating symptom-onset dosing of SRIs in PMS however have been published, suggesting this treatment strategy to be of some benefit, though perhaps less efficacious than continuous administration (Freeman *et al*, 2004; Kornstein *et al*, 2006; Yonkers *et al*, 2006). Also of interest in this context is the study by

Miner *et al* (2002) suggesting the administration of 90 mg of fluoxetine once, 7 days before menses, not to be superior to placebo. In none of these studies, however, the effect of treatment on individual symptoms, such as irritability, were presented; also, in contrast to our study, these trials were not designed to pinpoint the exact time from onset of medication to treatment response.

To conclude, we have shown that paroxetine reduces premenstrual irritability more effectively than placebo within a few days after the onset of treatment. To our knowledge, such a rapid, serotonin-mediated symptom-reducing effect of an antidepressant has previously not been documented in a placebo-controlled trial. The results are in line with studies suggesting that anger and irritability respond rapidly to SRIs, and challenge the notion that SRIs always require weeks of administration to enhance serotonergic output.

ACKNOWLEDGEMENTS

We thank study nurse Benita Gezelius for skillful assistance, and Gunnar Ekeröth for valuable statistical advice.

FINANCIAL DISCLOSURES

This study was supported by grants from Glaxo SmithKline and the Swedish Research Council (8668). There are no conflicts of interest.

REFERENCES

- Artigas F, Romero L, de Montigny C, Blier P (1996). Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT_{1A} antagonists. *Trends Neurosci* 19: 378–383.
- Brzezinski AA, Wurtman JJ, Wurtman RJ, Gleason R, Greenfield J, Nader T (1990). d-Fenfluramine suppresses the increased calorie and carbohydrate intakes and improves the mood of women with premenstrual depression. *Obstet Gynecol* 76: 296–301.
- Burns A, Russell E, Stratton-Powell H, Tyrell P, O'Neill P, Baldwin R (1999). Sertraline in stroke-associated lability of mood. *Int J Geriatr Psychiatry* 14: 681–685.
- Cohen LS, Miner C, Brown EW, Freeman E, Halbreich U, Sundell K *et al* (2002). Premenstrual daily fluoxetine for premenstrual dysphoric disorder: a placebo-controlled, clinical trial using computerized diaries. *Obstet Gynecol* 100: 435–444.
- Davidson JR, Landerman LR, Farfel GM, Clary CM (2002). Characterizing the effects of sertraline in post-traumatic stress disorder. *Psychol Med* 32: 661–670.
- Eriksson E, Andersch B, Ho HP, Landén M, Sundblad C (2002). Diagnosis and treatment of premenstrual dysphoria. *J Clin Psychiatry* 63: 16–23.
- Eriksson E, Lisjö P, Sundblad C, Andersson K, Andersch B, Modigh K (1990). Effect of clomipramine on premenstrual syndrome. *Acta Psychiatr Scand* 81: 87–88.
- Freeman EW (2003). Premenstrual syndrome and premenstrual dysphoric disorder: definitions and diagnosis. *Psychoneuroendocrinology* 28(Suppl 3): 25–37.
- Freeman EW, Rickels K, Sondheimer SJ, Polansky M, Xiao S (2004). Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. *Am J Psychiatry* 161: 343–351.
- Golden RN, Hsiao J, Lane E, Hicks R, Rogers S, Potter WZ (1989). The effects of intravenous clomipramine on neurohormones in normal subjects. *J Clin Endocrinol Metab* 68: 632–637.
- Gross-Isseroff R, Cohen R, Sasson Y, Voet H, Zohar J (2004). Serotonergic dissection of obsessive compulsive symptoms: a challenge study with m-chlorophenylpiperazine and sumatriptan. *Neuropsychobiology* 50: 200–205.
- Halbreich U, Borenstein J, Pearlstein T, Kahn LS (2003). The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology* 28(Suppl 3): 1–23.
- Halbreich U, Smoller JW (1997). Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. *J Clin Psychiatry* 58: 399–402.
- Ho HP, Olsson M, Westberg L, Melke J, Eriksson E (2001). The serotonin reuptake inhibitor fluoxetine reduces sex steroid-related aggression in female rats: an animal model of premenstrual irritability? *Neuropsychopharmacology* 24: 502–510.
- Jermain DM, Preece CK, Sykes RL, Kuehl TJ, Sulak PJ (1999). Luteal phase sertraline treatment for premenstrual dysphoric disorder. Results of a double-blind, placebo-controlled, crossover study. *Arch Fam Med* 8: 328–332.
- Kahn RS, Wetzler S, van Praag HM, Asnis GM, Strauman T (1988). Behavioral indications for serotonin receptor hypersensitivity in panic disorder. *Psychiatry Res* 25: 101–104.
- Knutson B, Wolkowitz OM, Cole SW, Chan T, Moore EA, Johnson RC *et al* (1998). Selective alteration of personality and social behavior by serotonergic intervention. *Am J Psychiatry* 155: 373–379.
- Kornstein SG, Pearlstein TB, Fayyad R, Farfel GM, Gillespie JA (2006). Low-dose sertraline in the treatment of moderate-to-severe premenstrual syndrome: efficacy of 3 dosing strategies. *J Clin Psychiatry* 67: 1624–1632.
- Landén M, Eriksson E (2003). How does premenstrual dysphoria relate to anxiety disorders? *Depress Anxiety* 17: 122–129.
- Landén M, Nissbrandt H, Allgulander C, Sörvik K, Ysander C, Eriksson E (2006). A placebo-controlled trial comparing intermittent and continuous paroxetine in premenstrual dysphoric disorder. *Neuropsychopharmacology* 32: 153–161.
- Lichtenberg P, Shapira B, Blacker M, Gropp C, Calev A, Lerer B (1992). Effect of fenfluramine on mood: a double-blind placebo-controlled trial. *Biol Psychiatry* 31: 351–356.
- McBride PA, DeMeo MD, Sweeney JA, Halper J, Mann JJ, Shear MK (1992). Neuroendocrine and behavioral responses to challenge with the indirect serotonin agonist dl-fenfluramine in adults with obsessive-compulsive disorder. *Biol Psychiatry* 31: 19–34.
- Miner C, Brown E, McCray S, Gonzales J, Wohlreich M (2002). Weekly luteal-phase dosing with enteric-coated fluoxetine 90 mg in premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled clinical trial. *Clin Ther* 24: 417–433.
- Muller U, Murai T, Bauer-Wittmund T, von Cramon DY (1999). Paroxetine versus citalopram treatment of pathological crying after brain injury. *Brain Inj* 13: 805–811.
- Nahas Z, Arlinghaus KA, Kotrla KJ, Clearman RR, George MS (1998). Rapid response of emotional incontinence to selective serotonin reuptake inhibitors. *J Neuropsychiatry Clin Neurosci* 10: 453–455.
- Reis M, Åberg-Wistedt A, Ågren H, Höglund P, Åkerblad AC, Bengtsson F (2004). Serum disposition of sertraline, N-desmethylsertraline and paroxetine: a pharmacokinetic evaluation of repeated drug concentration measurements during 6 months of treatment for major depression. *Hum Psychopharmacol* 19: 283–291.
- Reis C, Nakamura K, Sagart E, Sokolski KN, Fujimoto KA (2003). Impulsive aggressive behavior: open-label treatment with citalopram. *J Clin Psychiatry* 64: 81–85.
- Rothman RB, Baumann MH (2002). Therapeutic and adverse actions of serotonin transporter substrates. *Pharmacol Ther* 95: 73–88.

- Rubey RN, Johnson MR, Emmanuel N, Lydiard RB (1996). Fluoxetine in the treatment of anger: an open clinical trial. *J Clin Psychiatry* **57**: 398–401.
- Rutter JJ, Auerbach SB (1993). Acute uptake inhibition increases extracellular serotonin in the rat forebrain. *J Pharmacol Exp Ther* **265**: 1319–1324.
- Shin JG, Kim KA, Yoon YR, Cha JJ, Kim YH, Shin S (1998). Rapid simple high-performance liquid chromatographic determination of paroxetine in human plasma. *J Chromatogr B Biomed Sci Appl* **25**: 452–456.
- Sloan RL, Brown KW, Pentland B (1992). Fluoxetine as a treatment for emotional lability after brain injury. *Brain Inj* **6**: 315–319.
- Steiner M, Born L (2000). Diagnosis and treatment of premenstrual dysphoric disorder: an update. *Int Clin Psychopharmacol* **15**(Suppl 3): S5–17.
- Steiner M, Hirschberg AL, Bergeron R, Holland F, Gee MD, Van Erp E (2005). Luteal phase dosing with paroxetine controlled release (CR) in the treatment of premenstrual dysphoric disorder. *Am J Obstet Gynecol* **193**: 352–360.
- Steiner M, Korzekwa M, Lamont J, Wilkins A (1997). Intermittent fluoxetine dosing in the treatment of women with premenstrual dysphoria. *Psychopharmacol Bull* **33**: 771–774.
- Steiner M, Steinberg S, Stewart D, Carter D, Berger C, Reid R *et al* (1995). Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. *N Engl J Med* **332**: 1529–1534.
- Stone AB, Pearlstein TB, Brown WA (1991). Fluoxetine in the treatment of late luteal phase dysphoric disorder. *J Clin Psychiatry* **52**: 290–293.
- Su TP, Schmidt PJ, Danaceau M, Murphy DL, Rubinow DR (1997). Effect of menstrual cycle phase on neuroendocrine and behavioral responses to the serotonin agonist m-chlorophenylpiperazine in women with premenstrual syndrome and controls. *J Clin Endocrinol Metab* **82**: 1220–1228.
- Sundblad C, Hedberg MA, Eriksson E (1993). Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology* **9**: 133–145.
- Sundblad C, Modigh K, Andersch B, Eriksson E (1992). Clomipramine effectively reduces premenstrual irritability and dysphoria: a placebo-controlled trial. *Acta Psychiatr Scand* **85**: 39–47.
- Targum SD, Marshall LE (1989). Fenfluramine provocation of anxiety in patients with panic disorder. *Psychiatry Res* **28**: 295–306.
- Waldinger MD, Zwinderman AH, Olivier B (2004). On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. *Eur Urol* **46**: 510–515; discussion 516.
- Yonkers KA, Holthausen GA, Poschman K, Howell HB (2006). Symptom-onset treatment for women with premenstrual dysphoric disorder. *J Clin Psychopharmacol* **26**: 198–202.