Articles

Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review

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Summary

Background Selective serotonin-reuptake inhibitors (SSRIs) are increasingly being used as first-line therapy for severe premenstrual syndrome (PMS). We undertook a meta-analysis on the efficacy of SSRIs in this disorder.

Methods We searched medical and scientific databases, approached pharmaceutical companies, and reviewed citations of relevant articles to identify 29 studies of the use of SSRIs in PMS. 14 were excluded (no placebo group, preliminary report of included trial, or low quality). 15 randomised placebo-controlled trials were included. Information on study design, participants, drugs used and dosing regimens, outcome measures, side-effects, and sources of funding was extracted. Standardised mean differences between treatment and placebo groups were calculated to obtain an overall estimate of efficacy. The primary outcome measure was a reduction in overall PMS symptoms.

Findings The primary analysis included data on 904 women (570 assigned active treatment and 435 assigned placebo, including 101 in crossover trials). The overall standardised mean difference was −1·066 (95% CI −1·381 to −0·750), which corresponds to an odds ratio of 6·91 (3·90 to 12·2) in favour of SSRIs. SSRIs were effective in treating physical and behavioural symptoms. There was no significant difference in symptom reduction between continuous and intermittent dosing or between trials funded by pharmaceutical companies and those independently funded. Withdrawal due to side-effects was 2·5 times more likely in the active-treatment group than in the placebo group.

Interpretation SSRIs are an effective first-line therapy for severe PMS. The safety of these drugs has been demonstrated in trials of affective disorder, and the side-effects at low doses are generally acceptable.

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Introduction

Premenstrual syndrome (PMS) consists of regularly recurring psychological or somatic symptoms, or both; the symptoms occur specifically during the luteal phase of the cycle and are relieved by the onset of, or during, menstruation.[1] Mild physiological symptoms occur in about 95% of all women of reproductive age and can be managed by conservative lifestyle changes such as alterations in diet. However, for about 5% of women, symptoms are so severe that their lives are completely disrupted during the second half of the cycle; many of these women require pharmacological management.[2] Such severe PMS is classified under the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, as premenstrual dysphoric disorder.

The causes of PMS remain unclear and speculative, although many hypotheses have been advanced and many treatments suggested. Moreover, because there is a substantial placebo response, uncontrolled trials have resulted in a proliferation of claims for ineffective therapies. The current consensus is that differential sensitivity to circulating hormones, rather than abnormal hormone concentrations, causes PMS.[3] There is increasing evidence that serotonin is important in the pathogenesis of PMS,[4,5] and selective serotonin-reuptake inhibitors (SSRIs) are increasingly being used as the first-line therapy.[6] Fluoxetine has recently been licensed in the UK for premenstrual dysphoric disorder, and has received full approval from the US Food and Drug Administration this year.

We undertook this review to assess the efficacy of SSRIs in the management of severe PMS.

Methods

Trials

We searched databases for reports of published clinical trials of SSRIs in the management of PMS. MeSH terms used were premenstrual syndrome and SSRI, together with title and abstract searches for keywords serotonin and SSRI, premenstrual syndrome, premenstrual dysphoria, premenstrual tension, late luteal-phase dysphoric disorder, and premenstrual dysphoric disorder. We contacted pharmaceutical companies that manufacture SSRIs. The trials were identified by searches of EMBASE (1988 to 1998), MEDLINE (1966 to 1999), PsychLIT (1974 to 1997), CINAHL (1982 to 1999), and the Cochrane Controlled Trials Register database. References cited in all trials were searched iteratively to identify any missing studies. All languages were included. Trials investigating the effect of SSRIs on premenstrual syndrome were included if they were randomised, placebo-controlled, double-blind studies, for which data could be acquired.

All the data were independently extracted in duplicate by means of a standard protocol and data collection form by two investigators (PWD, KMW). Disagreements were resolved by discussion with the other two investigators. If insufficient data were presented for inclusion, authors were contacted for further details. Information on the dose and preparation of the SSRI administered was collected. The main outcome measure was a reduction in overall PMS symptoms. If individual symptoms were presented, scores for each symptom were combined to give an overall score. We chose combined or overall symptom pattern in an attempt to overcome the clinical heterogeneity in the measurement and scoring of PMS symptoms. We undertook secondary analyses of the improvement in physical symptoms of PMS compared with that in behavioural premenstrual symptoms, the efficacy of SSRIs in treating premenstrual irritability, and continuous versus intermittent dosing schedules if suitable information was presented. The numbers of women withdrawing from treatment and those complaining of side-effects were also recorded.

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Quality assessment

The quality of each trial was assessed by two different methods. The first method was the scale developed by Jadad and colleagues,[7] which assesses the randomisation, double blinding, and reports of dropouts and withdrawals. We developed the second quality scale ourselves to assess the trials for study design, reproducibility, and statistical analysis. Our 9-point scale assessed: prospective preliminary diagnosis of PMS baseline symptoms for all participants in the trial; confirmation that no other drugs or oral contraceptives were being taken concurrently; a power calculation to justify numbers of participants, or at least 65 participants in each study group (which would allow detection of an effect size of 0·3 at 5% significance and 80% power); a single clearly stated dose of drug; reproducible PMS symptom measurement including such techniques as visual analogue scales or the menstrual distress questionnaire of Moos; clear presentation of results; a description of the numbers and reasons for trial withdrawals; exclusion of, or a separate analysis of, participants with major psychiatric disorder; and whether or not the trial was supported by independent funding (independent funding, 1 point; drug company funding/not stated, 0 points). One point was awarded for each category. Each trial was independently scored by two investigators, and any areas of disagreement resolved by a third investigator. A score of 3 or more was required in the Jadad score (as recommended by Jadad and colleagues,[7] the maximum possible score being 5) for inclusion in the meta-analysis. A score of more than 6 on our own quality scale defined a high-quality trial. Our quality score is quoted but not used as an inclusion or exclusion criterion because it has not yet been validated.

Statistical analysis

For continuous data, a standardised mean difference was calculated. The standardised mean difference is equivalent to an effect size, which is a dimensionless quantity representing the difference between two means as a number of standard deviations. An effect size of 0·3 represents a small effect, 0·5 a medium effect, and 1·0 a large effect.[8] If medians and ranges were presented, the values were converted to means and SDs.[9] In one report that presented dichotomous data only, odds ratios were generated and converted to a standardised mean difference.[10] When comparisons were made between pooled standardised mean differences for various subanalyses, statistical significance was assessed by use of a Z test; $p<0·05$ was taken as significant. An overall standardised mean difference was calculated by both fixed-effects and random-effects models. We tested for homogeneity of the combined effect sizes with the χ^2 test; $p<0·05$ indicated significant heterogeneity.

The funnel-plot method of Egger and colleagues[11] was used to detect any bias (such as publication and location bias) in the selection of included trials. To assess quantitatively the asymmetry of the funnel plot, a linear regression of the standard normal deviate (defined as the effect size divided by its SE) was plotted against precision (inverse of the SE). A regression line that passes through the origin of the plot (within error limits) indicates symmetry and the absence of bias.

Results

We identified 29 published trials of SSRIs in the management of PMS. Of these, ten trials[12–21] were open and did not include a placebo group,[20] three were preliminary reports of included trials[22–24] and one was of low quality[25] as determined by the Jadad score. Thus, 15 randomised

Ref	Participants	Intervention	Outcome measures	Withdrawals	Side-effects	Jadad score	Our score
30	10 fluoxetine; 12 buproprion; 10 placebo	20 mg fluoxetine daily for 2 cycles	HAM-D, CGI, GAS	3 (1 from each group)	5 fluoxetine, 3 placebo	4	7
38	15 fluoxetine; 15 placebo	20 mg fluoxetine daily for 3 cycles	COPE	2 fluoxetine	5 fluoxetine, 2 placebo	3	6
32	17 cross-over design	20 mg fluoxetine daily for cycle 1, then 20–60 mg daily for 2 cycles	16-item VAS, 21-item daily rating form	2 fluoxetine	6 fluoxetine	3	6
6	96 fluoxetine 20 mg; 96 fluoxetine 60 mg; 95 placebo	20 mg or 60 mg fluoxetine daily for 6 cycles	VAS (observer and participant)	54 (35 fluoxetine 60 mg; 11 fluoxetine 20 mg; 8 placebo)	· ·	3	8
37	16 cross-over design	20 mg fluoxetine daily for 3 cycles	PAF	3 fluoxetine	10/16 fluoxetine	4	6
29	8 cross-over design	20 mg fluoxetine daily for 3 cycles	COPE, profile of mood states, BDI, STAI	None	None	4	8
36	10 fluoxetine; 10 placebo	20 mg fluoxetine daily for 2 cycles	10 item DSM-IIIR, DAF, GAS	1 placebo	· ·	3	7
34	9 cross-over design	100 mg sertraline for 2 cycles, luteal phase only	CGI, HAM-D	2 placebo	· ·	3	7
31	91 sertraline; 96 placebo	50–150 mg sertraline daily for 3 cycles	Daily record of severity of problems, HAM-D, CGI, SAS	8% sertraline; 2% placebo withdrew (side-effects)	· ·	5	7
27	11 cross-over design	50 mg sertraline day 15 to menses*	COPE	2 sertraline; 1 placebo	· ·	3	7
28	27 paroxetine; 28 maprotiline; 26 placebo	10–30 mg paroxetine daily for 3 cycles	VAS	3 paroxetine; 2 placebo	· ·	4	7
35	40 cross-over design	50 mg sertraline luteal phase only for 3 cycles	COPE, BDI	17 (4 due to side-effects on sertraline, 2 on placebo)	· ·	5	7
33	62 sertraline; 50 desipramine; 55 placebo	50–150 mg sertraline luteal phase only	DSR, HAM-D, CGI	57 (26 due to side-effects, majority on desipramine)	· ·	5	7
39	10 fluvoxamine; 10 placebo	50–150 mg fluoxetine daily for 2 cycles	Moos MDQ, symptom checklist 90 items	None	None	3	5
26	69	10–30 mg citalopram for 3 cycles†	VAS for various symptoms	2 on continuous; 2 on semi-intermittent; 1 on intermittent and 3 on placebo	· ·	4	7

HAM-D=Hamilton rating scale for depression; CGI=clinical global impression scale; GAS=global assessment scale; VAS=visual analogue scale; COPE=calendar of premenstrual experiences; PAF=premenstrual assessment form; BDI=Beck depression inventory; STAI=state-strait anxiety inventory. DSM-IIIR=Diagnostic and Statistical Manual III Revision; DAF=daily assessment form; SAS=social adjustment scale; MDQ=menstrual distress questionnaire; DSR=daily symptom report. 13 of the 15 trials used a DSM III/IV classification of PMS (late luteal phase dysphoric disorder or premenstrual dysphoric disorder).
*Two cycles treatment, two placebo, separated by one washout cycle. †18 placebo follicular then citalopram luteal; 17 citalopram (5 mg) follicular then citalopram luteal; 17 citalopram continuous; 17 placebo.

Table 1: **Characteristics of studies included in the meta-analysis**

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Study	Participants	Intervention	Reason for exclusion	Reported results	Side-effects
12	9 PMDD+major depression; 11 PMDD	20 mg fluoxetine daily for 6 cycles	Open; not placebo controlled	Significant improvement in HAM-A, HAM-D, CGI, TDP after treatment	No withdrawals
13	60 completed at least one cycle	20–40 mg fluoxetine (mean 18·6 cycles)	Open; not placebo controlled	After 1 month's treatment all women experienced at least partial relief of symptoms	6 withdrew on 20 mg 1 on 40 mg
14	10 completed at least one cycle	20–40 mg fluoxetine for 3–20 cycles	Open; not placebo controlled	10 participants experienced moderate or marked relief of symptoms	1 withdrew on fluoxetine
15	9	20 mg fluoxetine daily for 3 cycles	Open; not placebo controlled	5 complete remission of PMS symptoms, 4 improvement	1 withdrew
23	. .	. .	Preliminary report of 36	. .	. .
16	17 sertraline; 15 desipramine	50–100 mg sertraline; 100–150 mg desipramine daily for 2 cycles	Open; not placebo controlled	Both reduced depressive symptoms; reduction greater in sertraline group but not statistically significant	No withdrawals in sertraline group; side-effects in all but 2
17	22 PMDD+psychiatric disorder on continuous; 20 PMDD only on intermittent	20 mg fluoxetine/day or 20 mg fluoxetine day 14 to menses for 3 cycles	Open; not placebo controlled	16/22 on continuous medication and 18/20 on intermittent medication improved	2 dropouts on continuous and 3 dropouts on intermittent; 9/22 continuous and 5/20 intermittent experienced side-effects
21	10	20 mg fluoxetine daily for 2 cycles	Not blinded; not randomised, placebo group from parallel trial	Highly significant symptom relief compared with placebo group	1 withdrew; 8/10 experienced side-effects
18	18	5–30 mg paroxetine daily for 10 cycles	Open; not placebo controlled	Significant reduction in premenstrual symptom ratings	5 dropouts
24	14	10–30 mg paroxetine daily for 3 cycles	Open; not placebo controlled	7/14 complete response 4/14 partial response on CGI	1 withdrew (no reason reported)
20	. .	. .	Preliminary data from 31	. .	. .
25	120	10 mg fluoxetine *vs* 3 other medications. Cross-over design 2×3 months	Low quality	27/30 had >50% improvement on fluoxetine	None reported
22	. .	. .	Preliminary data from 37	. .	. .
19	26	Full-cycle *vs* half-cycle sertraline 50–150 mg for 3 cycles	Open; not placebo controlled	Premenstrual symptoms did not differ significantly between groups	3 withdrew

PMDD=premenstrual dysphoric disorder; HAM-A=Hamilton rating scale for anxiety; TDP=trastorno disfòrico premenstrual scale.

Table 2: **Characteristics of 14 excluded studies**

placebo-controlled trials were included in the meta-analysis (table 1).[6,26–39] One trial[6] used two dosing regimens and another[26] used three dosing regimens; these two trials were treated as five separate studies, although the same placebo groups were used in each. Table 2 lists the 14 excluded trials and the reasons for exclusion.

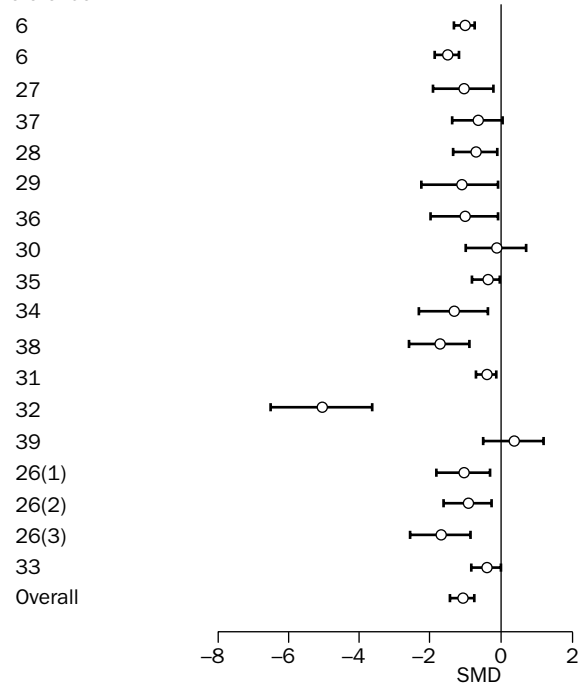

Figure 1: **Standardised mean differences (SMD) for proportion of patients who showed improvement in overall PMS (SSRI versus placebo)**

Error bars show 95% CI. Negative values indicate a reduction in PMS symptoms, favouring SSRIs.

The overall quality of the trials was high. All included trials met the Jadad scale cut-off score of 3. 11 trials scored more than 6 on our quality scale, although none scored the maximum of 9. Only one randomised placebo-controlled trial was excluded, because it was of low quality (scored 2 on the Jadad scale, and 4 on our 9-point scale).[25]

Most of the trials presented continuous data, so an overall standardised mean difference was calculated by both fixed-effects and random-effects models. Little difference was found between these models, so the results with the more conservative random-effects model are presented. The overall standardised mean difference for reduction in PMS symptoms in favour of SSRIs was −1·066 (95% CI −1·381 to −0·750). This value is equivalent to an odds ratio of 6·91 (3·90 to 12·2).[10] The pooled trials were statistically heterogeneous ($p<0·0001$), as a result of the size of the included trials and the magnitude of the standardised mean differences.[40] Assessment of the individual standardised mean differences showed little absolute variation among trials, so data pooling was assumed to remain valid.[40] Figure 1 shows the individual standardised mean difference for each trial and for the pooled data.

A regression analysis of the funnel plot (figure 2) to investigate bias indicated no significant asymmetry (intercept 15·16 [90% CI 25·17 to 35·48], $p=0·210$) and thus no evidence of bias.[11] An assessment of unreported negative trials was undertaken;[40] it showed that 1078 negative trials would be required to overturn the pooled standardised mean difference at 95% significance. A more conservative procedure[40] was used to calculate the number of unreported trials required to reduce the average effect size to a negligible value (taken in this analysis to be 0·2); the number of trials required was 66. Data were extracted on the source of funding; the difference between drug-company-funded trials and those for which funding was not stated or was independent did not achieve significance (−1·170 [−1·581 to −0·759] *vs* −0·700 [−0·968 to −0·432], $p=0·06$). The overall standardised mean difference even for

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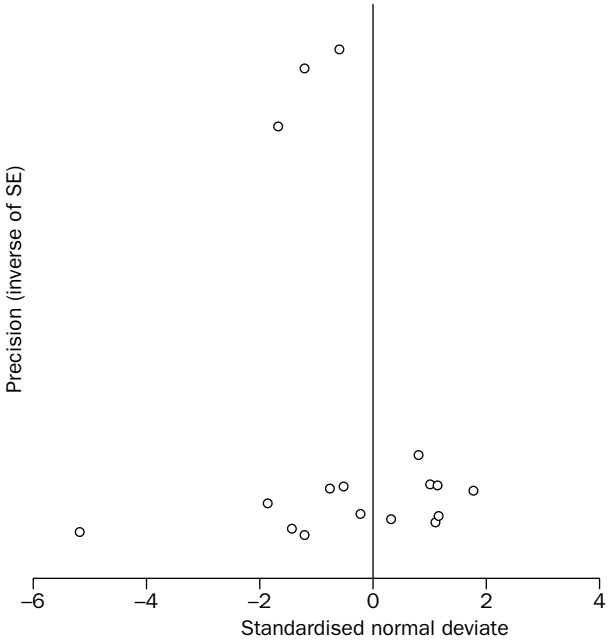

Figure 2: **Funnel plot of included studies**

the trials that had independent funding was a highly significant positive effect.

Figure 3 shows the overall standardised mean differences grouped by individual drug. A comparison between physical and behavioural symptoms was undertaken for the seven trials from which data could be extracted[27–33] (figure 4). SSRIs were effective on both physical and behavioural

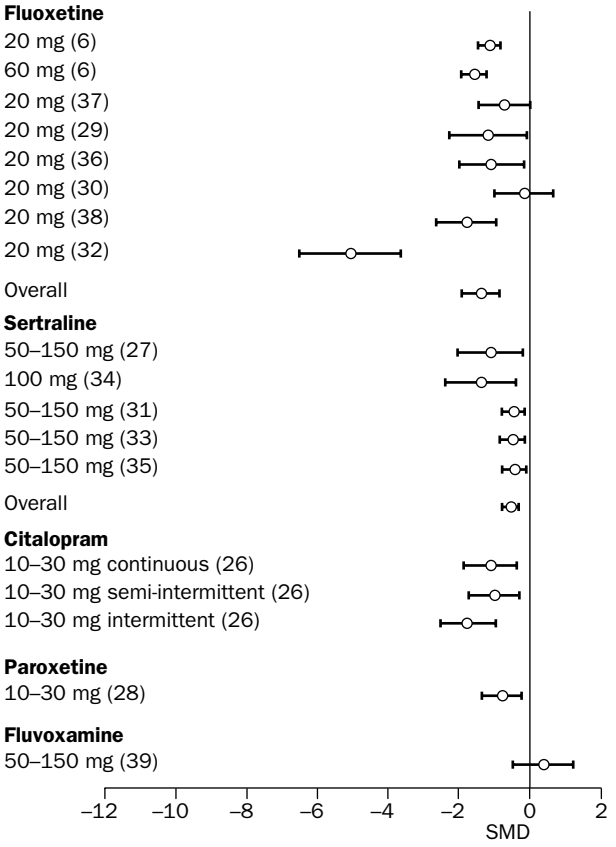

Figure 3: **Standardised mean differences (SMD) for proportion of patients who showed improvement in overall premenstrual symptoms by individual SSRI and dose used**

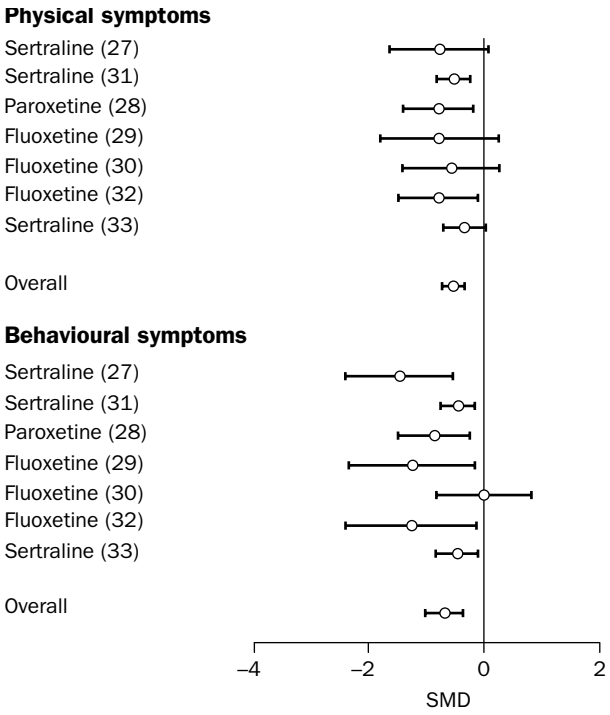

Figure 4: **Standardised mean differences (SMD) for proportion of patients who showed improvement in premenstrual behavioural versus physical symptoms**

symptoms, with no significant variation in the overall standardised mean differences (p=0·386). Figure 5 shows the effect of SSRIs on premenstrual irritability for the four trials from which data could be extracted.

Four of the included trials[26,27,34,35] had intermittent or semi-intermittent dosing regimens, and a comparison of these with the continuous dosing regimens showed no significant difference (standardised mean difference −1·060 [−1·456 to −0·664] *vs* −1·134 [−1·817 to −0·451], p=0·854). Because only one trial[26] included a semi-intermittent regimen, this option was not included in the calculation. Many studies on PMS have recorded a high placebo response; several of the included trials incorporated a single-blind placebo run-in period before randomisation so that placebo responders could be withdrawn. We found that trials with placebo run-in periods[6,30,31,36] had a lower, but not significantly so, overall standardised mean difference than those without (−0·950 [−1·457 to −0·444] *vs* −1·275 [−1·782 to −0·769], p=0·375). One trial[34] could not be included in this analysis because it had a single-blind drug run-in.

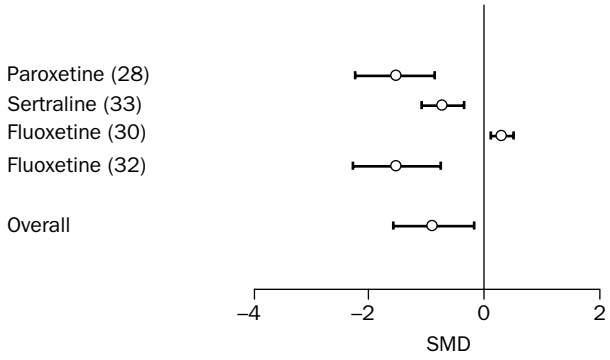

Figure 5: **Standardised mean differences (SMD) for proportion of patients who showed improvement in premenstrual irritability**

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Side-effect	Drug (n=323)	Placebo (n=222)
Decreased libido (including delayed orgasm)	23	6
Rash	3	0
Fatigue (and tiredness)	46	24
Insomnia	56	17
Palpitations	4	4
Headache	24	16
Dry mouth	41	13
Gastrointestinal irritability*	30	11
Nausea	66	13
Dizziness (and lightheadedness)	32	46
Dysphoria	5	0
Tremor	27	1
Appetite disturbance	21	7
Decreased concentration	26	4
Sweating	30	6
Visual disturbance	18	7
Mild cardiovascular	15	0
Yawning	10	0
Menstrual disturbance	3	0
Sedation	12	4
Urinary frequency	4	3
Confusion	2	0
Abdominal cramps	1	0
Anxiety (nervousness, tension)	8	6
Numbness	2	0
Vertigo	2	2
Breast tenderness	0	1

*Includes diarrhoea, constipation, and flatulence.

Table 3: **Side-effects reported in the included trials**

Three of the included placebo-controlled trials[28,30,33] included a comparison of SSRIs with another antidepressant (bupropion, maprotiline, desipramine). The overall standardised mean difference favoured SSRIs but was not significant (−0·287 [−0·586 to 0·011]).

Data on side-effects were extracted from the included trials (table 3). These data are incomplete because some trials did not quote a detailed breakdown of side-effects or the numbers of participants affected.[23,27,29,31,35,39] Also, most of the reported side-effects occurred in one study group of one trial,[6] so the data may be biased. The rate of withdrawal because of side-effects was significantly higher in active-treatment groups than in placebo groups (odds ratio 2·42 [1·59 to 3·67]).

Discussion

The pooled standardised mean difference for the effect of SSRIs on PMS strongly favours treatment over placebo.

We found no significant evidence of bias in study selection, and our check of unreported negative trials confirmed that there would need to be twice as many missing trials as existing published trials. The existence of so many unreported trials is unlikely, and therefore the pooled standardised mean difference is unlikely to be a result of biased study sampling. A subanalysis of the trials by individual drug and identical dose also produced a heterogeneous result. No logical grouping of the trials (by clinical characteristics such as drug, dose, or outcome measure) produced a homogeneous result. Arbitrary grouping of trials resulted in several small homogeneous sets for which the individual pooled standardised mean differences did not vary significantly. A comparison of the trials funded directly by drug companies with those that had independent (or unstated) funding showed no evidence of bias. This subanalysis was undertaken because reports of negative trials may not be released by drug companies.

Consideration of individual drugs was limited because three of the drugs were studied in only one included trial each. The two most studied SSRIs were fluoxetine (seven trials, 398 participants) and sertraline (five trials, 364 participants). Fluoxetine was the most effective. All but one of the trials that compared fluoxetine with placebo used a 20 mg dose. The exception[6] compared 20 mg and 60 mg fluoxetine with placebo; therefore no dose-response analysis could be undertaken. Nor could we assess dose-response for sertraline, because three of the trials had an intermittent and two a flexible dosing regimen.

SSRIs had positive effects on both physical and behavioural symptoms in PMS. We should emphasise, however, that most of the included trials (13/15) enrolled patients presenting with a classification of PMS that predominantly assesses behavioural symptoms. Thus, we cannot exclude the possibility that SSRIs are not as effective for women presenting with predominantly physical symptoms. Premenstrual irritability is commonly cited as a major reason for women seeking medical treatment for PMS. In the four trials for which data could be extracted, SSRIs had a significant positive effect in treating this symptom.

Clinical trials of PMS treatments have shown unusually large placebo effects.[41] Several of the trials we included had a single-blind placebo run-in stage so that placebo responders could be withdrawn; such trials may overestimate the efficacy of a particular intervention. A subanalysis of trial protocols with and without placebo run-in periods showed that the deliberate withdrawal of placebo responders reduced the apparent efficacy of the intervention, but even so it remained significantly positive.

Most of the trials included in this review had continuous dosing regimens (ie, a dose was taken each day throughout the menstrual cycle). Studies of depression and obsessive compulsive disorder suggest that this approach is appropriate, because clinical efficacy of SSRIs in these disorders is reached only after 4–8 weeks.[26] In PMS, however, SSRIs may become effective in a few days and in most cases within one menstrual cycle after the start of treatment.[6] This effect has been postulated to arise from the cyclical nature of PMS and may reflect SSRI action at a different receptor site from that in affective disorders.[26] The rapid onset of efficacy of SSRI treatment in PMS allows the possibility of intermittent or semi-intermittent dosing regimens to induce a temporary luteal-phase increase in serotonin concentrations. Four of the trials[26,27,34,35] had non-continuous dosing schedules but we found no difference between continuous and non-continuous regimens in the overall result. Intermittent dosing is cheaper, and the cyclical nature of PMS implies that a targeted dosing schedule centred on the luteal phase of the menstrual cycle may be effective, and could also reduce the frequency of side-effects, which are often cited as reasons for stopping SSRI medication. Wikander and colleagues[26] compared a continuous dosing regimen of citalopram with intermittent and semi-intermittent regimens; the intermittent schedule was the most effective in relieving premenstrual symptoms and was associated with fewer withdrawals due to side-effects than the other two regimens. Other studies have noted a reduction in side-effects with intermittent or semi-intermittent regimens.[17,18]

Insomnia, gastrointestinal disturbances, and fatigue were the three most commonly reported side-effects in the drug groups. Active-treatment groups had significantly higher frequencies of side-effects than placebo groups, and more women withdrew from the trials during active treatment. These results may be skewed because the recording of side-effects was not uniform, and one study group in one trial (with a high, 60 mg daily dose of fluoxetine)[6] accounted for most of the reported side-effects and withdrawals. There were no reports of suicidal ideation, akathasia, or self abuse and no ovulation disturbances; thus, SSRIs seem not to act directly on ovarian steroid production. Decreased libido and anorgasmia are commonly reported side-effects associated with SSRIs used as a treatment for depression.[42]

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In this meta-analysis, we did not find a high frequency of reported sexual side-effects. This observation should be treated with caution because information on side-effects may not be systematically recorded and there is a paucity of information on baseline sexual dysfunction in PMS.

Most women suffering from premenstrual symptoms can be effectively and satisfactorily treated with conservative therapies such as lifestyle changes, cognitive behavioural therapy, exercise, or dietary regulation. However, for the minority who experience severe premenstrual symptoms pharmacological intervention is needed. Remission rates are low on cessation of treatment[13,18] and PMS can be expected to last until the menopause, so any intervention must be effective, safe for long-term use, and free from side-effects. SSRIs, as shown in this meta-analysis, are effective in the treatment of severe PMS. Their long-term safety has been demonstrated in studies on affective disorders. The side-effects encountered at low doses are generally manageable and may be reduced or eliminated by intermittent or semi-intermittent dosing regimens. SSRIs are an effective and potentially acceptable first-line treatment for severe PMS.

Contributors

Paul Dimmock and Katrina Wyatt did the literature search, study selection, and data analysis. Peter Jones did the statistical analysis. Shaughn O'Brien developed the idea for the systematic review and supervised the project. All the investigators contributed to the writing of the paper.

Acknowledgments

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