Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder: a meta-analysis

CRD summary
The authors concluded that selective serotonin re-uptake inhibitors effectively relieved the symptoms of pre-menstrual syndrome and pre-menstrual dysphoric disorder. Continuous dosing regimens may be more effective than intermittent regimens. The review was in most respects well conducted and the conclusions seemed reliable, though the marked heterogeneity between studies meant that the overall effect size of the intervention is unclear.

Authors' objectives
To evaluate the effectiveness of selective serotonin re-uptake inhibitors (SSRIs) for the symptoms of severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder.

Searching
MEDLINE, Web of Science, the Cochrane Database of Systematic Reviews, DARE, EMBASE, PsycINFO and CINAHL were searched from inception to March 2007. Search terms were reported. The reference lists of reviews, meta-analyses and selected studies were handsearched, as were five relevant journals for the previous five years. The search was limited to studies with titles in English and published in peer-reviewed journals.

Study selection
Double-blind randomised controlled trials (RCTs) of women of any age who met diagnostic criteria for PMS, premenstrual dysphoria, premenstrual dysphoric disorder or late luteal phase dysphoric disorder were eligible for inclusion, provided the trial compared any dose or regimen of an SSRI versus placebo for more than one menstrual cycle. The diagnosis was required to have been made by a health care professional prior to study inclusion. Studies were required to report change in overall premenstrual symptoms measured by a validated severity score. Studies of non-serotonin-specific inhibitors were excluded, as were crossover trials which did not report first-phase data.

SSRIs in the included studies were given continuously, intermittently or (in a single study) at symptom onset. The SSRIs used were fluoxetine (range 10 to 90 milligrams (mgs)), sertraline (25 to 150 mgs), paroxetine (10 to 30 mgs), citalopram (5 to 20 mgs) and fluvoxamine (50 to 150 mgs). Outcomes were measured with a wide range of ordinal and visual analogue scales, the most commonly used being the Daily Record of Severity of Problems.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Study quality was evaluated using the Jadad scale: each study was awarded a score out of a maximum of five points. Two reviewers independently assessed study validity.

Data extraction
Mean differences between the groups in final symptom scores were extracted (or calculated from change scores), with 95% confidence intervals (CIs). Two reviewers independently extracted the data using a standardised format. Disagreements were resolved by consensus. Authors of included studies were contacted to request unpublished data.

Methods of synthesis
Data were combined using the methods of DerSimonian and Laird to calculate standardised mean differences (SMDs), with 95% CIs. Both random- and fixed-effects models were used; as these did not differ significantly, the results of a random-effects model were presented. SMDs were converted to pooled odds ratios (ORs) using published methods (Chinn 2000). Predetermined subgroup analyses were conducted (where there were sufficient studies) to investigate the effect of dosing regimen (intermittent versus continuous, symptomatic versus standard), type of SSRI and year of study publication. Heterogeneity was assessed using the Q test and the $I^2$ statistic and was explored by meta-regression of variables (for example, study country, pharmaceutical sponsorship, outcomes tool). Publication bias was assessed using...
a funnel plot and the Egger test.

**Results of the review**

Twenty-nine RCTs (n=2,964, range 20 to 249) from 19 publications were included in the review: 27 parallel-group RCTs and two RCTs reporting first-phase crossover data. Jadad scores ranged from 3 to 5.

Pooling of all RCTs found a significantly lower PMS/premenstrual dysphoric disorder symptom score in the intervention group (SMD -0.50, 95% CI: -0.64, -0.37; OR 0.40, 95% CI: 0.31, 0.51). Significant statistical heterogeneity was evident ($I^2=66\%$).

Subgroup analyses and meta-regression. Subgroup analyses found that intermittent dosing studies were associated with a significantly smaller treatment effect (OR 0.55, 95% CI: 0.45, 0.68, 13 RCTs) than continuous dosing studies (OR 0.28, 95% CI: 0.18, 0.42, 15 RCTs), though there was significant heterogeneity among continuous dosing studies ($I^2=70\%$). No statistically significant association was found between effect size and SSRI type. A stronger treatment effect was generally associated with an earlier year of publication. The overall effect size was similar in studies of PMS and those of premenstrual dysphoric disorder, with significant heterogeneity in results for both subgroups ($I^2=67\%$). Meta-regression analyses indicated that the choice of outcomes tool was strongly associated with effect size, and stratification by outcomes tool markedly reduced statistical heterogeneity. There was also an association between effect size and quality, with a larger effect size in studies where the method randomisation used was unclear.

Tests suggested a low likelihood of publication bias.

**Authors’ conclusions**

SSRIs effectively relieve the symptoms of PMS and pre-menstrual dysphoric disorder. Continuous dosing regimens may be more effective than intermittent regimens.

**CRD commentary**

The objectives and inclusion criteria of the review were clear, though the failure to include adverse effects as an outcome may limit the clinical applicability of the findings. Relevant sources were searched for studies, although the restriction to English language titles and published studies meant that the review was prone to language and publication biases. However, a formal check for publication bias found no evidence of this. Steps were taken to minimise the risk of bias and error by having more than one reviewer independently conduct study selection, data extraction and validity assessment. Few details were provided on the clinical and methodological characteristics of included studies: the Jadad scale evaluates a very limited range of criteria and detailed information about factors such as allocation concealment, numbers lost to follow up and duration of follow up would make it easier to evaluate the reliability and applicability of the evidence presented. Appropriate statistical techniques appeared to have been used to pool data, check for publication bias and assess and explore heterogeneity. However, although the marked heterogeneity in the main analyses appeared to be largely attributable to the choice of measurement tool, the clinical implications of this finding were unclear. The review was in most respects well conducted and the authors’ conclusions seemed likely to be reliable, though the marked heterogeneity between studies meant that the overall effect size of the intervention was unclear.

**Implications of the review for practice and research**

Practice: the authors stated that clinicians should consider the superior effect of continuous (rather than intermittent) dosage when initiating SSRI treatment of women with PMS or premenstrual dysphoric disorder.

Research: the authors stated that further research should directly compare continuous versus intermittent dosing strategies and different types of SSRI, explore the duration of treatment and the differential effects on various symptom clusters, and include adverse effects as an outcome.

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**Bibliographic details**

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Citalopram /therapeutic use; Female; Fluoxetine /therapeutic use; Fluvoxamine /therapeutic use; Humans; Odds Ratio; Paroxetine /therapeutic use; Premenstrual Syndrome /drug therapy; Serotonin Uptake Inhibitors /therapeutic use; Sertraline /therapeutic use; Treatment Outcome

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.