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

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Authors' objectives
To assess the efficacy of selective serotonin-reuptake inhibitors (SSRIs) in severe premenstrual syndrome (PMS).

Searching
The authors searched EMBASE (1988 to 1998), MEDLINE (1966 to 1999), PsycLIT (1974 to 1997), CINAHL (1982 to 1999) and the Cochrane Controlled Trials Register using the MeSH terms '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'. The authors also searched the references of retrieved articles and contacted the manufacturers of SSRIs for additional relevant studies. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled, double-blind trials (RCTs) which scored 3 or more points on the Jadad score.

Specific interventions included in the review
Selective serotonin-reuptake inhibitors (SSRIs) versus other active treatment (different doses of SSRIs or other antidepressants) and/or placebo. Included medications were: fluoxetine, bupropion, sertraline, paroxetine, maprotiline, desipramine, fluvoxamine, citalopram.

Participants included in the review
Women diagnosed with severe premenstrual syndrome (PMS).

Outcomes assessed in the review
The primary outcome measure was a reduction in overall PMS symptoms. This was measured using a variety of scales including: the Hamilton rating scale for depression (HAM-D), clinical global impression scale (CGI), global assessment scale (GAS), visual analogue scale (VAS), calendar of premenstrual experiences (COPE), premenstrual assessment form (PAF), Beck depression inventory (BDI), state-strait anxiety inventory (STAI), Diagnostic and Statistical Manual III Revision (DSM-III-R), daily assessment form (DAF), social adjustment scale (SAS), menstrual distress questionnaire (MDQ), or daily symptom report (DSR). Thirteen of the fifteen trials used a DSM III/IV classification of PMS (late luteal phase dysphoric disorder or premenstrual dysphoric disorder).

How were decisions on the relevance of primary studies made?
Two of the authors performed the selection of papers for inclusion however it is not stated whether this was done independently.

Assessment of study quality
Trials were assessed using two methods:

1. The 5-point Jadad scale assessing randomisation, double-blinding and reports of drop-outs and withdrawals (see Other Publications of Related Interest no.1)

2. A second 9-point (non-validated) scale designed by the authors to assess for study design, reproducibility, and statistical analysis.

Two authors independently scored each trial for quality, and any areas of disagreement were resolved by a third
Data extraction
Two authors independently extracted the data using a standard protocol and data collection form. Disagreements were resolved by discussion with two other investigators. If insufficient data were available then original authors were contacted for additional information.

Data were extracted for the categories of: study reference number, number of participants and treatments, intervention dosage and schedule, outcome measures, withdrawals, side-effects, Jadad score and authors' own quality score and study design.

In one report that presented dichotomous data only, odds ratios were calculated and converted to a standardised mean difference.

Methods of synthesis
How were the studies combined?
For continuous data, a standardised mean difference (SMD) was calculated using both fixed-effect and random-effects models with 95% confidence intervals (CIs). The results of the random-effects calculations are reported.

A funnel-plot analysis (Egger's test) was used to check for publication bias. The symmetry of the funnel plot was further analysed using linear regression.

How were differences between studies investigated?
The authors used the chi-squared statistic to test for heterogeneity. Secondary analyses were also conducted of:

1. The improvement in physical symptoms of PMS compared with that in behavioural premenstrual symptoms.
2. The efficacy of SSRIs in treating premenstrual irritability.
3. Continuous versus intermittent dosing schedules if suitable information was available.
4. By individual drug and drug-company funded versus non-drug-company funded.

Results of the review
Fifteen RCTs were included with 1,063 participants. Six of the trials were cross-over studies with 84 participants.

The overall quality of the trials was high. Only one RCT was excluded as poor quality.

The overall standardised mean difference was -1.066 (95% CI: -1.381, -0.750) and an OR of 6.91 (95% CI: 3.90, 12.2) in favour of SSRIs. The pooled trials were statistically heterogeneous (p<0.0001).

SSRIs were effective in treating physical and behavioural symptoms.

A regression analysis of the funnel plot to investigate publication bias indicated no statistically significant asymmetry (intercept 15.16 (90% CI: 25.17, 35.48, p = 0.210)) and thus no evidence of publication bias.

There was no statistically 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, OR 2.42 (95% CI: 1.59, 3.67).

SSRIs were not statistically significantly more effective than other antidepressants (3 trials), SMD 0.287 (95% CI:
-0.586, 0.011).

**Authors’ conclusions**
The authors state that 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.

**CRD commentary**
The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search was thorough. There were no language restrictions.

The quality of the included studies was formally assessed using two assessment methods and the authors have also reported how the articles were selected and who performed the validity assessment and the data extraction. Study details are well reported and are listed along with review results in tables and discussed in the text.

Heterogeneity was tested for both the main measures and for subgroup analyses. Statistical pooling was performed even though significant heterogeneity was found. Differences between subgroups were investigated with further subgroup analyses.

The authors’ conclusions appear to follow from the results, however they should be treated with caution as significant heterogeneity means that pooling should not have been undertaken.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

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**Bibliographic details**

**PubMedID**
11030291

**Other publications of related interest**

This additional published commentary may also be of interest. Smith RC. Review: selective serotonin reuptake inhibitors reduce symptoms in premenstrual syndrome. Evid Based Med 2001;6:75.

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Female; Humans; Patient Dropouts; Premenstrual Syndrome /drug therapy; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors /adverse effects /therapeutic use; Treatment Outcome

**AccessionNumber**
Record Status
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.