Selective serotonin reuptake inhibitors for premenstrual syndrome (Review)

Brown J, O'Brien PMS, Marjoribanks J, Wyatt K

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[Intervention Review]

Selective serotonin reuptake inhibitors for premenstrual syndrome

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ABSTRACT

Background

This is a substantive update of a previous review. Severe premenstrual syndrome (PMS) affects between 3% to 5% of women of reproductive age. Severe PMS is classified under the Diagnostic and Statistical Manual of Mental Disorders as premenstrual dysphoric disorder (PMDD). Selective serotonin reuptake inhibitors (SSRIs) are increasingly used as front-line therapy for PMS. A systematic review was undertaken on the efficacy of SSRIs in the management of severe PMS, or PMDD, to assess the evidence for this treatment option.

Objectives

The objective of this review was to evaluate the effectiveness of SSRIs in reducing premenstrual syndrome symptoms in women diagnosed with severe premenstrual syndrome.

Search strategy

Electronic searches for relevant randomised controlled trials were undertaken in the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE, PsycInfo, and CINAHL (March 2008). Where insufficient data were presented in a report the original authors were contacted for further details.

Selection criteria

All trials were considered in which women with a prospective diagnosis of PMS, PMDD or late luteal phase dysphoric disorder (LPDD) were randomised to receive SSRIs or placebo for the treatment of premenstrual syndrome in a blinded trial.

Data collection and analysis

Forty randomised controlled trials were identified which reported the use of SSRIs in the management of PMS. Fifty-six trials were excluded. The review authors extracted the data independently and estimated standardised mean differences for continuous outcomes.

Main results

Due to heterogeneity, analyses were subgrouped into change and absolute scores. The primary analysis of reduction in overall symptomatology included data on 2294 women with premenstrual syndrome. SSRIs were found to be highly effective in treating the premenstrual symptoms (SMD -0.53, 95% CI 0.68 to -0.39; P < 0.00001). Secondary analysis showed that they were effective in treating physical (SMD -0.34, 95% CI -0.45 to -0.22; P < 0.00001), functional (SMD -0.30, 95% CI -0.43 to -0.17; P < 0.00001), and behavioural symptoms (SMD -0.41, 95% CI -0.53 to -0.29; P < 0.00001). Luteal phase only and continuous administration were both effective and there was no influence of a placebo run-in period on reduction in symptoms. All SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and clomipramine) were effective in reducing premenstrual symptoms. Withdrawals due to side effects were twice as likely to occur in the treatment group (OR 2.18, 95% CI 1.62 to 2.92; P < 0.00001).

Authors' conclusions

The evidence supports the use of selective serotonin reuptake inhibitors in the management of severe premenstrual syndrome.

PLAIN LANGUAGE SUMMARY

Selective serotonin reuptake inhibitors for premenstrual syndrome

Premenstrual syndrome (PMS) is a common cause of physical, behavioural, and also social dysfunction in women. Often the associated symptoms are evident as irritability, which is relieved by the onset of, or during, menstruation. PMS can severely disrupt the lives of some women to the extent that they seek medical treatment. Although the precise cause is unknown, PMS is probably caused by an increased sensitivity to circulating progesterone and its metabolites rather than abnormal concentrations of hormones. This review of trials using selective serotonin reuptake inhibitors (SSRIs) indicates that they are effective in relieving severe premenstrual symptoms when compared with placebo. The most common adverse effects of selective serotonin reuptake inhibitors include nausea, insomnia, headache and decreased libido.

BACKGROUND

Description of the condition

Premenstrual syndrome exists when women complain of regularly recurring psychological or somatic symptoms, or both, that occur specifically during the luteal phase of the menstrual cycle and are resolved by the onset of, or during, menstruation (O'Brien 1997). In addition, the symptoms are severe enough to disrupt normal, everyday life. Mild physiological symptoms occur in approximately 95% of all women of reproductive age and can be managed by conservative lifestyle changes. The most common physical complaints are bloating, weight gain, mastalgia (breast pain), abdominal discomfort and pain, lack of energy, headache, and exacerbation of chronic illnesses such as asthma, allergies, epilepsy, or migraine. The most commonly reported behavioural changes are dysphoria, irritability (the cardinal symptom), anxiety, tension, aggression, feelings of being unable to cope and a sense of loss of control. For approximately 5% of symptomatic women symptoms are so severe that their lives are completely disrupted during the second half of the menstrual cycle; many of these women will require pharmacological management of their PMS (Wyatt 1999a). The aetiology of the condition remains unclear although the speculative current consensus is that it is differential sensitivity to circulating progesterone metabolites rather than abnormal hormone concentrations which can cause PMS (Rapkin 1997).

Description of the intervention

The uncertainty in the pathogenesis of PMS has led to many treatments being suggested as possible therapies. Moreover, as there is a substantial placebo response, a large number of uncontrolled trials have resulted in a proliferation of claims for ineffective therapies (Magos 1986). There is increasing evidence that serotonin (5-hydroxytryptamine) could be related to the differential sensitivity to progesterone metabolites and is important in the pathogenesis of PMS (Rapkin 1987; Steiner 1995 a). Consequently, serotonin reuptake inhibitors are increasingly being used as the first-line therapy (Steiner 1995 a). Severe PMS is classified under the Diagnostic

and Statistical Manual of Mental Disorders as premenstrual dysphoric disorder (PMDD). The treatment of PMDD with SSRIs is accepted within and outside the European Union (EU).

How the intervention might work

SSRIs are thought to increase the extracellular levels of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cells and so increasing the amount of serotonin available to bind to the postsynaptic receptor. SSRIs are most commonly used as antidepressants and in anxiety disorders.

Why it is important to do this review

The range of possible symptoms associated with premenstrual syndrome is wide. It is the mood disorders that often prompt women to seek medical intervention (O'Brien 1997). The symptoms can be very debilitating and identifying an intervention which may improve the functional ability, physical, and psychological well being of this group of women is important. This is an update of a Cochrane review first published in 2002.

OBJECTIVES

To determine the effectiveness of SSRIs in reducing the symptoms of premenstrual syndrome in women. The following hypotheses were tested.

1. Treatment with SSRIs is more effective than placebo in reducing overall PMS symptoms and specifically:

- physical symptoms;
- behavioural symptoms;
- functional symptoms.

2. Treatment with SSRIs is effective in reducing premenstrual irritability.

3. Treatment with luteal phase only and continuous dosing regimens of SSRIs are equally effective.

4. Treatment with high doses of SSRIs are more effective than low doses of SSRIs in managing PMS.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of SSRIs versus placebo when used as treatment for severe forms of PMS were considered for inclusion. Quasi-randomised controlled trials and open-label studies without blinding were excluded.

Types of participants

Women of any age who met the medically defined diagnostic criteria for premenstrual syndrome (PMS), premenstrual dysphoria (PMD), premenstrual dysphoric disorder (PMDD), or late luteal phase dysphoric disorder (LLPDD). Diagnosis of PMS must have been made prior to inclusion in the trial by a GP, hospital clinician, or other healthcare professional. Women with a self-diagnosis of PMS were excluded.

Types of interventions

Selective serotonin reuptake inhibitors (SSRIs) at any dosage and in any dosing regimen for any duration longer than one menstrual cycle versus placebo. Tricyclic antidepressants were not included, even when described as serotonin reuptake inhibitors, as they are not selective and act in a different manner to SSRIs.

Types of outcome measures

The primary outcome measure was change in overall self-rated premenstrual symptomatology. All diagnoses of PMS using prospective screening tools, for example Moos' MDQ, Abraham's classification, or pre-defined medical diagnostic criteria were considered. Secondary outcome measures included the separate assessment of physical, functional, and behavioural symptoms; a separate analysis of irritability (the 'cardinal' symptom of PMS); and measures of efficacy of treatment. All side effects, adverse events, and numbers of women withdrawing from the study were recorded.

Search methods for identification of studies

This is a substantive update of an original review. Additional studies have been identified and added to the meta-analysis. All sections of the review have been amended and updated in line with the current requirements of the Cochrane Menstrual Disorders and Subfertility Group (MDSG).

Electronic searches

The most recent electronic searches were conducted in March 2008 using the Cochrane Menstrual Disorders and Subfertility Review Group search strategy. All publications which described a treatment for PMS, PMT, PMD or PMDD, LLPDD or LLPD involving the use of an SSRI were assessed. a) The Cochrane Menstrual Disorders and Subfertility Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) were searched for appropriate trials. b) Electronic databases MEDLINE, EMBASE, PsychINFO, and CINAHL were searched. The MEDLINE search string (Appendix 1) was adapted, where necessary, for the other electronic databases.

Searching other resources

a) All references in the included and excluded trials and relevant review articles were searched.
b) Drug and pharmaceutical companies manufacturing SSRIs (fluoxetine: Eli Lilly; paroxetine: Smith Kline Beecham; sertraline: Invicta; fluvoxamine: Solvay; Citalopram: Du Pont) were contacted to identify other published or unpublished trials.
c) The personal databases maintained by the authors on PMS therapies were searched for relevant articles.
d) The UK-based National Association for Premenstrual Syndrome (NAPS) was also contacted for any relevant articles. Any unpublished studies are referenced according to their source.

Data collection and analysis

Trials being considered were assessed for appropriateness of inclusion and adequate methodology without regard to their results.

Selection of studies

All the publications identified in the search strategy were originally assessed by PWD and KMW working in parallel. Selection of the trials for inclusion was performed by PWD and KMW, with consultation. Any disagreements were assessed by PMSOB and other uncertainties regarding inclusion were resolved by contacting the authors. An additional 22 studies were identified by JB and JM during the update.

Data extraction and management

The quality of the trials was assessed using the methodology of the Menstrual Disorders and Subfertility Group. The trials were assessed for the following: allocation concealment; rate of contamination with concurrent medications; randomisation procedure; power calculation; dose and mode of intervention; use of a valid symptomatic measurement; clear presentation of results; a description of the number of and reasons for trial withdrawals; exclusion, or separate analysis, of participants with a major psychiatric disorder; and whether or not the trial was supported by independent funding. All new trials in the update were assessed by JB and JM working in parallel.
Where there were multiple arms in a study with a common placebo, the placebo numbers were divided equally between the arms. Where crossover studies provided data, the arm before crossover was used; otherwise the trial was classified as included but left out of the numerical analyses. Publication bias was avoided by identifying articles from as many sources as possible.

Assessment of risk of bias in included studies

Data regarding the method of randomisation, allocation, concealment, blinding, and exclusion were independently extracted from the included trials by JB and JM using forms designed according to the Cochrane guidelines for this update. Where trials contained insufficient data for analysis the missing information was sought from the authors of the trials.

Measures of treatment effect

Continuous data were extracted and transformed into standardised effect sizes by dividing the mean values by their standard deviations. They were weighted by participant number in the meta-analysis. Due to the diversity of scales which had been used as outcome measures, standardised mean differences were calculated in order to reduce the heterogeneity. A random-effects model was used. In order to deal with missing data, in trials where women dropped out before completion, the assumption was made that those who did not complete the study had a negative outcome. Homogeneity was tested for using a Chi^2 test with $P < 0.01$ indicating significant heterogeneity; the amount of heterogeneity was determined with the I^2 statistic. A funnel plot was used to look for bias, including as a result of location, language, citation, and publication bias. A further sensitivity analysis that included and then excluded studies which had a large dropout rate was also conducted. Dichotomous data were reported as odds ratios (OR) with 95% confidence intervals (CI).

Unit of analysis issues

None known and data were presented as per woman randomised.

Dealing with missing data

Authors of trials with missing data were contacted, where possible.

Assessment of heterogeneity

This was evaluated using the I^2 statistic and Chi^2 test. Where heterogeneity was high (> 50%) in the meta-analysis an attempt was

made to explain possible causes by looking at differences between the studies.

Assessment of reporting biases

Data were obtained from full papers, conference abstracts, and unpublished sources where found. A funnel plot was conducted to look at issues around publication bias.

Data synthesis

Where possible, continuous data were obtained as mean scores and standard deviations (± sd) for the primary outcome and standardised mean differences (SMD) were calculated using a random-effects model. Mean change scores were obtained if these data were unavailable. Where change scores and absolute scores were combined, standardised mean differences (SMD) were used in a random-effects model. For dichotomous data ORs were calculated.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted on absolute and change scores; high versus low doses of SSRIs; intermittent versus continuous administration; placebo run in versus non-placebo run in; individual drug regimens; physical, behavioural, functional, and irritability symptoms.

Sensitivity analysis

Publication bias, sample size, and quality of studies were examined when heterogeneity was high.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Ninety-six potential papers and abstracts were retrieved. Forty studies were identified as randomised controlled trials which used selective serotonin reuptake inhibitors in the management of premenstrual syndrome and were included (Arrendondo 1997; Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Crnobaric 1998; Eriksson 1995; Freeman 1999a; Freeman 2004 a; Freeman 2004 b; Halbreich 1997; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Menkes 1993; Miner 2002a; Miner 2002b; Ozeren 1997; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Steiner 2005 a; Steiner 2005 b; Stone 1991; Su 1997; Sundblad 1992; Sundblad 1993; Veeninga 1990; Wikander 1998a; Wikander 1998b; Wikander 1998c; Wood 1992; Yonkers 1997; Young 1998).

Included studies

Description of participants

Below is a description of the participants recruited into the included trials. The site of recruitment, age range, method of diagnosis, range of the menstrual cycle duration, and exclusion criteria have been listed.

Site

No details were provided in five studies (Arrendondo 1997; Crnobaric 1998; Halbreich 1997; Menkes 1993; Young 1998). Twelve studies were multicentre (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Steiner 2005 a; Steiner 2005 b); three were conducted within a premenstrual syndrome programme (Freeman 1999a; Freeman 2004 a; Freeman 2004b); and 11 recruited from psychiatric, gynaecological outpatient, or PMS clinics (Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b; Stone 1991; Wood 1992; Yonkers 1997). In 16 studies women were recruited via media, television, or local newspaper advertising (Eriksson 1995; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Stone 1991; Su 1997; Sundblad 1992; Sundblad 1993; Veeninga 1990; Wikander 1998a; Wikander 1998b; Wikander 1998c; Young 1998). Two studies used self-referred women (Ozeren 1997; Su 1997). University affiliated clinics or research centres recruited women in four of the studies (Jermain 1999; Steiner 1995 a; Steiner 1995b; Steiner 2001).

Age range

No details were provided in seven studies (Arrendondo 1997; Su 1997; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c). The overall age range across all the included studies was 18 to 49 years. The majority of the studies recruited women between 18 to 45 years. Below are the actual age ranges in the studies:

- 18 to 45 years (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Miner 2002a; Miner 2002b; Ozeren 1997; Pearlstein 1997; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Steiner 2005 a; Steiner 2005 b; Veeninga 1990; Young 1998);

- 18 to 40 years (Crnobaric 1998);
- 18 plus (Eriksson 1995; Länden 2007 a; Länden 2007b);
- 24 to 45 years (Halbreich 1997; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Yonkers 1997);
- 19 to 49 years (Jermain 1999);
- 18 to 48 years (Menkes 1993);
- 27 to 45 years (Stone 1991);
- 23 to 35 years (Su 1997);
- 33 to 42 years (Wood 1992).

Diagnosis

All but the two studies that failed to detail how they diagnosed women (Veeninga 1990; Wood 1992) used some form of diagnostic criteria involving self-rating on a recognised scale over more than one cycle. The different methods are detailed below.

- Meeting defined criteria for Penn Daily Self Rating Symptoms for two cycles (Arrendondo 1997).
- Meeting defined criteria for DRSP items which were self-rated for two cycles (Cohen 2002a; Cohen 2002b).
- Meeting diagnostic criteria for PMDD using DSM-IV (Cohen 2004 a;Cohen 2004b; Crnobaric 1998; Freeman 1999a; Halbreich 1997; Halbreich 2002; Miner 2002a; Miner 2002b (based on screening over two cycles); Jermain 1999; Länden 2007 a; Länden 2007b; Ozeren 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b; Wikander 1998a; Wikander 1998b; Wikander 1998c; Young 1998).
- Meeting DSM III-R criteria for LLPDD (Eriksson 1995; Stone 1991; Sundblad 1992; Sundblad 1993).
- Meeting predefined criteria based on a self-rating scale: not detailed (Pearlstein 1997), for three cycles (Freeman 2004 a; Freeman 2004b; Su 1997); and for two cycles (Kornstein 2006 a; Kornstein 2006b; Yonkers 1997).
- Confirmation by psychiatric evaluation (Menkes 1993).
- Meeting diagnostic criteria for LLPDD (Steiner 1995 a; Steiner 1995b; Steiner 2001).

Regular menstrual cycles

The definition of regular menstrual cycles varied between the studies from a minimum of 22 days between periods to a maximum of 36 days. These are detailed below:

- 22 to 35 days (Arrendondo 1997; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Länden 2007 a; Länden 2007b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a);
- 25 to 35 days (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Wikander 1998a; Wikander 1998b; Wikander 1998c);
- 25 to 34 days (Halbreich 1997);
- 24 to 31 days (Veeninga 1990);
- 24 to 36 days (Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Yonkers 1997);
- 24 to 35 days (Pearlstein 1997; Steiner 1995 a; Steiner 1995b; Steiner 2001);
- 23 to 35 days (Jermain 1999; Miner 2002a; Miner 2002b);
- 26 to 32 days (Wood 1992);
- here was no definition by Crnobaric 1998 and no details in six studies (Eriksson 1995; Menkes 1993; Ozeren 1997; Sundblad 1992; Sundblad 1993; Young 1998).

Exclusion criteria in included studies

There were a wide range of exclusion criteria, although most of the studies used similar criteria. There were differences in the time frame allowed for some of the variables. These are outlined below.

- No current major psychiatric diagnosis (Arrendondo 1997; Crnobaric 1998; Eriksson 1995; Ozeren 1997; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c; Wood 1992; Yonkers 1997; Young 1998).
- No current Axis 1 psychiatric diagnosis (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b) with the exception of PMDD: in past six months; within past year (Freeman 1999a; Freeman 2004 a; Freeman 2004b; Länden 2007 a; Länden 2007b); no time frame mentioned (Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b; Pearlstein 1997; Pearlstein 2005 a; Steiner 2005 a; Steiner 2005 b; Su 1997).
- No hormonal contraceptive use: within two months of screening (Cohen 2002a; Cohen 2002b; Eriksson 1995; Halbreich 2002); for previous six months (Jermain 1999; Kornstein 2006 a; Kornstein 2006b); in previous three months (Länden 2007 a; Länden 2007b; Menkes 1993; Miner 2002a; Miner 2002b); no time detailed (Ozeren 1997; Pearlstein 1997; Pearlstein 2005 a; Steiner 1995 a; Steiner 2001; Steiner 2005 a; Steiner 2005 b; Su 1997; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c).
- Any other clinically significant disease (Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Pearlstein 1997; Pearlstein 2005 a; Steiner 1995 a; Steiner 2005 a; Steiner 2005 b; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c; Wood 1992; Yonkers 1997).

- Depressive symptoms during the follicular phase (Cohen 2004 a; Cohen 2004b; Halbreich 2002; Länden 2007 a; Länden 2007b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b; Su 1997).

- Concurrent medication for PMDD (Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001).

- Concurrent medication including use of psychotropics (Eriksson 1995; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Halbreich 2002; Jermain 1999; Länden 2007 a; Länden 2007b; Menkes 1993; Ozeren 1997; Pearlstein 1997; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Su 1997; Sundblad 1993; Veeninga 1990; Wikander 1998a; Wikander 1998b; Wikander 1998c; Young 1998).

- Ongoing or planned pregnancy (Eriksson 1995; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Steiner 2005 a; Steiner 2005 b; Stone 1991; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998c; Young 1998).

- Under 18 years of age (Eriksson 1995; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c).

- Under 15 years of age (Sundblad 1992).

- Previous treatment with antidepressants for premenstrual complaints (Eriksson 1995; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b; Stone 1991; Wikander 1998a; Wikander 1998b; Wikander 1998c.).

- Lactation (Freeman 1999a; Freeman 2004 a; Freeman 2004b; Kornstein 2006 a; Kornstein 2006b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995b; Steiner 2001; Steiner 2005 a; Steiner 2005 b).

- Irregular menstrual cycles (Freeman 1999a; Freeman 2004 a; Freeman 2004b; Menkes 1993; Ozeren 1997; Pearlstein 1997; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Sundblad 1992; Wikander 1998a; Wikander 1998b; Wikander 1998c).

- Not using approved form of contraception (Freeman 1999a; Freeman 2004 a; Freeman 2004b).

- Substance abuse: within past year (Menkes 1993; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Pearlstein 1997); no time defined (Su 1997; Sundblad 1992; Sundblad 1993;Wikander 1998a; Wikander 1998b; Wikander 1998c; Yonkers 1997).

- Placebo response (Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b).

Description of the interventions

Drug type

Six different SSRIs that were compared with placebo were identified in the included studies: fluoxetine, sertraline, citalopram, fluvoxamine, paroxetine, and clomipramine. Fourteen of the trials used fluoxetine (Cohen 2002a; Cohen 2002b; Crnobaric 1998; Menkes 1993; Miner 2002a; Miner 2002b; Ozeren 1997; Pearlstein 1997; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Su 1997; Wood 1992), 11 used sertraline (Arrendondo 1997; Freeman 1999a; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Yonkers 1997; Young 1998), and there were three trials for citalopram (Wikander 1998a; Wikander 1998b; Wikander 1998c). One study used fluvoxamine (Veeninga 1990), paroxetine was used in nine studies (Cohen 2004 a; Cohen 2004b; Eriksson 1995; Länden 2007 a; Länden 2007b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b), with two studies administering clomipramine (Sundblad 1992; Sundblad 1993).

Multiple treatment arms

Some of the papers had multiple arms of treatment compared with a placebo. Seven papers compared different dosages of medication versus placebo and were, therefore, split into 15 separate trials for the purpose of the review, with the placebo group being divided equally between groups for analysis (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Kornstein 2006 a; Kornstein 2006b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2005 a; Steiner 2005 b; Wikander 1998a; Wikander 1998b; Wikander 1998c).
Fluoxetine 10 mg was used in Cohen 2002a and 20 mg in Cohen 2002b whereas Steiner 1995 a used fluoxetine 20 mg and Steiner 1995b used a 60 mg dosage. Paroxetine 25 mg was given (Cohen 2004 a; Pearlstein 2005 a; Steiner 2005 b) with a lower dose of 12.5 mg in the alternate active arm of the studies (Cohen 2004b; Pearlstein 2005b; Steiner 2005 a). Sertraline 50 mg was administered by Kornstein 2006b in one arm and 25 mg in the second active arm (Kornstein 2006 a).
Four of the papers compared luteal phase only and continuous dosages with placebo and have, therefore, been split into nine separate trials for the purpose of the review; the placebo group being divided equally between groups for analysis (Freeman 2004 a; Freeman 2004b; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Wikander 1998a; Wikander 1998b; Wikander 1998c).

All of the studies detailed above had two treatment arms and one control arm with the exception of Wikander 1998 (Wikander 1998a; Wikander 1998b; Wikander 1998c) who used three treatment arms and a control. Where placebo arms were divided between treatment groups and a non-integer number was obtained, the value was rounded up to the nearest whole number.

Study design

Seven trials were crossover studies (Jermain 1999; Su 1997; Menkes 1993; Halbreich 1997; Wood 1992; Young 1998). The first-arm data (before crossover) for overall symptom reduction could be extracted for only one of these trials (Jermain 1999) and the remaining crossover trials were not used in the data pooling. Where data were incomplete, all authors were contacted; however, no additional data were received. The remaining studies were all parallel studies.

Outcomes

A wide variety of physical, functional, and psychological outcome measures were used in the selected studies. For clarity, these have been listed and described (where details were provided in the papers) in the 'Additional tables' section of the review.

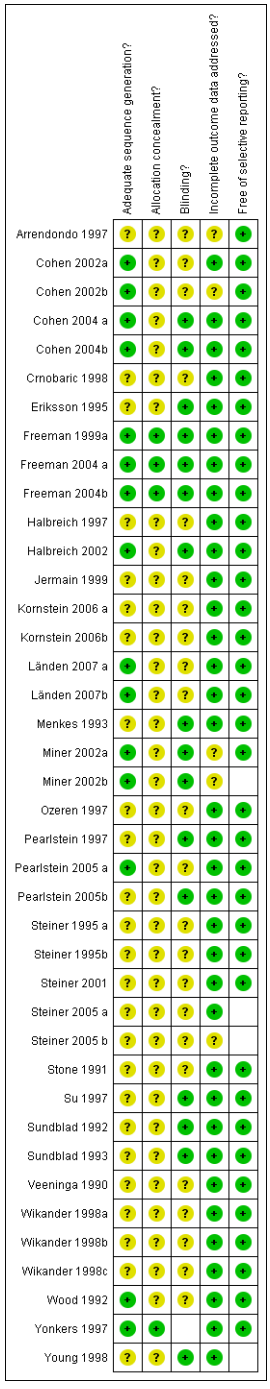
Excluded studies

Fifty-six studies were excluded (refer to 'Characteristics of excluded studies' table for details) because they were: conference proceedings or preliminary reports of full papers included in the review; open label or unblinded studies; did not contain a placebo group; or were quasi-randomised. One trial was excluded because the treatment was only administered for one treatment cycle before crossover (Yonkers 2006).

Risk of bias in included studies

Details of the risk of bias are given in Figure 1.

Figure 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

Four studies had an allocation concealment rated A. Yonkers 1997 used a central location for randomisation and three (Freeman 1999a; Freeman 2004 a; Freeman 2004b) used a technician for allocation at the beginning of the study with no clinical contact. There were no details of allocation in the remaining studies, which scored B. No trials scored C.

Randomisation

Sixteen studies detailed methods of randomisation (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Wood 1992; Yonkers 1997). The remaining studies did not detail their methods of randomisation.

Blinding

Twenty-eight studies reported double-blind methods but did not provide details as to who was blinded (Arrendondo 1997; Cohen 2002a; Cohen 2002b; Crnobaric 1998; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Ozeren 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Steiner 2005 a; Steiner 2005 b; Stone 1991; Veeninga 1990; Wikander 1998a; Wikander 1998b; Wikander 1998c; Wood 1992; Yonkers 1997). Both patient and rater were described as blinded to allocation in five studies (Eriksson 1995; Menkes 1993; Su 1997; Sundblad 1992; Sundblad 1993).

Miner 2002a and Miner 2002b described patients and an unspecified 'other' as being blinded; Pearlstein 1997 and Young 1998 described the physician and unspecified 'other' as being blinded; in Cohen 2004 a and Cohen 2004b, participants, those administering the study and those assessing the outcomes were blinded.

Incomplete outcome data

There were a number of withdrawals in these studies, which ranged from 0% to 42.5%. These withdrawals were due to: loss to follow up, protocol violation, withdrawal of consent, lack of efficacy; and adverse events or side effects. The percentage of women withdrawing from the study due to side effects ranged from 2% to 18% of the study population. Further details are given in the Risk of bias and comparisons tables.

Selective reporting

The review authors have not excluded any studies based on language, country, positive or negative findings, whether the data was published or unpublished, full journal articles or conference abstracts. The majority of the studies originated in the USA or Canada (Arrendondo 1997; Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Su 1997 Wood 1992; Yonkers 1997; Young 1998). Other countries included Yugoslavia (Crnobaric 1998), Sweden (Eriksson 1995; Länden 2007 a; Länden 2007b; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c), New Zealand (Menkes 1993), Turkey (Ozeren 1997), Netherlands (Veeninga 1990), and international collaborations (Miner 2002a; Miner 2002b; Steiner 2005 a; Steiner 2005 b).There was no evidence of publication bias; funnels plots conducted for absolute and change scores indicated symmetrical plots. In all cases the outcomes stated in the methods section of the papers were reported in the results section. All the anticipated outcomes for this type of study were included.

Other potential sources of bias

Some studies recruited women who were attending PMS clinics or psychiatric outpatients, other studies relied on the self referral of women through advertising and subsequent screening. The risk of bias was, therefore, somewhat reduced in the meta-analysis as all these avenues of recruitment were used.

Power

Nineteen studies showed evidence of power calculations to estimate an appropriate sample size (Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b; Wikander 1998a; Wikander 1998b; Wikander 1998c; Yonkers 1997; Young 1998). These calculations were based on changes in mood scores, daily rating of the symptoms irritability and reduction in dysphoria, which appeared to be appropriate for the primary outcomes of the studies.

Intention to treat

Intention-to-treat analysis was reported by 22 studies (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 2002;

Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b Menkes 1993; Miner 2002a; Miner 2002b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2005 a; Steiner 2005 b; Yonkers 1997). Wikander 1998 (Wikander 1998a; Wikander 1998b; Wikander 1998c) only used intention-to-treat analysis for irritability. In three studies all women completed the trial and were analysed (Crnobaric 1998; Pearlstein 1997; Veeninga 1990). Erikson (Eriksson 1995) did not use intention to treat as the drop outs occurred before treatment and Sundblad (Sundblad 1993) only analysed those women who completed the trial. None of the remaining studies reported on or used intention-to-treat analysis.

Funding

Funding from pharmaceutical company sources alone was reported by 19 trials (Cohen 2002a; Cohen 2002b; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Su 1997; Yonkers 1997). Funding from a combination of pharmaceutical and independent sources was reported by seven studies (Eriksson 1995; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Menkes 1993; Sundblad 1992; Sundblad 1993). Six studies were funded independently (Freeman 1999a; Wikander 1998a; Wikander 1998b; Wikander 1998c; Wood 1992; Young 1998). No details on sources of funding were reported in the remaining studies. For independently funded trials the overall SMD showed evidence of a significant effect in favour of SSRIs (SMD -0.95, 95% CI -1.41 to -0.48; z = 3.97, P < 0.0001, I^2 = 30%). The heterogeneity among pharmaceutical trials was high at 73% and the studies were, therefore, subgrouped into change and absolute scores. Both analyses showed evidence of a significant reduction in premenstrual symptoms in favour of SSRIs compared with placebo (change scores SMD -0.26, 95% CI -0.41 to -0.11; z = 3.45, P = 0.0006, I^2 = 0%) (absolute scores SMD -0.64, 95% CI -0.86 to -0.41; z = 5.52, P < 0.00001, I^2 = 36%). For those studies with combined funding a similar effect in favour of SSRIs was found (SMD -0.47, 95% CI -0.78 to -0.15; z = 2.89, P = 0.04). There did not appear to be any bias in terms of the sources of funding between the studies.

Duration of screening prior to treatment cycles

Two of the studies screened women for one month (Kornstein 2006 a; Kornstein 2006b); 28 comparative studies screened for two months (Arrendondo 1997; Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Crnobaric 1998; Eriksson 1995; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Jermain 1999; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Stone 1991; Sundblad 1992; Wikander 1998a; Wikander 1998b; Wikander 1998c; Yonkers 1997; Young 1998); three studies for two to three months (Steiner 2005 a; Steiner 2005 b; Wood 1992); and four studies for three months (Freeman 1999a; Menkes 1993; Ozeren 1997; Su 1997). This was prior to randomisation and the commencement of medication.

Number of treatment cycles

Ten studies treated women for two cycles (Crnobaric 1998; Halbreich 1997; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Pearlstein 1997; Stone 1991; Su 1997; Veeninga 1990; Young 1998) and 26 studies used three cycles (Arrendondo 1997; Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Eriksson 1995; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Ozeren 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 2005 a; Steiner 2005 b; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c; Wood 1992; Yonkers 1997). Three studies administered six cycles of treatment (Steiner 1995 a; Steiner 1995b; Steiner 2001).

Placebo run in

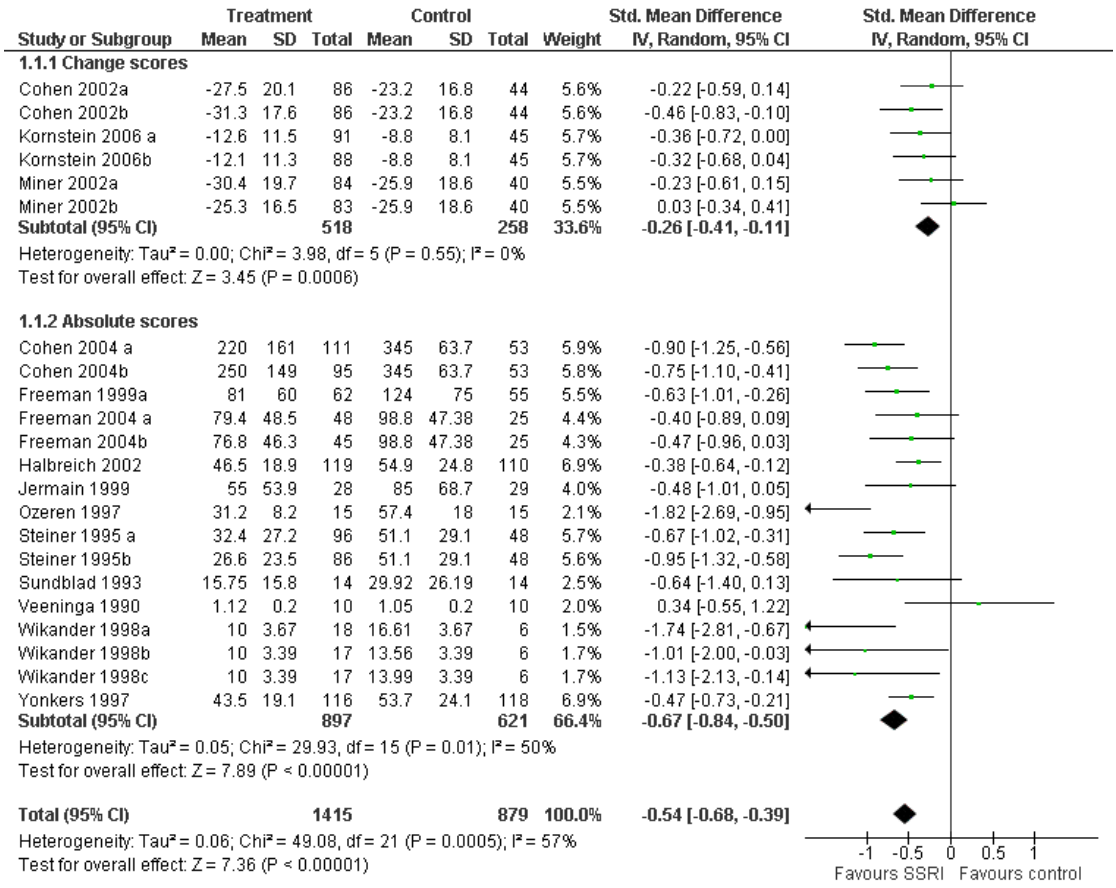
Some studies used a placebo run-in period prior to the administration of the SSRI or control. Women who responded to this placebo run in were then excluded from randomisation.Twenty-two studies used a placebo run-in method (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 2004 a; Freeman 2004b; Halbreich 1997; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2001; Steiner 2005 a; Steiner 2005 b; Stone 1991; Yonkers 1997). The remaining studies randomised the intervention or placebo immediately after the screening cycles.

Effects of interventions

From 22 studies there were 2294 women with data to be combined in the meta-analysis. There was evidence of a significant effect of SSRIs compared with placebo for reducing overall PMS symptomology, in favour of SSRIs. However, heterogeneity was high (I^2 = 57%) (Figure 2). This could be partly explained by the vast number of different outcome measures used in these studies, listed in the Additional tables. Some questionnaires were self completed and others as assessed by clinicians. It was, therefore, not appropriate to conduct a meta-analysis on overall symptoms. One of the obvious differences between the studies was how the data were reported (absolute versus change scores). The data were therefore subgrouped into those studies reporting absolute and those reporting change scores for the purpose of analysis. Data for self-reported PMS symptoms were presented as change scores in six studies (Cohen 2002a; Cohen 2002b; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b); and 20 studies reported

data on absolute scores (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 2004 a; Freeman 2004b; Freeman 1999a; Halbreich 2002; Jermain 1999; Ozeren 1997; Pearlstein 1997; Steiner 1995 a; Steiner 1995b; Stone 1991; Sundblad 1993; Veeninga 1990; Wikander 1998a; Wikander 1998b; Wikander 1998c; Yonkers 1997). When change scores were examined in isolation, there was evidence that SSRIs performed better than placebo (SMD -0.26, 95% CI -0.41 to -0.11; z = 3.45, P = 0.0006, I^2 = 0%) (see Figure 2). Absolute scores also showed evidence of superior performance of SSRIs in reducing overall symptoms (SMD -0.67, 95% CI -0.83 to -0.50; z = 7.82, P < 0.00001, I^2 = 50%) (see Figure 2). The studies also differed in dosing regimens, cycles of treatment, type of drug, and placebo versus no placebo run in. These potential confounding variables have been addressed individually in subgroup analyses.

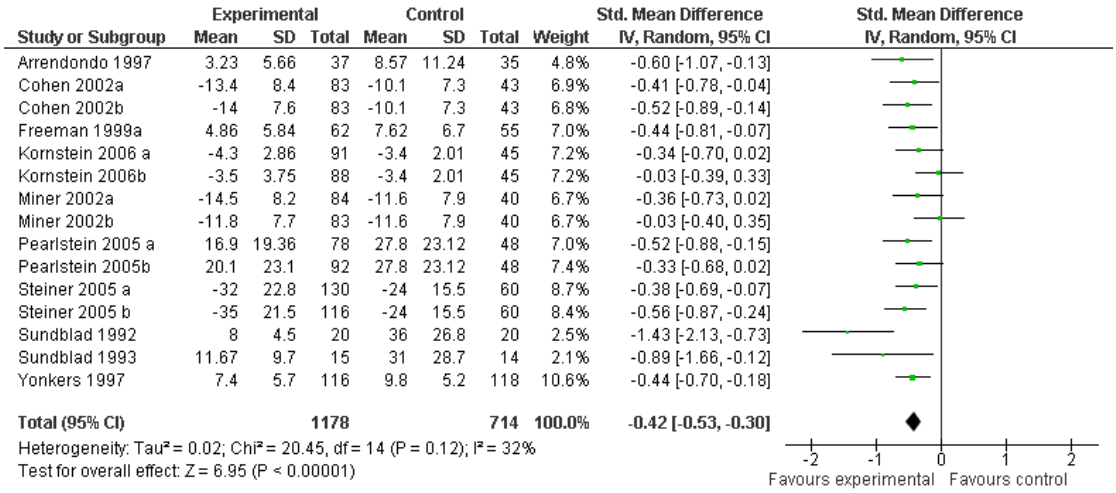
Figure 2. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.1 overall symptoms.



Behavioural and mood

There were 15 studies which assessed changes in behavioural outcome measures (Arrendondo 1997; Cohen 2002a; Cohen 2002b; Freeman 1999a; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b; Pearlstein 1997; Pearlstein 2005 a; Steiner 2005 a; Steiner 2005 b; Sundblad 1992; Sundblad 1993; Yonkers 1997). Table 1 illustrates the variety of tools used for outcome measures. Heterogeneity (I^2) was 32%. With absolute and change scores combined, behavioural symptoms appeared to be reduced by the use of SSRIs compared to placebo (SMD -0.42, 95% CI -0.53 to -0.30; z = 6.95, P < 0.00001) (Figure 3). Eight of the studies reported change scores (Cohen 2002a; Cohen 2002b; Kornstein 2006 a; Miner 2002a; Steiner 2005 b) (SMD -0.34, 95% CI -0.47 to -0.20; z = 4.82, P < 0.00001, I^2 = 17%) and seven studies reported absolute scores (SMD -0.54, 95% CI -0.73 to -0.35), z = 5.51, P < 0.00001, I^2 = 34%) (Arrendondo 1997; Freeman 1999a; Pearlstein 2005 a; Pearlstein 2005b; Sundblad 1993; Yonkers 1997). There was, therefore, evidence to suggest that SSRIs were more effective at reducing behavioural symptoms than placebo.

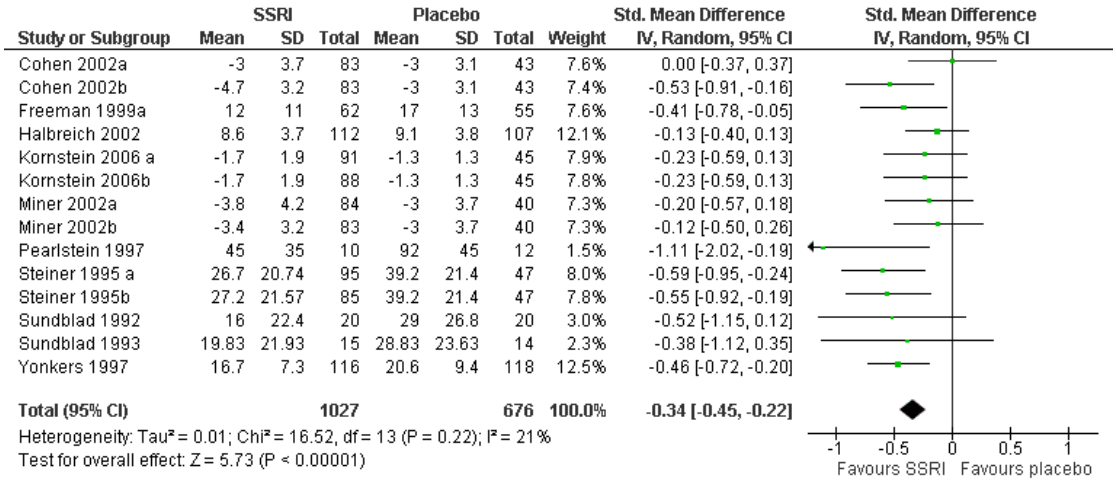
Figure 3. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.2 behavioural premenstrual symptoms.



Physical

Twelve studies assessed changes in physical symptoms (Cohen 2002a; Cohen 2002b; Freeman 1999a; Halbreich 2002; Kornstein 2006 a; Miner 2002a; Pearlstein 1997; Steiner 1995 a; Steiner 1995b; Sundblad 1992; Sundblad 1993; Yonkers 1997). The Additional table on the outcome measures used illustrates the variety of tools used. Heterogeneity (I^2) was 21% and when the absolute and change scores were combined the SMD was -0.34 (95% CI -0.45 to -0.22; z = 5.73, P < 0.00001) (Figure 4). The six studies reporting change scores (Cohen 2002a; Cohen 2002b; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b) had an I^2 of 0% and SMD of -0.22 (95% CI -0.37 to -0.07; z = 2.83, P = 0.005). The remaining eight studies reporting absolute scores for physical outcomes with an I^2 of 16% and SMD of -0.43 (95% CI -0.58 to -0.28; z = 5.63, P < 0.00001). There appeared to be evidence of a significant reduction in physical symptoms for women receiving SSRIs compared to placebo using both absolute and change scores.

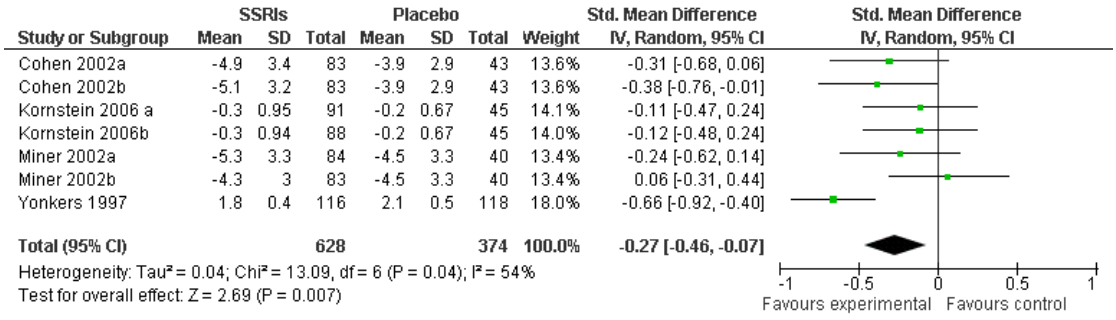
Figure 4. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.3 physical premenstrual symptoms.



Functional

Seven studies reported using functional outcome measures (Cohen 2002a; Cohen 2002b; Kornstein 2006 a; Miner 2002a; Yonkers 1997); these reflected difficulties in social and work life. I^2 was 54%, SMD -0.27 (95% CI -0.46 to -0.017; z = 2.69, P < 0.007) (Figure 5). There was one study which used absolute as opposed to change scores (Yonkers 1997). If this study was removed from the analysis the I^2 statistic was reduced to 0% and the reduction in functional symptoms for women receiving SSRIs remained (SMD -0.18, 95% CI 0.33 to -0.03; z = 2.38, P = 0.02), in favour of SSRIs.

Figure 5. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.4 Functional symptoms.

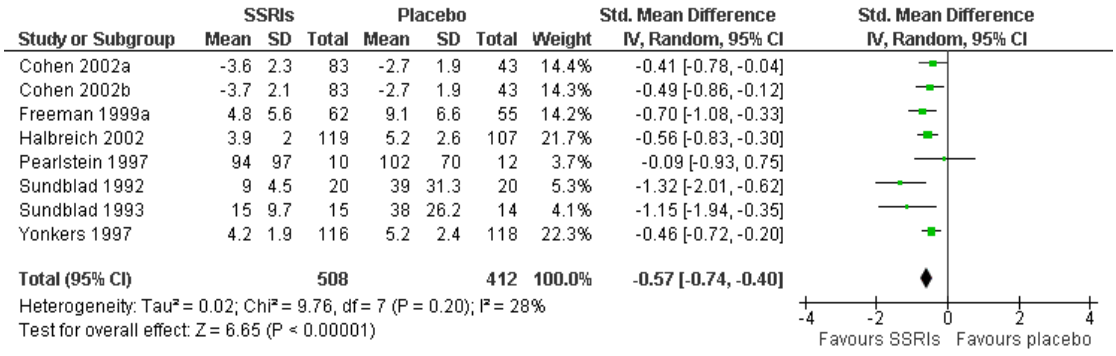


Irritability

Eight studies reported data on the single item of irritability (Cohen 2002a; Cohen 2002b; Freeman 1999a; Halbreich 2002; Pearlstein

1997; Sundblad 1992; Sundblad 1993; Yonkers 1997). Heterogeneity was 28% (I^2), SMD 0.57 (95% CI -0.74 to -0.40; z = 6.65, P < 0.00001) (Figure 6). The results showed a favourable response to the use of SSRIs in the management of severe premenstrual syndrome for the cardinal symptom of irritability.

Figure 6. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.5 irritability.



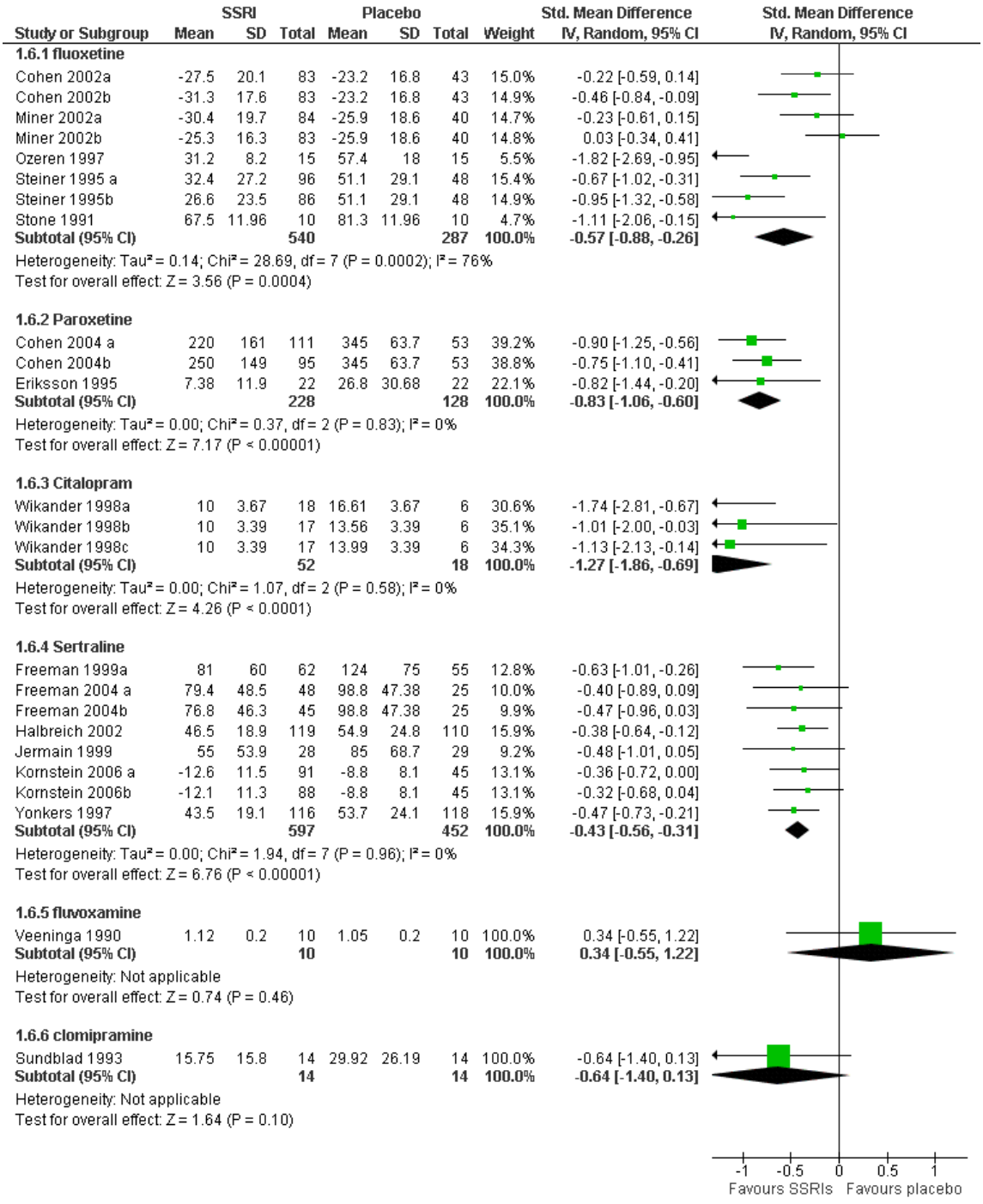
Subgroup analyses

A number of subgroup analyses were conducted to try to explain heterogeneity.

Drug type

Refer to Figure 7.

Figure 7. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.6 Specific SSRI.



Fluoxetine

Eight studies had evaluable data which compared fluoxetine with placebo (Cohen 2002a; Cohen 2002b; Miner 2002a; Miner 2002b; Ozeren 1997; Steiner 1995 a; Steiner 1995b; Stone 1991). Although a significant effect in favour of fluoxetine was found, the heterogeneity was high (I^2 = 76%). Four studies (Cohen 2002a; Cohen 2002b; Miner 2002a; Miner 2002b) used change scores, for which heterogenity was 12% (I^2) and the SMD was -0.22 (95% CI -0.42 to -0.02; z= 2.19, P = 0.03). The remaining four studies reported absolute scores with SMD -0.99 (95% CI -1.39 to -0.60; z = 4.96, P < 0.00001, I^2 = 52%).

Paroxetine

Three studies compared paroxetine with placebo (Cohen 2004 a; Cohen 2004b; Eriksson 1995). A significant effect in favour of paroxetine compared with placebo was identified (SMD -0.83, 95% CI -1.06 to -0.60; z = 7.17, P < 0.00001). There was no heterogeneity between the studies (I^2 = 0%). This was primarily because two of the comparative studies were one trial with two arms.

Citalopram

Three studies (Wikander 1998a; Wikander 1998b; Wikander 1998c) compared citalopram with placebo. Heterogeneity was 0% (I^2) as this was one trial with three arms and a shared placebo. The study findings appeared to indicate an overall effect in favour of citalopram (SMD -1.27, 95% CI -1.86 to -0.69; z = 4.26, P < 0.0001).

Sertraline

Eight studies compared sertraline with placebo (Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Yonkers 1997). There was evidence of a significant effect in favour of sertraline for reducing premenstrual symptoms: heterogeneity was 0% (I^2), SMD -0.43 (95% CI -0.56 to -0.31; z = 6.76, P < 0.00001).

Fluvoxamine and clomipramine

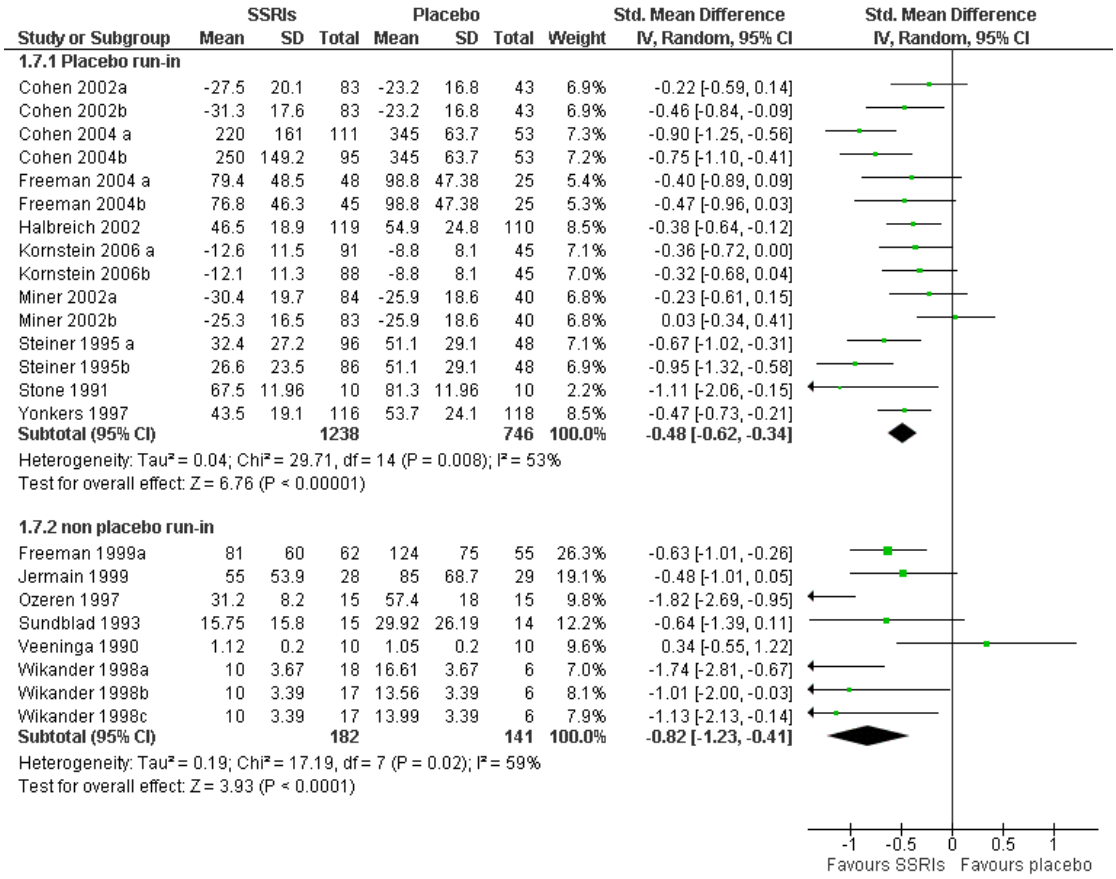
One study used fluvoxamine (Veeninga 1990) and although two studies (Sundblad 1992; Sundblad 1993) used clomipramine only Sundblad 1993 provided data on overall symptoms. Therefore, no meta-analysis was conducted on these individual drugs.

Placebo versus non-placebo run in

Placebo run in

Fifteen studies (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b; Steiner 1995 a; Steiner 1995b; Stone 1991; Yonkers 1997) used a placebo run in before women were randomised; those women who responded to this run in were subsequently excluded from randomisation. Heterogeneity was high (I^2 =53%), therefore the studies were analysed separately for absolute and change scores. Seven studies (Cohen 2004 a; Cohen 2004b; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Steiner 1995 a; Yonkers 1997) reported absolute scores: there was evidence of a significant reduction in premenstrual symptoms for women receiving SSRIs (SMD -0.63, 95% CI -0.79 to -0.47; z = 7.83, P < 0.00001, I^2 = 38%). Six studies using placebo run in (Cohen 2002a; Cohen 2002b; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b) reported data using change scores: these also showed evidence of a significant reduction in premenstrual symptomology with (SMD -0.26, 95% CI -0.41 to -0.11; z = 3.42, P = 0.0006, I^2 = 0%) (Figure 8).

Figure 8. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.7 Type of run-in.



Non-placebo run in

Eight studies (Freeman 1999a; Jermain 1999; Ozeren 1997; Sundblad 1993; Veeninga 1990; Wikander 1998a; Wikander 1998b; Wikander 1998c) did not use a placebo run in; all used absolute scores for the measurement of outcome. These studies showed evidence of a reduction in premenstrual symptoms for those women receiving SSRIs (SMD -0.82, 95% CI -1.23 to -0.41; z = 3.90, P = 0.0001, I^2 = 59%). With both placebo and non-placebo run in, the studies showed evidence of a significant reduction in premenstrual symptomology in favour of SSRIs; however, heterogeneity amongst studies using absolute scores remained relatively high and findings should be interpreted with caution (Figure 8).

Continuous versus luteal phase only (intermittent) administration

Continuous

Eleven studies reporting on overall symptom reduction used a continuous dosing regimen (Cohen 2004 a; Cohen 2004b; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Ozeren 1997; Steiner 1995 a; Steiner 1995b; Stone 1991; Veeninga 1990; Yonkers 1997). There was a significant reduction in premenstrual symptomology (SMD -0.72, 95% CI -0.92 to -0.52; z = 7.06, P < 0.00001). Heterogeneity among these studies was 52% (I^2) and some caution may be needed in interpreting the results. All studies reported on outcomes using absolute scores.

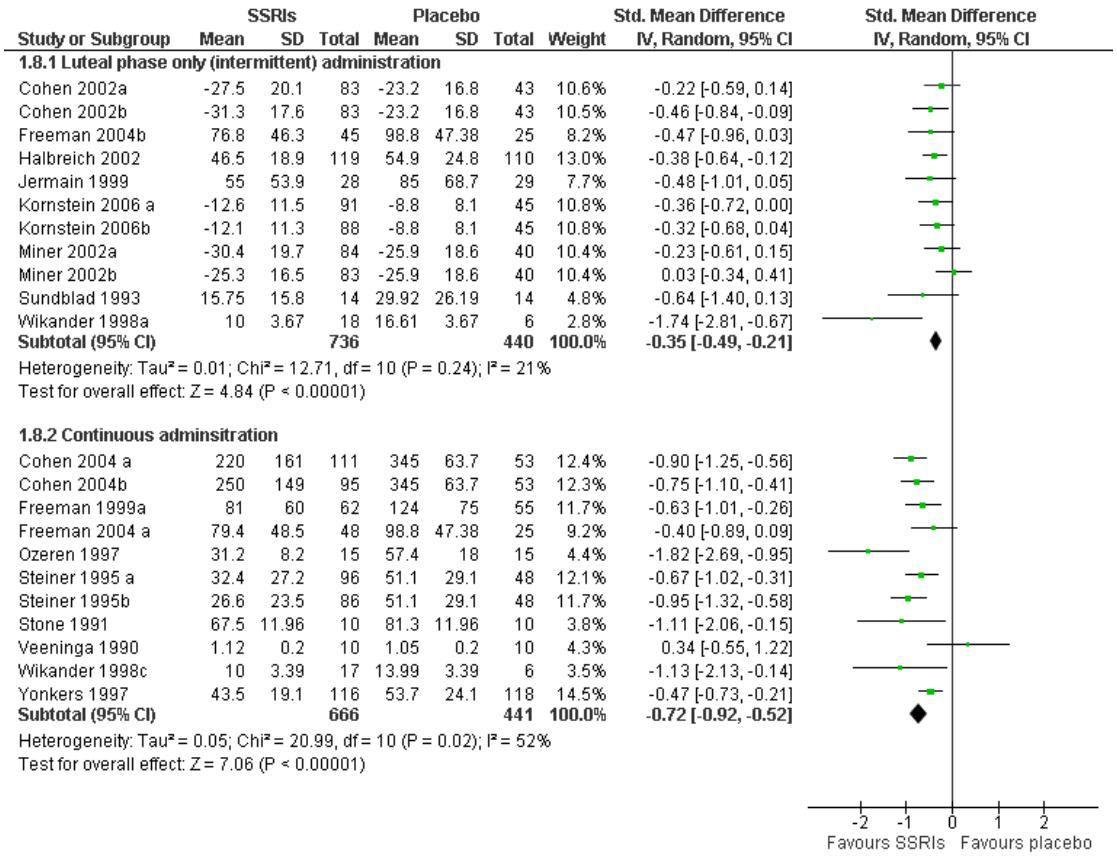
Luteal phase

Twelve of the studies reporting on overall symptom reduction used an intermittent or luteal phase only dosing regimen (Cohen 2002a; Cohen 2002b; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Miner 2002a;

Miner 2002b; Sundblad 1993; Wikander 1998a). There was evidence of a significant reduction in premenstrual symptomology in favour of SSRIs compared with placebo (SMD -0.35, 95% CI -0.49 to -0.21; z = 4.84, P < 0.00001). There was little heterogeneity between the studies (I^2 = 21%).

Both dosing regimens appeared to be effective in symptom reduction when compared to placebo (Figure 9). It is important for physicians to know the relative efficacy of these two regimens. However, only two studies (Freeman 2004 a; Freeman 2004b) directly compared luteal phase only (intermittent) and continuous regimens. Researchers should take this into consideration when designing future studies.

Figure 9. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.8 luteal or continous administration.



High versus low dose

Eight studies compared different doses of drug (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Kornstein 2006 a; Kornstein 2006b; Steiner 1995 a; Steiner 1995b) with placebo. However, different drugs were used and dose comparisons may not be appropriate across such regimens. Therefore the authors looked

at studies for each of the drugs. For fluoxetine, lower doses (10 to 20 mg) were administered in three studies (Cohen 2002a; Cohen 2002b; Steiner 1995 a) (SMD -0.46, 95% CI -0.71 to -0.20; z = 3.53, P = 0.0004, I^2 = 30.6%); and higher doses in three studies (Ozeren 1997; Steiner 1995b; Stone 1991) (SMD -1.19, 95% CI -1.70 to -0.68; z = 4.60, P < 0.00001, I^2 = 38.8%). Comparisons were not possible for other drugs because a range of drug dosages were administered.

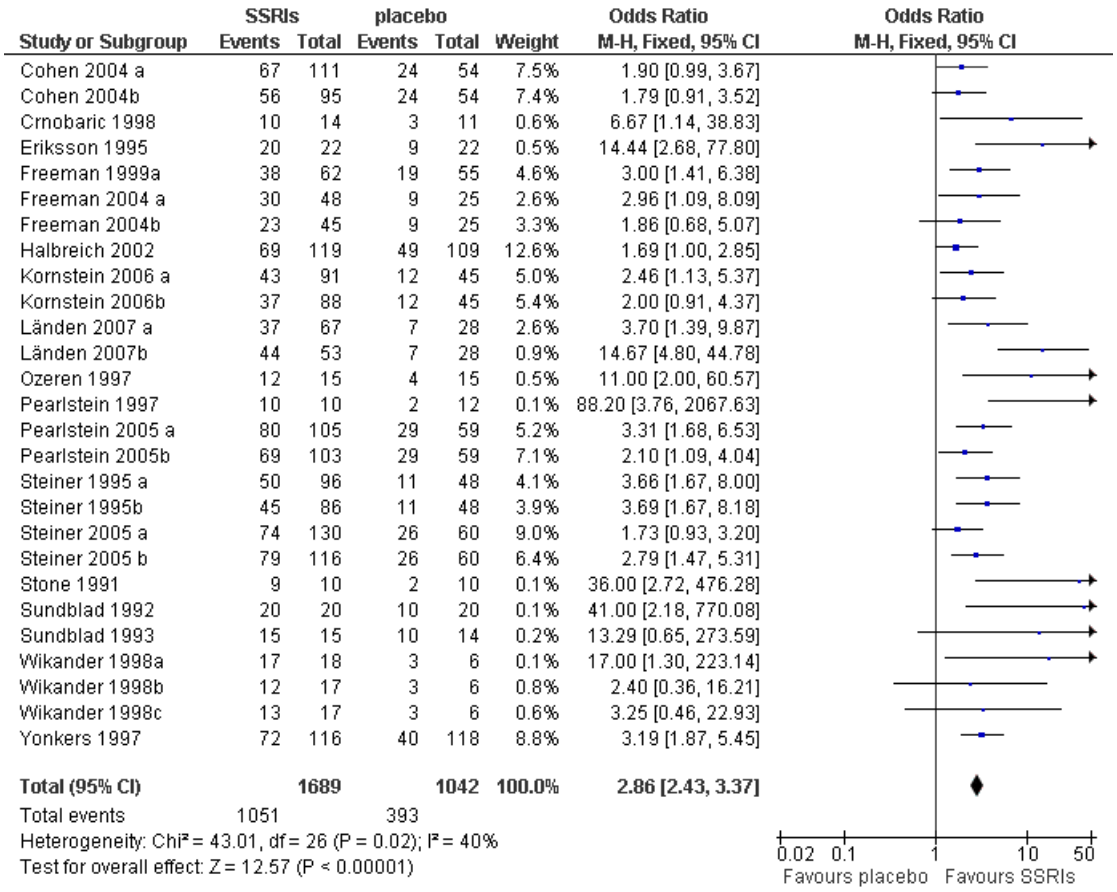
Treatment cycles

The number of treatment cycles varied between two, three, and six cycles. These were examined separately. Of the 10 studies (see section above: Number of treatment cycles) which treated women for two cycles only, four had evaluable data and the SMD was -0.32 (95% CI -0.54 to -0.10; z = 2.38, P = 0.005, I^2 = 0%). Of the 28 studies (see above) that used three cycles, there were evaluable data in 16 studies. Heterogeneity was high (I^2 = 59.9%) and, therefore, data were divided into absolute and change scores. For absolute scores (12 studies) the SMD was -0.69 (95% CI -0.88 to 0.50; Z = 6.98, P<0.0001, I^2 = 50%). The four studies (Cohen 2002a; Cohen 2002b; Miner 2002a; Miner 2002b) which used change scores had an I^2 of 13%, SMD -0.22 (95% CI -0.42 to -0.02; z = 2.2, P = 0.03). Only two of the three studies using six cycles of treatment had evaluable data (Steiner 1995 a; Steiner 1995b) and the SMD was -0.80 (95% CI -1.08 to -0.53; z = 5.70, P < 0.0001, I^2 = 13.7%). Three cycles of treatment appeared to be effective when compared with placebo. No additional benefits appeared to be gained with six cycles of treatment. No studies directly compared the effectiveness of different numbers of cycles of treatment.

Response to treatment

Twenty-seven studies reported this outcome (Cohen 2004 a; Cohen 2004b; Crnobaric 1998; Eriksson 1995; Freeman 1999a; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Ozeren 1997; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2005 a; Steiner 2005 b; Stone 1991; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c; Yonkers 1997). The main outcome measures used in the papers were the Clinical Global Improvement scale and 50% reduction in symptoms as an indicator of improvement. In the treatment groups, 1051 of 1689 participants (62%) were considered to be responders compared to 393 of 1042 women in the placebo groups (38%). The difference was statistically different and was in favour of SSRIs (Figure 10) (OR 2.86, 95% CI 2.43 to 3.37; z = 12.57, P < 0.00001, I^2 = 40%).

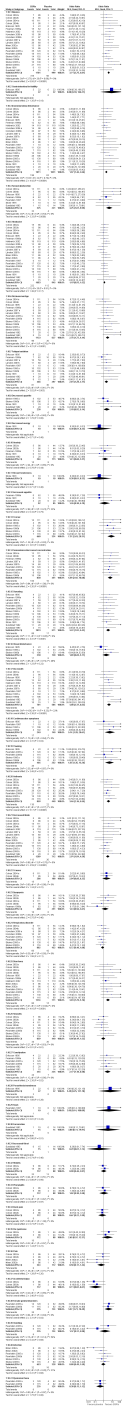
Figure 10. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.9 Response to treatment.



Side effects

Twenty-two of the studies reported on side effects and adverse events (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Eriksson 1995; Freeman 1999a; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Pearlstein 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2005 a; Stone 1991; Sundblad 1992; Sundblad 1993). The most commonly reported side effects were nausea: 316/1781 (18%) for treatment compared with 56/999 (5.6%) for placebo; insomnia 196/1811 (11%) for treatment compared with 62/1031 (6%) for placebo; headache 222/1603 (14%) for treatment compared with 112/945 (12%) for placebo; asthenia 130/859 (15%) for treatment compared to 25/440 (6%) for placebo; decreased libido 113/1289 (9%) for treatment compared to 20/712 (3%) for placebo. Other less frequent side effects reported included dizziness or vertigo, fatigue or sedation, anxiety, tremor, decreased concentration, sweating and dry mouth (Figure 11). There was evidence of a significant increase in the proportion of women treated with SSRIs experiencing side effects when compared with women treated with placebo.

Figure 11. Forest plot of comparison: 1 SSRI versus placebo, outcome: 1.10 Adverse events.



Study withdrawal

Women withdrew or were withdrawn from the studies for a variety of reasons: adverse events or side effects, loss to follow up, protocol violation, lack of efficacy, some other reason not specified. Study withdrawal for any reason ranged from 0% (Crnobaric 1998; Stone 1991; Veeninga 1990) to 42.5% (Steiner 1995 a; Steiner 2005 b). Five of the studies (Halbreich 1997; Menkes 1993; Su 1997; Wood 1992; Young 1998) were crossover trials and it was not possible to ascertain whether attrition occurred before or after crossover. These studies have been excluded from this analysis. Data from Arrendondo 1997 are missing for this outcome. There were 493/2183 (22.5%) withdrawals for the treatment groups and 286/1303 (21.9%) for the placebo groups. There was no evidence of heterogeneity between the studies (I^2 = 0%) and no evidence of a significant difference in the rate of withdrawal for any reason between treatment and placebo groups (OR 1.03, 95% CI 0.87 to 1.22; z = 0.35, P = 0.73). Withdrawal of women due to side effects or adverse events was recorded in 27 studies (Cohen 2002a; Cohen 2002b; Cohen 2004 a; Cohen 2004b; Eriksson 1995; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Kornstein 2006 a; Kornstein 2006b; Länden 2007 a; Länden 2007b; Miner 2002a; Miner 2002b; Ozeren 1997; Pearlstein 2005 a; Pearlstein 2005b; Steiner 1995 a; Steiner 1995b; Steiner 2005 a; Steiner 2005 b; Sundblad 1992; Sundblad 1993; Wikander 1998a; Wikander 1998b; Wikander 1998c; Yonkers 1997). As with withdrawals for any reason, the studies which used a crossover design were excluded from this analysis as it is not possible to identify whether withdrawal occurred prior to or after crossover. There was evidence of a significantly higher number of withdrawals due to side effects and adverse events in the treatment groups (218/2049, 11%) compared to the placebo groups (62/1182, 5%) (OR 2.11, 95% CI 1.58 to 2.03; z = 5.01, P < 0.00001).

DISCUSSION

Summary of main results

A key requirement for PMS diagnosis is that the charts or rating scales are completed prospectively and daily. However, the sheer volume of data which arises from collecting multiple, daily data points has meant that most diagnoses of PMS are made on the woman's own perception of her problem. Studies in PMS have shown that less than half of the women presenting with the complaint of PMS actually have the disorder. In many instances the symptoms are of insufficient severity to fulfil criteria, or the symptoms fail to improve following menstruation and the problem is actually a continuous psychological disorder and not PMS.

All the studies included in this review looked at the effectiveness of SSRIs in the management of clinically diagnosed PMS or PMDD. There are an enormous range of self-reported methods of assessing PMS and so the main outcome measure was a reduction in overall premenstrual symptoms. Combined or overall symptomatology was chosen in an attempt to overcome the clinical heterogeneity concerned with the measurement and scoring of premenstrual symptoms. Correct diagnosis of PMS is essential, as is distinguishing the disorder from an underlying psychiatric disorder, however objective assessment is difficult and it has been estimated that up to 50% of women with reported PMS do not have the disorder (Plouffe 1993).

Overall symptoms

The overall results indicated evidence of a reduction of premenstrual symptoms for women receiving SSRIs when compared with placebo. The overall result was statistically heterogeneous and an analysis of bias was undertaken since heterogeneity may result from bias in the study selection (Egger 1997). Subanalysis by change and absolute scores continued to identify significant differences between SSRIs and placebo in favour of SSRIs reducing premenstrual symptoms. An analysis of the trials funded directly by drug companies versus those with independent funding showed no evidence of funding bias. This subanalysis was undertaken as negative drug company trials may not be released. Indeed, the only negative trial was funded by a drug company (Veeninga 1990). This was a small trial with 10 women in each arm and, unlike the other selected trials data, was not collected on a prospective daily basis but on specific days within the cycle.

A detailed subanalysis of the included trials was undertaken. Consideration of the individual drugs was limited to fluoxetine and sertraline as the remaining drug types were used in a limited number of studies. Fluoxetine was studied in 14 trials and sertraline in 11 trials. Both drug types showed evidence of a favourable response to SSRIs compared to placebo.

Behavioural, physical and functional symptoms

A notable aspect of SSRIs used in PMS treatment is the positive effect on physical, functional and behavioural symptoms. Therapies developed to treat affective disorders such as depression would be expected to impact favourably on behavioural symptoms. However this comparison shows that SSRIs are equally effective in treating physical and functional symptoms.

Placebo run in versus no placebo run in

Clinical trials of PMS treatments have been shown to have unusually large placebo effects (Rubinow 1984), making rigorous controlled trials essential. The proliferation of ineffective treatments for PMS has arisen out of uncontrolled trials with large placebo responses that mask poor treatment responses (O'Brien 1993). To allow for this, several of the trials included in this analysis had a single-blind placebo run-in stage to eliminate placebo responders. As inclusion of placebo responders may over-estimate the efficacy of a particular intervention, a subanalysis of trials with and without placebo run-in protocols was carried out. Trials including placebo run in and those having no placebo run in both showed favourable responses to treatment with SSRIs when absolute and change scores were examined.

Continuous versus luteal phase (intermittent) dosage

The majority of the trials included in this review had continuous dosing regimes, that is a dose taken every day throughout the menstrual cycle. Previous evidence from studies of depression and obsessive compulsive disorder indicate that this is appropriate as SSRIs take four to eight weeks to reach clinical efficacy in these disorders (Freeman 1999a; Wikander 1998a). In PMS, however, it has been shown that SSRIs may become effective in a matter of days and usually within four weeks after the start of treatment (Steiner 1995b). This effect has been postulated to arise from the cyclical nature of PMS and may reflect SSRI action at a different receptor site to that in affective disorders (Sunblad 1997; Wikander 1998a). The rapid efficacy of SSRI treatment in PMS allows the possibility of using intermittent or semi-intermittent dosing regimes to induce a temporary luteal phase enhancement of serotonin levels. Twelve of the trials included in the review (Cohen 2002a; Cohen 2002b; Freeman 2004 a; Freeman 2004b; Halbreich 2002; Jermain 1999; Kornstein 2006 a; Kornstein 2006b; Miner 2002a; Miner 2002b; Sundblad 1993; Wikander 1998a) had non-continuous dosing schedules. As well as obvious savings in prescription costs, the cyclical nature of PMS implies that a targeted dosing schedule centred on the luteal phase of the menstrual cycle may be efficacious. These schedules may also reduce the incidence of side effects from SSRIs, which are often cited as reasons for reluctance to persevere with a course of SSRI medication. Wikander 1998a compared a continuous dosing regime of citalopram with an intermittent and a semi-intermittent dosing regimen and found the intermittent schedule to be the most effective in relieving premenstrual symptoms. The intermittent arm of this trial also had fewer dropouts due to side effects than with the other two regimes.

Duration of treatment

No treatment effect compared with placebo was identified with less than three cycles of treatment. The first indication of benefit of treatment over placebo appears to occur after three treatment cycles. No additional benefit appears to be conferred with six treatment cycles.

High versus low dosages

The trial by Steiner et al in 1995 (Steiner 1995 a; Steiner 1995b) studied both 20 and 60 mg continuous fluoxetine regimes. The 60 mg dose would be considered high when using fluoxetine conventionally to treat affective disorders and is the only trial to use fluoxetine at greater than a 20 mg dose. This one arm of the trial accounted for more than half of all the withdrawals from the treatment group summed over all the trials. It was noted in the original report of the trial that such a high dose may not be appropriate given the efficacy of the lower 20 mg dose. It is also relevant that there are no reports in any of the studies of suicide ideation (a fixation with contemplating suicide), akathisia (irrational restlessness) or self abuse. No ovulation disturbances were reported, which suggests that SSRIs probably do not act directly on ovarian steroid production. Decreased libido (sexual desire) and anorgasmia (inability to attain orgasm) are commonly reported side effects that are associated with SSRIs. This effect may be exacerbated by the reduction in libido which occurs naturally in the luteal phase of the menstrual cycle in some women (Dennerstein 1994). Sexual dysfunction and decreased libido were reported by trials included in this meta-analysis and this confirms the evidence reporting this side effect as a major and persistent complaint in studies using SSRIs for depression (Balon 1993; Shen 1995). However, this observation should be treated with caution because information on side effects affecting sexuality or sex drive may not be systematically recorded and there is a paucity of information on baseline sexual dysfunction in PMS. The responsiveness of PMS symptoms to different SSRI dosing regimes is varied, and it appears that a relatively low dose is needed compared to that required for affective disorders (Eriksson 1995; Sunblad 1997). Reports have shown that individual poor responders did not increase their response with high doses (Steiner 1997b), but the higher dose does increase the incidence of side effects (Steiner 1995 a). Trials monitoring serum SSRI levels found no correlation with response or incidence of side effects. This heterogeneous individual response has also been noted with SSRIs in the treatment of affective disorders (Fredricson Overo 82). SSRIs are unique among affective disorder treatments in avoiding addiction with long-term use. There also appears to be little build up of tolerance in the relatively short-term trials on PMS included in this review. This is in agreement with studies on affective disorders. It may be possible to remove the small reduction in efficacy over time that was noted in two trials (Steiner 1995 a; Wikander 1998a) using intermittent dosing regimes.

The mechanism of action of SSRIs on PMS is unknown, as is the aetiology of PMS. Several relevant studies have indicated a serotonergic disturbance in PMS, including premenstrual serotonin abnormalities (Ashby 1988; Rapkin 1987; Taylor 1984); decreased imipramine platelet binding (Rojansky 1991); luteal phase carbohydrate craving (Both-Orthman 1988); a blunted prolactin response to tryptophan (Bancroft 1991); increased platelet monoamine oxidase activity premenstrually (Rapkin 1988); and

characteristic responses to serotonin agonists buspirone (Rickels 1989) and meta-chlorophenylpiperazine (m-CPP) (Rapkin 1988). PMS has similarities with serotonin-deficient affective disorder symptoms such as depression, anxiety, aggression, appetite disturbance, and irritability (Harrison 1989; Pearlstein 1990; Steiner 1997a). Additionally animal models have demonstrated alterations in neurotransmission and neuroreception with ovarian hormones (Cohen 1988; Ladisich 1977). The serotonin disturbance postulated in PMS appears to be distinct from that in affective disorders such as depression. This is evident, for example, in the time to clinical efficacy after commencement of treatment.

Treatment of premenstrual symptomatology with antidepressants has met with some success but suffers from lower rates of acceptance among patients due to sedating side effects. The three trials comparing an antidepressant with an SSRI (Eriksson 1995; Freeman 1999a; Pearlstein 1997) favour SSRIs overall but the result is close to statistical non-significance. Another trial that compared an SSRI with an antidepressant has been published (Elks 1993) but could not be included in the analysis as it did not have a placebo arm. This comparison illuminates the debate as to whether SSRIs are treating a depressive illness in PMS or treating a serotonin deficiency, possibly induced by sensitivity to ovarian hormones and their metabolites. Diegoli 1998 compared fluoxetine with alprazolam and propranolol and found that fluoxetine was more effective in relieving premenstrual symptoms than alprazolam or propranolol although this did not reach statistical significance. The low quality of this trial meant that it could not be included in the meta analysis (Table of excluded studies).

The acute changes in PMS are different from those in affective disorders such as depression and have been compared to panic disorder and obsessive compulsive disorder, which respond to SSRIs and not to noradrenergic antidepressants. This is similar to PMS. A range of side effects were noted in the trials. The most commonly reported side effects in the drug group were nausea, insomnia, headache and asthenia. There was evidence of a significantly higher incidence of side effects in the drug group compared with the placebo group although withdrawals from the trials were similar in the two groups.

Most women suffering from premenstrual symptoms can be effectively and satisfactorily treated using conservative therapies such as lifestyle changes, cognitive behavioural therapy, exercise or dietary regulation. However, a minority will experience such severe premenstrual symptoms that their life is significantly disrupted and these women require pharmacological intervention.

As remission rates are low upon cessation of treatment (Pearlstein 1994; Sunblad 1997) and PMS can be expected to last until the menopause, the intervention must be effective, safe for long-term use and relatively free from side effects. SSRIs, as shown in this meta-analysis, are effective in the treatment of severe PMS. Their long-term safety has already been demonstrated in studies on affective disorders.

The side effects encountered at low doses are often manageable and may be significantly reduced or eliminated by intermittent or semi-intermittent dosing regimes. This makes SSRIs an effective and potentially acceptable first-line treatment for severe PMS.

Overall completeness and applicability of evidence

The authors have tried to ensure the completeness of evidence by obtaining data from a wide range of sources. The data appear to be applicable to the target population.

Quality of the evidence

Only four of the studies demonstrated evidence of acceptable allocation concealment; evidence pertaining to blinding was lacking in many studies. Future research in this area needs to focus on the quality of study design.

Potential biases in the review process

The authors are unaware of any biases in the review process; all conflicts of interest have been declared.

Agreements and disagreements with other studies or reviews: this update concurs with the previous review.

AUTHORS' CONCLUSIONS

Implications for practice

Mild physiological premenstrual symptoms occur in 95% of women of reproductive age. However, for about 5% of women, symptoms are so severe that their lives are completely disrupted during the second half of their cycle; many of these women require pharmacological management. This meta-analysis has demonstrated the efficacy of selective serotonin reuptake inhibitors in managing severe premenstrual symptoms. We believe that this makes an SSRI an effective and potentially acceptable first-line treatment for severe PMS.

There is now very convincing evidence to support the use of SSRIs in PMS. This review also suggests that both luteal phase only and continuous dosing regimes are effective in reducing symptoms.

Implications for research

Future research should be aimed at direct comparisons between luteal phase only and continuous dosing regimes and also further investigation into safety issues and adverse events.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arrendondo 1997

Methods	Randomised, double blind, placebo controlled, parallel two arm trial
Participants	Country: USA Site: No details Recruitment: 72 women no other details. Refer to Table of bias for details of attrition. Inclusion: Meeting defined criteria for PMS using Penn Daily Self Rating Symptoms. (DSR) for two cycles. Regular menstrual cycles (22-35 days), general good health. No current major psychiatric diagnoses as assessed by Structured Clinical Interview (SCID) No explicit exclusion criteria noted.
Interventions	Screening: Screening for two cycles Placebo run in: None Interventions: Placebo (n=35) versus sertraline 50mg administered orally (n=37) Duration: Treatment administered for three cycles. Timing of administration: No details of when in the cycle this was first administered Summary measures: Data presented as individual treatment cycles. Review has used mean data across all three cycles
Outcomes	Penn Daily Self Rating Symptoms. (DSR)
Notes	Daily recording of symptoms. Measured depression and food cravings No details of ITT or power calculation No details of funding source

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	States randomised. No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	Double blind. No details
Incomplete outcome data addressed? All outcomes	Unclear	772 women randomised, no further details
Free of selective reporting?	Yes	

Cohen 2002a

Methods	Randomised, double blind, placebo controlled, 3 arm parallel study. Cohen 2002b describes fluoxetine 20mg versus placebo
Participants	Country:USA Site: Multicentre (19 investigators at 20 sites). Recruitment: 1276 women screened for study (Cohen 2002 a,b) 86 randomised to fluoxetine 10mg (77 completed), 88 randomised to placebo (75 completed) Mean age placebo group 35.6±4.9 years, fluoxetine 10mg group 37.2±5.1 years, fluoxetine 20mg group 35.1±5.3 years Inclusion: 18 to 45 years, regular menstrual cycles (23 to 35 days). two consecutive cycles in which scores averaged 3.0 or more each for five of the eleven DRSP items during the luteal phase, and their scores averaged 2.5 or less for each of the same items during the follicular week; and if they showed 50% or more increase from follicular to luteal scores for these items; and if at least twice during the defined luteal period, they had scores of 4 or more on any of the three functional items Exclusion: Having Axis 1 disorder other than PMDD, History of Axis 1 pathology occurring within the past six months (exception of specific phobias), women using hormonal contraception
Interventions	Screening: Two screening cycles Placebo run in: One cycle single blind placebo run-in Interventions: Fluoxetine 10mg administered orally daily during the luteal phase for three cycles(n=86) versus placebo administered orally daily during the luteal phase for three cycles. (n=88) followed by one cycle single blind placebo run out Duration: Three cycles of treatment. Timing of administration: Medication administered 14 days before the expected date of the next menses and until the first day of active bleeding Summary measures: For change scores no details as to whether this is an average over treatment or endpoint score. For absolute scores data presented for baseline and three cycles of treatment. Review authors calculated average over the three cycles presented
Outcomes	Hand held electronic diary used to record Daily Record of Severity of Problems (DRSP) - self rated Rating Scale for Premenstrual Tension - Clinician rated Adverse events Arizona Sexual Experience Scale
Notes	Daily recording of symptoms luteal score calculated using scores from the five most symptomatic days occurring from six days before menses to the first day of menses Funded by Eli-Lilly

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer randomisation stratified by investigative site
Allocation concealment?	Unclear	No details

Cohen 2002a (*Continued*)

Blinding? All outcomes	Unclear	Double blind, no details
Incomplete outcome data addressed? All outcomes	Yes	In total Cohen 2002a,b screened 1276 women and 260 were randomised to three arms. Fluoxetine 10mg was allocated 86 subjects, nine of which discontinued (2 adverse events, 1 lack of efficacy, 2 patient decision, 5 protocol requirement) 77 completed the trial. Of the eight eight women allocated to placebo thirteen discontinued (1 adverse event, 3 lack of efficacy, 3 patient decision, 1 physician decision, 2 protocol requirement, and three lost to follow up
Free of selective reporting?	Yes	

Cohen 2002b

Methods	Randomised, double blind placebo controlled 3 arm parallel study. Cohen 2002a describes fluoxetine 10 mg versus placebo
Participants	Country: USA Site: Multicentre (19 investigators at 20 sites). Recruitment: 1276 women screened for study (Cohen 2002 a,b) 86 randomised to fluoxetine 20mg (64 completed), 88 randomised to placebo (75 completed) Inclusion: 18 to 45 years, regular menstrual cycles (23 to 35 days). two consecutive cycles in which scores averaged 3.0 or more each for five of the eleven DRSP items during the luteal phase, and their scores averaged 2.5 or less for each of the same items during the follicular week; and if they showed 50% or more increase from follicular to luteal scores for these items; and if at least twice during the defined luteal period, they had scores of 4 or more on any of the three functional items Exclusion: Having Axis 1 disorder other than PMDD, History of Axis 1 pathology occurring within the past six months (exception of specific phobias), women using hormonal contraception
Interventions	Screening: Two screening cycles Placebo run in: One cycle single blind placebo run-in Intervention: Fluoxetine 20mg administered orally daily during the luteal phase for three cycles.(n=86)Versus placebo administered orally daily during the luteal phase for three cycles.(n=88)followed by one cycle single blind placebo run out Duration: Three cycles of treatment. Timing of administration: Medication administered 14 days before the expected date of the next menses and until the first day of active bleeding Summary measures: For change scores no details as to whether this is an average over treatment or endpoint score. For absolute scores data presented for baseline and three cycles of treatment. Review authors calculated average over the three cycles presented

Cohen 2002b (*Continued*)

Outcomes	Hand held electronic diary used to record Daily Record of Severity of Problems (DRSP) - self rated Rating Scale for Premenstrual Tension - Clinician ratedAdverse eventsArizona Sexual Experience Scale
Notes	Daily recording of symptoms luteal score calculated using scores from the five most symptomatic days occurring from six days before menses to the first day of menses Funded by Eli-Lilly

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer randomisation stratified by investigative site
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	Double blind, no details
Incomplete outcome data addressed? All outcomes	Unclear	Of the eight six women allocated to fluoxetine 20mg twenty two discontinued (4 adverse events, 2 lack of efficacy, 5 patient decision, 1 physician decision, 3 protocol requirement and 7 loss to follow up). Of the eight eight women allocated to placebo thirteen discontinued (1 adverse event, 3 lack of efficacy, 3 patient decision, 1 physician decision, 2 protocol requirement, and three lost to follow up
Free of selective reporting?	Yes	

Cohen 2004 a

Methods	Randomised, double blind, placebo controlled, 3 arm parallel study. Cohen 2004 b describes 12.5 mg dosage arm
Participants	Country: USA and Canada Site: Multicentre. Recruited from 43 outpatient centres. Recruitment: 1751 women screened 327 randomised. Paroxetine 25mg 113 randomised 111 analysed, placebo 55 randomised 54 analysed. (Data for the 12.5mg paroxetine group is reported in Cohen 2004b). Refer to Table of bias for details of attrition Inclusion: Women aged 18-45 years with regular menstrual cycles (22 to 35 days) meeting diagnostic criteria for PMDD using DSM-IV. Having symptoms of PMDD in at least 9 of 12 menstrual cycles over previous year. Onset of severe symptoms in the luteal phase subsided in the follicular phase on the four core symptoms of PMDD. Required to show a 200% worsening on one core symptom or a 100% worsening on two or more

Cohen 2004 a (*Continued*)

	core symptoms during the luteal phase relative to their follicular phase score. A baseline Clinical Global Impression severity of illness (CGI-S) score of >/3 Exclusion: Presence of a primary psychiatric disorder (Axis 1 using DSM-IV) except specific phobias in the previous 6 months; gynaecological or other clinically significant diseases, significant depressive symptoms during the follicular phase or current use of medication for PMDD symptoms
Interventions	Screening: Two reference cycle for screening Placebo run in: Single blind placebo for one cycle. An additional cycle was available to patient who met all entry criteria before the first reference cycle but failed to achieve the predefined severity of core PMDD symptoms after a period of symptom tracking Interventions: Paroxetine CR 25mg (n=113), versus placebo (n=111) for three treatment cycles administered daily Duration: Three treatment cycles. Timing of administration: Study visits began within the first three days of menses Summary measures: Data was based on the study end point using the LOCF
Outcomes	Patient rated VAS- Mood (irritability, tension, depressed mood and affective lability); Clinical Global Impression of Severity (CGI-S); Clinical Global Impression of disease Improvement (CGI-I); Patient rated Sheehan Disability Scale (SDS); Adverse events
Notes	Symptoms rated daily No details of funding source

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation code
Allocation concealment?	Unclear	B- unclear
Blinding? All outcomes	Yes	Double blind (participants, those administering the study and those assessing outcomes)
Incomplete outcome data addressed? All outcomes	Yes	327 women randomised, 25 women allocated to paroxetine 12.5mg did not complete the study (9 adverse events, 3 protocol deviation, 3 lost to follow up, 6 other reason, 4 lack of efficacy), 39 paroxetine 25mg did not complete the trial (15 adverse event, 10 protocol violation, 7 loss to follow up, 6 other reason, 1 lack of efficacy); 28 placebo did not complete trial (7 adverse events, 7 protocol deviations, 5 loss to follow up, 4 other reason, 5 lack of efficacy)

Cohen 2004 a (*Continued*)

Free of selective reporting?	Yes	

Cohen 2004b

Methods	Randomised, double blind placebo controlled 3 arm parallel study. Cohen 2004 a describes 25 mg dosage arm
Participants	Country: USA and Canada Site: Multicentre. Recruited from 43 outpatient centres. Recruitment: 1751 women screened 327 randomised. Paroxetine 12.5mg 103 randomised 95 analysed, placebo 56 randomised 53 analysed. (Data for the 25mg paroxetine group is reported in Cohen 2004a). Refer to Table of bias for details of attrition Inclusion: Women aged 18-45 years with regular menstrual cycles (22 to 35 days) meeting diagnostic criteria for PMDD using DSM-IV. Having symptoms of PMDD in at least 9 of 12 menstrual cycles over previous year. Onset of severe symptoms in the luteal phase subsided in the follicular phase on the four core symptoms of PMDD. Required to show a 200% worsening on one core symptom or a 100% worsening on two or more core symptoms during the luteal phase relative to their follicular phase score. A baseline Clinical Global Impression severity of illness (CGI-S) score of >/3 Exclusion: Presence of a primary psychiatric disorder (Axis 1 using DSM-IV) except specific phobias in the previous 6 months; gynaecological or other clinically significant diseases, significant depressive symptoms during the follicular phase or current use of medication for PMDD symptoms
Interventions	Screening: Two reference cycle for screening Placebo run in: Single blind placebo for one cycle. An additional cycle was available to patient who met all entry criteria before the first reference cycle but failed to achieve the predefined severity of core PMDD symptoms after a period of symptom tracking Interventions: Paroxetine CR 12.5mg (n=103), versus placebo (n=111) for three treatment cycles administered daily Duration: Three treatment cycles. Timing of administration: Study visits began within the first three days of menses Summary measures: Data was based on the study end point using the LOCF
Outcomes	Patient rated VAS- Mood (irritability, tension, depressed mood and affective lability); Clinical Global Impression of Severity (CGI-S); Clinical Global Impression of disease Improvement (CGI-I); Patient rated Sheehan Disability Scale (SDS); Adverse events
Notes	Symptoms rated daily No details of funding source

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation code

Cohen 2004b (*Continued*)

Allocation concealment?	Unclear	B- unclear
Blinding? All outcomes	Yes	Double blind (Participants, those administering the study and those assessing outcomes)
Incomplete outcome data addressed? All outcomes	Yes	327 women randomised, 25 women allocated to Paroxetine 12.5mg did not complete the study (9 adverse events, 3 protocol deviation, 3 lost to follow up, 6 other reason, 4 lack of efficacy), 39 Paroxetine 25mg did not complete the trial (15 adverse event, 10 protocol violation, 7 loss to follow up, 6 other reason, 1 lack of efficacy); 28 placebo did not complete trial (7 adverse events, 7 protocol deviations, 5 loss to follow up, 4 other reason, 5 lack of efficacy)
Free of selective reporting?	Yes	

Crnobaric 1998

Methods	Randomised, double blind, placebo controlled, parallel study
Participants	Country: Yugoslavia. Site: No details in abstract Recruitment: 25 women randomised. Age 18-40 years (mean 29.5). See Table of bias for details of attrition Inclusion: Aged 18 to 40 with regular menstrual cycles. Meeting DSM-IV criteria for PMDD Exclusion:- Current history of major depressive disorder, current mental disorder
Interventions	Screening:Two cycle screening Placebo run in: None Interventions: Fluoxetine 20mg (n=14) versus placebo (n=11) taken daily Duration: Two cycles of treatment. Timing of administration: No details as to when in the cycle medication was commenced Summary measures: No details as to whether the data was the mean of two treatment cycles or the last cycle data
Outcomes	Clinical Global Impression Scale (CGI); Hamilton Rating Scale of Depression (HAM-D); Calender of Premenstrual Experience (COPE)
Notes	No details of funding source
Risk of bias	

Crnobaric 1998 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	States randomised. No details
Allocation concealment?	Unclear	B unclear
Blinding? All outcomes	Unclear	Double blind no details
Incomplete outcome data addressed? All outcomes	Yes	25 women randomised. No attrition
Free of selective reporting?	Yes	

Eriksson 1995

Methods	Randomised, double blind, placebo controlled, 3 parallel arms (paroxetine vs maprotiline vs placebo) study
Participants	Country: Sweden Site: No details. Recruitment: Recruited via newspaper advertisements followed by telephone and then structured interview. 171 women recruited, 81 randomised, 65 completed (22 paroxetine, 21 maprotiline (not reported on in this review), 22 placebo). Refer to Table of bias for details of attrition. Mean age 37.5 years Inclusion: Marked irritability and/or depressed mood starting regularly around ovulation or during two weeks preceding menstrual bleeding and terminating within a few days of onset of menstruation. Meeting DSM-III-R criteria for LLPDD. Increase of over 100% in either irritability or depressed mood (or both) during the premenstrual phase as compared to the postmenstrual phase, mean premenstrual irritability rating or depressed mood exceeding 20mm Exclusion: Previous or ongoing psychiatric illness, ongoing major depressive disorder or dysthymic disorder, major depressive disorder or dysthymic disorder less than 2 years from time of interview,ongoing medication for somatic or psychiatric illness (excluding casual analgesics), use of oral contraceptives, ongoing alcohol abuse, ongoing or planned pregnancy, under 18 years of age, previous treatment with antidepressants for premenstrual complaints
Interventions	Screening:Two screening cycles Placebo run in: None Intervention: 10-30mg paroxetine every day for 3 cycles (n=27) versus Placebo (n=26) Duration: Three cycles of medication. Timing of administration: Treatment started on the first day of menstruation Summary measures: Medians presented for three treatment cycles
Outcomes	Visual analogue scales (VAS); Self reported global assessment of improvement (Enormously improved to enormously deteriorated); Adverse events

Eriksson 1995 (*Continued*)

Notes	Daily symptom rating Funding from Swedish Medical Research Council, NovoNordisk and Ciba AB, Sweden

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	States randomised. No details
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Double blind (patients and investigators unaware of allocation until end of study)
Incomplete outcome data addressed? All outcomes	Yes	171 recruited. 81 randomised to three arms (two of which used in analysis here). Paroxetine n=27 lost five subjects during the study, three because of side effects, one due to pregnancy and one because of irregular menstruations. Placebo n= 26 lost four women during the study, two due to side effects, one due to onset of another illness and one due to protocol violation
Free of selective reporting?	Yes	

Freeman 1999a

Methods	Randomised, double blind placebo controlled, 3 arm parallel trial. (sertraline vs desipramine vs placebo). Only sertraline and placebo reported in this review
Participants	Country: USA Site: Premenstrual Syndrome Program, University of Pennsylvania, Philadelphia Recruitment: 278 eligible women. 189 randomised, 167 analysed 131 completed. Refer to Table of bias for details of attrition Inclusion: 18-45 years, regular menstrual cycles (22-35 days), ovulating, experiencing distressing premenstrual symptoms for at least six months, reporting moderate to severe impairment in work, family life or social activity on subject global ratings, meeting PMS criteria on DSR ratings, good health, no major psychiatric (DSM-IV) diagnosis within past year Exclusion: use of psychotropic drugs that could not be discontinued during the study period, all other prescription and non prescriptions drugs for PMS, pregnancy, lactation, hysterectomy, symptomatic endometriosis, irregular menstrual cycles, not using medically approved contraception, serious health problems, any major axis 1 psychiatric diagnosis, including major depression , current or within the past year, risk of suicide and alcohol or drug abuse within the past year

Freeman 1999a (*Continued*)

Interventions	Placebo run in: None Intervention: 50mg -150mg sertraline administered orally during luteal phase only (average 105mg) for 3 cycles versus placebo administered orally for 3 cycles Timing of administration: Drug commenced on day 1 of the menstrual cycle Summary measures: Data for LOCF for all patients with treatment data and also for all completers
Outcomes	Daily Symptom Report, Hamilton Scale for Depression, Clinical Global Impression Scale
Notes	Daily symptom rating Drug provided by Pfizer Inc NY, Funding from National Institute of child health and human development

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised via computer generated number tables
Allocation concealment?	Yes	A - Adequate. Allocation by a technician with no clinical contact
Blinding? All outcomes	Yes	Double blind, medication prepared in pharmacy in identical capsules
Incomplete outcome data addressed? All outcomes	Yes	Of the one hundred and eighty nine women randomised, twenty two dropped out immediately leaving 167 for analysis. 13/66 dropped out of the sertraline group and 15/59 from the placebo group
Free of selective reporting?	Yes	

Freeman 2004 a

Methods	Randomised double blind placebo controlled 3 arm parallel study (continuous, intermittent dosing and placebo) see Freeman 2004b for intermittent comparison
Participants	Country: USA Site: University based Premenstrual Syndrome Program. Recruitment: Women requesting treatment for premenstrual syndrome were screened (n=555) in full study (Freeman a,b). One hundred and sixty seven randomised 56 to continuous and 40 completed; 55 to placebo and 43 completed. Refer to Table of bias for details of attrition.Mean age continuous dosing 34.5±6.2, placebo group 33.4±6.5 years

	Inclusion: Age 18-45 years, regular menstrual cycles of 22-35 days, positive urine test for ovulation, persistent premenstrual symptoms for at least 6 months, global report of at least moderate to severe impairment in work, family life or social activity; general good health; no major psychiatric diagnosis within past year, meeting stated PMS criteria based on prospective daily rating of symptoms. Required a total premenstrual Daily Symptom Rating Score >/80 and an increase of >/50% over the postmenstrual score for the mean of the three screen cycles and for the single blind placebo cycle Exclusion: Any major Axis 1 psychiatric diagnosis, including major depression, currently or within previous year as assessed by SCID; use of psychotropic medications that could not be discontinued for the duration of the study, use of any prescription, non-prescription, herbal or other therapies for PMS, pregnancy, lactation, hysterectomy, symptomatic endometriosis, irregular menstrual cycles, not using medically approved contraception, serious health problems, suicide risk, alcohol or drug abuse within the past year
Interventions	Screening: Two screening cycles Placebo run in: One single blind placebo run in cycle. Interventions: 50 -100mg of sertraline taken throughout cycle orally (n=56) (mean dosage during trial was 75mg/day +/-25) for three cycles versus placebo taken orally (n= 55) for three cycles. In the absence of improvement dose could be increased to 100mg sertraline or 2 tablets (sertraline or placebo) Timing of administration: Bottle A started on Day 3 of menses, switching to bottle B at 14 days before the expected date of menses and continuing through day 2 of menses Summary measures: Data is presented as end of treatment, LOCF, mean values
Outcomes	Daily Symptom Rating Form Subject Global Ratings of Functioning
Notes	Women had PMS as well as PMDD Daily symptom rating Funding: National Institute of child health and human development. Drugs provided by Pfizer, inc

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation using random number tables
Allocation concealment?	Yes	A- clear. Allocation conducted by a technician at the beginning of the study with no clinical contact
Blinding? All outcomes	Yes	Double blind, medication identical and taken from Bottle A and Bottle B on the same day of the menstrual cycle whatever the allocation

Freeman 2004 a (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	555 women screened. One hundred and sixty seven randomised; fifty six to continuous dosing, sixteen discontinued (adverse event = 7, withdrawn consent = 4, medical problem =2, non -compliance =1, loss to follow up = 2. Fifty six were randomised to intermittent dosing, twenty one were discontinued (adverse event =5, lack of efficacy =2, withdrawn consent = 8, medical problem =2, non-compliance = 1, loss to follow up = 3), Fifty five randomised to placebo, twelve discontinued (adverse event =1, lack of efficacy =1, withdrawal of consent =5, noncompliance = 2, loss to follow-up = 3)
Free of selective reporting?	Yes	

Freeman 2004b

Methods	Randomised double blind placebo controlled 3 arm parallel study (continuous, intermittent dosing and placebo) see Freeman 2004a for intermittent comparison
Participants	Country: USA Site: University based Premenstrual Syndrome Program. Recruitment: Women requesting treatment for premenstrual syndrome were screened (n=555) in full study (Freeman a,b). One hundred and sixty seven randomised 56 to intermittent and 35 completed; 55 to placebo and 43 completed. Refer to Table of bias for details of attrition.Mean age intermittent dose group 32.9+/-6.4, placebo group 33.4+/-6.5 years Inclusion: Age 18-45 years, regular menstrual cycles of 22-35 days, positive urine test for ovulation, persistent premenstrual symptoms for at least 6 months, global report of at least moderate to severe impairment in work, family life or social activity; general good health; no major psychiatric diagnosis within past year, meeting stated PMS criteria based on prospective daily rating of symptoms. Required a total premenstrual Daily Symptom Rating Score >80 and an increase of >50% over the postmenstrual score for the mean of the three screen cycles and for the single blind placebo cycle Exclusion: Any major Axis 1 psychiatric diagnosis, including major depression, currently or within previous year as assessed by SCID; use of psychotropic medications that could not be discontinued for the duration of the study, use of any prescription, non-prescription, herbal or other therapies for PMS, pregnancy, lactation, hysterectomy, symptomatic endometriosis, irregular menstrual cycles, not using medically approved contraception, serious health problems, suicide risk, alcohol or drug abuse within the past year
Interventions	Screening: Two screening cycles followed by one single blind placebo run in cycle Placebo run in: Placebo taken from day 3 of menses to 14 days before expected onset of menses Intervention: 50mg sertraline taken orally until day 2 menses (n=56) for three cycles

Freeman 2004b (*Continued*)

	versus placebo taken orally throughout cycle (n=55) for three cycles. In the absence of improvement dose could be increased to 100mg sertraline or 2 tablets (sertraline or placebo) Timing of administration: Bottle A started on Day 3 of menses, switching to bottle B at 14 days before the expected date of menses and continuing through day 2 of menses Summary measures: Data is presented as end of treatment, LOCF, mean values
Outcomes	Daily Symptom Rating Form Subject Global Ratings of Functioning
Notes	Women had PMS as well as PMDD Daily symptom rating Funding: National Institute of child health and human development. Drugs provided by Pfizer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation using random number tables
Allocation concealment?	Yes	A - Clear. Allocation conducted by a technician at the beginning of the study with no clinical contact
Blinding? All outcomes	Yes	Double blind, medication identical and taken from Bottle A and Bottle B on the same day of the menstrual cycle whatever the allocation
Incomplete outcome data addressed? All outcomes	Yes	555 women screened. One hundred and sixty seven randomised; fifty six to continuous dosing, sixteen discontinued (adverse event = 7, withdrawn consent = 4, medical problem =2, non -compliance =1, loss to follow up = 2. Fifty six were randomised to intermittent dosing, twenty one were discontinued (adverse event =5, lack of efficacy =2, withdrawn consent = 8, medical problem =2, non-compliance = 1, loss to follow up = 3), Fifty five randomised to placebo, twelve discontinued (adverse event =1, lack of efficacy =1, withdrawal of consent =5, noncompliance = 2, loss to follow-up = 3)
Free of selective reporting?	Yes	

Halbreich 1997

Methods	Crossover trial 2X2 cycles
Participants	Country: USA Site: Not stated. Recruitment: Women recruited by advertisement in local newspapers and posted notices. Over 60 screened by structured telephone interview, 32 women interviewed, Twenty seven eligible for study; fifteen entered single blind phase. 11 were randomised, 8 completed. Refer to Table of bias for details of attrition Inclusion: Age 24 to 45 years, regular menstrual cycles (25 to 34 days), not meeting criteria for DSM-IV major diagnoses for at least 6 months, meeting DSM-IV criteria for PMDD and criteria for dysphoric PMS. Physically healthy and not taking any medications. Confirmed PMDD symptoms during late luteal phase and no symptoms during mid follicular phase
Interventions	Screening: Two screening cycles. Placebo run in : Single blind drug run in Intervention: 100mg sertraline orally for 2 cycles versus placebo orally for 2cycles luteal phase only Timing of administration: Intervention administered fourteen days before expected onset of menses or for full cycle, unclear as to which day commenced Summary measures: Data from both arms pooled.
Outcomes	Clinical Global Impression - Improvement Scale (CGI-I)Hamilton Rating Scale for Depression (HAM-D)modified Daily Rating Form (DRF)
Notes	Only responders to drug randomised. Symptoms rated daily Funded by Pfizer

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Only responders to drug randomised.States randomised. No details
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Double blind, no details
Incomplete outcome data addressed? All outcomes	Yes	Over 60 screened, 32 women interviewed, Twenty seven eligible for study; fifteen entered single blind phase. 11 were randomised, 8 completed. 2 withdrawals due to side effects, both on placebo. Unclear which arm this was from
Free of selective reporting?	Yes	

Halbreich 2002

Methods	Randomised, double blind, 2 arm parallel study.
Participants	Country: USA and Canada Site: Multicentre study in 14 psychiatric and gynaecological outpatient clinics Recruitment: 907 screened, 281 women randomised and 221 completed study. Refer to Table of bias for details of attrition.Women recruited by advertisements in media and by referrals.Mean age 35.9+/-5.4 and 36.5+/-4.8 years Inclusion: Age 24 to 45 years, regular menstrual cycles (24 to 36 days), two year self reported history of PMDD, meeting DSM-IV criteria for PMDD based on 2 cycles prospective screening using DRSP. Mean luteal phase score during 5 most symptomatic days to be at least 75% higher than mean mid follicular phase score. Also a marked level of functional impairment for a minimum of 2 premenstrual days. Required to have at least one of the following symptoms rated as moderate or greater in severity for at least two days during the late luteal phase: depression, irritability, anxiety/tension, or mood lability as well as at least four additional DSM-IV criterion symptoms of PMDD Exclusion: Follicular phase Hamilton Rating Scale of Depression score >10, use of oral contraceptives or other hormonal preparations within 2 months before screening, current or lifetime diagnosis of psychiatric disorder, current (or past 6 month) of major depressive disorder (other than PMDD), panic disorder, generalised anxiety disorder, posttraumatic stress disorder or eating disorder, > 38 years having luteinizing hormone levels >38U/L or follicle stimulating hormone levels > 20U/L, hysterectomy or failure to demonstrate ovulation in screening cycles, failure to respond to two or more adequate trials of antidepressants to treat their PMDD, current use of psychotropic medication
Interventions	Screening: Two screening cycles Placebo run in: One cycle single blind placebo run in Intervention: Sertraline 50-100mg given orally for 3 cycles during luteal phase only (n= 142) VERSUS placebo given orally for 3 cycles during luteal phase (n=139) Timing of administration: Based on an algorithm of individual cycle length. Women with twenty eight day cycle had first dose on day fourteen before onset of menses Summary measures: Data based on LOCF data.
Outcomes	Hamilton Rating Scale for Depression (HRS-D); Daily Record Severity of Problems (DRSP); Clinical Global Impression Severity scale (CGI-S); Clinical Global Impression Improvement scale (CGI-I); Patient Global Evaluation; Social Adjustment scale (SES); Quality of Life Enjoyment and Satisfaction Questionnaire
Notes	Daily symptom rating Direct expenses funded by Pfizer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation
Allocation concealment?	Unclear	B- unclear

Halbreich 2002 (*Continued*)

Blinding? All outcomes	Yes	identical medication in blister packs containing placebo or sertraline, Double blind, no details
Incomplete outcome data addressed? All outcomes	Yes	907 women were screened, 281 completed the single blind placebo run in and randomised. Twenty seven withdrew from sertraline group (protocol violation =3, lost to follow up/ other reason = 13, adverse events = 11) and thirty three form the placebo group (insufficient clinical response = 4, protocol violation =7, lost to follow up / other reason = 21 and adverse events = 1)
Free of selective reporting?	Yes	

Jermain 1999

Methods	Randomised, double blind, crossover trial.
Participants	Country: USA Site: Research centre in large multi-speciality clinic. Recruitment: Women recruited via advertisements and from referral from affiliated psychiatric and gynaecological clinics.189 women screened, of these 57 had increases in COPE score to be randomised.57 randomised, 40 completed. Refer to Table of bias for details of attrition.Mean age Sertraline first arm 35±7 (25-47) years, Placebo first arm 38±5 (23-48) years Inclusion: women aged 19 to 49 years with regular menstrual cycles (23 to 35 days) meeting DSM -IV criteria for PMDD. Pre treatment luteal phase score (using COPE) >41 and double follicular phase score for two consecutive menstrual cycles. Follicular phase score < 40 and follicular to luteal phase increase to increase by 30% for at least five pre menstrual symptoms Exclusion: Current Axis 1 disorder, pregnant, significant medical or gynaecologic disorders, taking psychotropic drugs or hormonal medications including the oral contraceptive
Interventions	Screening:Two cycles Placebo run in: None Intervention:Two cycles treatment with 50mg sertraline luteal phase only increasing to 100mg for non-improvers versus placebo followed by crossover for two cycles. No washout Timing of administration: Drug was commenced fourteen days before the expected onset of menses and discontinued when menses began Summary data: Data was summarised for luteal phase as a sum of the last seven days of the cycle and averaged over two cycles in the paper. No details of average drug received
Outcomes	Calendar of Premenstrual Experiences (COPE) patient rated daily assessment; Beck Depression Inventory (BDI) patient rated; Adverse events

Jermain 1999 (*Continued*)

Notes	Some data such as adverse events and BDI was not extractable from the first arm of the crossover Funded by Pfizer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	States randomised. No details
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Double blind (no details)
Incomplete outcome data addressed? All outcomes	Yes	189 screened, 57 were randomised. Seventeen patients withdrew in total from the study. Thirteen in the first arm. Five from placebo and nine from sertraline group
Free of selective reporting?	Yes	

Kornstein 2006 a

Methods	Randomised double blind placebo controlled 3 arm study with parallel groups
Participants	Country: USA Site: Conducted in 22 psychiatric and gynaecological outpatient clinics in the US Recruitment: Women recruited through advertisements in the media. Refer to Table of bias for details of attrition Inclusion:- Aged between 24 and 45 years, having regular menstrual cycles (24 to 36 days), and meeting criteria for PMS based on Daily Symptom Report (DSR) for 2 cycles. A total score >80 for luteal phase, along with at least 3 DSR items showing at least moderate severity for 2 out of 6 premenstrual days, moderate distress for at least 2 out of 6 premenstrual days and minimal to no symptoms during the follicular phase (days 5-10) Exclusion:- Decrease of 30% or more in DSR total score for the 6 premenstrual days during the single blind placebo cycle, use of oral contraceptives or other hormonal preparations within six months prior to screening, pregnant, lactating or planning pregnancy, LH levels > 38 or FSH > 20 in patients aged >38 years, post hysterectomy or failure to demonstrate ovulation in the two screening cycles, failure to respond to an adequate trial of 2 or more antidepressants to treat premenstrual symptoms, symptomatic endometriosis (or treatment in the past 3 months), history of major depressive episode or other mental disorder or substance misuse in past year, history of eating disorder in previous 2 years, current or lifetime history of psychiatric disorders, current use of any psychotropic medication, positive urine drug screen, current suicide risk, any acute or unstable medical illness or clinically significant laboratory abnormality

Kornstein 2006 a (*Continued*)

Interventions	Screening: Two cycles Placebo run in: None Intervention: Two cycles treatment with 25mg sertraline luteal phase only versus placebo followed by crossover for two cycles. No washout Timing of administration: Drug was commenced fourteen days before the expected onset of menses and discontinued when menses began. No details of average drug received Summary measures: Data was summarised for luteal phase as a sum of the last seven days of the cycle and averaged over two cycles in the paper
Outcomes	Daily Symptom Report; Clinical Global Impression- Severity of Illness (CGI- S); Clinical Global Improvement (CGI-I); Patient Global Evaluation (PGE); Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q); Social Adjustment Scale Self Report (SAS-SR)
Notes	As this study had several sequential treatment regimens without washout periods only the first treatment cycles was used for the meta- analysis Study funded by Pfizer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Appears to be randomised but no details of randomisation
Allocation concealment?	Unclear	B- unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind no details
Incomplete outcome data addressed? All outcomes	Yes	314 women randomised of which 18 were lost to follow up. 98 allocated to Sertraline 25mg and 74 completed (adverse events = 7, protocol violation = 5, withdrew consent = 4, loss to follow up = 2, other/administrative = 6); 97 allocated to sertraline 50mg 77 completed (adverse events = 10, protocol violation= 1, withdrew consent = 1, loss to follow up = 5, other/administrative = 3) , placebo allocated 101 and 79 competed (adverse events = 8, protocol violation = 2, withdrew consent = 6, loss to follow up = 2, other administrative = 4)
Free of selective reporting?	Yes	

Kornstein 2006b

Methods	Randomised double blind placebo controlled 3 arm study with parallel groups
Participants	Country: USA Site: Conducted in 22 psychiatric and gynaecological outpatient clinics in the US Recruitment: Women recruited through advertisements in the media. Refer to Table of bias for details of attrition Inclusion:- Aged between 24 and 45 years, having regular menstrual cycles (24 to 36 days), and meeting criteria for PMS based on Daily Symptom Report (DSR) for 2 cycles. A total score >80 for luteal phase, along with at least 3 DSR items showing at least moderate severity for 2 out of 6 premenstrual days, moderate distress for at least 2 out of 6 premenstrual days and minimal to no symptoms during the follicular phase (days 5-10) Exclusion:- Decrease of 30% or more in DSR total score for the 6 premenstrual days during the single blind placebo cycle, use of oral contraceptives or other hormonal preparations within six months prior to screening, pregnant, lactating or planning pregnancy, LH levels > 38 or FSH > 20 in patients aged >38 years, post hysterectomy or failure to demonstrate ovulation in the two screening cycles, failure to respond to an adequate trial of 2 or more antidepressants to treat premenstrual symptoms, symptomatic endometriosis (or treatment in the past 3 months), history of major depressive episode or other mental disorder or substance misuse in past year, history of eating disorder in previous 2 years, current or lifetime history of psychiatric disorders, current use of any psychotropic medication, positive urine drug screen, current suicide risk, any acute or unstable medical illness or clinically significant laboratory abnormality
Interventions	Screening: Two cycles Placebo run in: None Intervention: Two cycles treatment with 50mg sertraline luteal phase only increasing to 100mg for non-improvers versus placebo followed by crossover for two cycles. No washout Timing of administration: Drug was commenced fourteen days before the expected onset of menses and discontinued when menses began. No details of average drug received Summary measures: Data was summarised for luteal phase as a sum of the last seven days of the cycle and averaged over two cycles in the paper
Outcomes	Daily Symptom Report; Clinical Global Improvement (CGI-I); Patient Global Evaluation (PGE); Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q); Social Adjustment Scale Self Report (SAS-SR)
Notes	As this study had several sequential treatment regimens without washout periods only the first treatment cycles was used for the meta- analysis Study funded by Pfizer

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Appears to be randomised but no details of randomisation

Kornstein 2006b (*Continued*)

Allocation concealment?	Unclear	B- unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind no details
Incomplete outcome data addressed? All outcomes	Yes	314 women randomised of which 18 were lost to follow up. 98 allocated to Sertraline 25mg and 74 completed (adverse events = 7, protocol violation = 5, withdrew consent = 4, loss to follow up = 2, other/administrative = 6); 97 allocated to sertraline 50mg 77 completed (adverse events = 10, protocol violation= 1, withdrew consent = 1, loss to follow up = 5, other/administrative = 3) , placebo allocated 101 and 79 competed (adverse events = 8, protocol violation = 2, withdrew consent = 6, loss to follow up = 2, other administrative = 4)
Free of selective reporting?	Yes	

Länden 2007 a

Methods	Randomised, double blind placebo controlled trial with three parallel arms (intermittent versus continuous versus placebo). Continuous versus placebo is described in Landen 2007b (continuous)
Participants	Country: Sweden Site: Multicentre study by four investigators at four centres. Unclear as to what or where these were Recruitment: Mean age placebo group 37+/-7.1 and intermittent group was 37+/-5.9 years.Women responding to advertisements, interviewed by telephone and then invited to a screening visit Inclusion:- >18 years, reporting regular menstrual cycles (22-35 days) and meeting DSM-IV criteria A-C for PMDD. To meet criterion D women had to display a 50% increase in irritability and/or depressed mood during the luteal phase as compared to the follicular phase during two screening cycles using a VAS. Mean luteal phase rating of the symptom >/25mm Exclusion:- Meeting DSM-IV criteria for any Axis 1 disorder other than PMDD during previous 12 months before screening as assessed by Mini International Neuropsychiatric Interview; display a baseline score >10 on Montgomery Asperg Depression Rating Scale in the follicular phase, having tried a SRI for PMDD, taking oral contraceptives or reporting any regular use of any psychoactive drug or any other kind of medication motivating exclusion due to safety reasons
Interventions	Screening: Two screening cycles Placebo run in: None Intervention: Placebo until estimated time of ovulation followed by Paroxetine 10mg/

	day given orally for four days and 20mg for the rest of the luteal phase. During the first four days of the follicular phases they received 10mg daily paroxetine for three treatment cycles (n=59).Versus Placebo administered orally throughout the study for three treatment cycles (n=59) Timing of administration: Treatment commenced during the follicular phase starting on the first day of menstruation. Time of ovulation was estimated on the basis of a normal cycle length for the patient. On this day, the patient switched to a second pack that was to be used for the rest of the cycle Summary measures: LOCF data presented.
Outcomes	VAS scales; Premenstrual Tension Scale (observer and self rated); Clinical Global Improvement (CGI-I); Patient Global Evaluation (PGE); Sheehan Disability Scale (SDS); Adverse events
Notes	Symptoms rated daily. Authors contacted, no response. Novo Nordisk and Glaxo SmithKline

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer randomisation list
Allocation concealment?	Unclear	B - unclear
Blinding? All outcomes	Unclear	Double blind. No details
Incomplete outcome data addressed? All outcomes	Yes	Two hundred and seventy four women screened and one hundred and eighty six randomised. Fifty nine randomised to placebo and fifty one completed trial(adverse events = 1, other reason = 7). Fifty nine randomised to intermittent dosing and fifty completed trial (adverse event = 3, other reason =6). Sixty randomised to continuous dosing and fifty one completed trial (adverse event = 5, and other reason =4)
Free of selective reporting?	Yes	

Länden 2007b

Methods	Randomised, double blind placebo controlled trial with three parallel arms (intermittent versus continuous versus placebo). Intermittent versus placebo is described in Landen 2007a (intermittent)
Participants	Country: Sweden Site: Multicentre study by four investigators at four centres. Unclear as to what or where these were Recruitment: Mean age placebo group 37±7.1 and continuous group was 38±6 years.Women responding to advertisements, interviewed by telephone and then invited to a screening visit Inclusion: >18 years, reporting regular menstrual cycles (22-35 days) and meeting DSM-IV criteria A-C for PMDD. To meet criterion D women had to display a 50% increase in irritability and/or depressed mood during the luteal phase as compared to the follicular phase during two screening cycles using a VAS. Mean luteal phase rating of the symptom >/25mm Exclusion: Meeting DSM-IV criteria for any Axis 1 disorder other than PMDD during previous 12 months before screening as assessed by Mini International Neuropsychiatric Interview; display a baseline score >10 on Montgomery Asperg Depression Rating Scale in the follicular phase, having tried a SRI for PMDD, taking oral contraceptives or reporting any regular use of any psychoactive drug or any other kind of medication motivating exclusion due to safety reasons
Interventions	Screening: Two screening cycles Placebo run in: None Intervention: Placebo administered orally throughout the study for three treatment cycles (n=59). Paroxetine administered daily (n=60) Timing of administration: Treatment commenced during the follicular phase starting on the first fay of menstruation. Time of ovulation was estimated on the basis of a normal cycle length for the patient. On this day, the patient switched to a second pack that was to be used for the rest of the cycle Summary measures: LOCF data presented.
Outcomes	VAS scales, Premenstrual Tension Scale (observer and self rated), Clinical Global Improvement (CGI-I), Patient Global Evaluation (PGE), Sheehan Disability Scale (SDS), Adverse events
Notes	Symptoms rated daily. Authors contacted, no response. Novo Nordisk and Glaxo SmithKline

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer randomisation list
Allocation concealment?	Unclear	B - unclear
Blinding? All outcomes	Unclear	Double blind. No details

Länden 2007b (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Two hundred and seventy four women screened and one hundred and eighty six randomised. Fifty nine randomised to placebo and fifty one completed trial(adverse events = 1, other reason = 7). Fifty nine randomised to intermittent dosing and fifty completed trial (adverse event = 3, other reason = 6). Sixty randomised to continuous dosing and fifty one completed trial (adverse event = 5, and other reason = 4)
Free of selective reporting?	Yes	

Menkes 1993

Methods	Randomised , double blind, placebo controlled, crossover trial 2x3 cycles
Participants	Country: New Zealand Site: No details Recruitment: Community sample of volunteers23 women screened , 21randomised, 16 completed. Refer to Table of bias for details of attrition.Mean age 37.8±4.7 years Inclusion: Age 18 to 48 years. Confirmation of PMS by psychiatric evaluation Exclusion: Taking regular psychotropics, diuretics, or using hormonal contraception. Any appreciable menstrual irregularity, psychiatric or substance use disorder
Interventions	Screening: Three cycles of screening Placebo run in: None Intervention: Crossover trial of 20mg fluoxetine PO every day for 3 cycles versus placebo PO every day for 3 cycles with 12 day washout period between arms Timing of administration: Medication commenced on twelfth day of menstrual cycle and continued through three cycles stopping at the onset of menses Summary measures: Mean data over three months of treatment presented in paper
Outcomes	Premenstrual Assessment Form Side effects
Notes	No data extracted as unable to distinguish first and second arm of study Same patient group as excluded study, Menkes 1992 Daily symptom rating Fluoxetine provided by Eli-Lilly

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	States randomised. No details of randomisation.

Menkes 1993 (*Continued*)

Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Double blind (patient and rater)
Incomplete outcome data addressed? All outcomes	Yes	Twenty three women met provisional criteria, after two cycles of screening twenty three women had PMS confirmed by psychiatric interview, Daily Symptom Scores and ratings of PAF. One woman was excluded because of insufficient symptom severity and one because symptoms were not specific to luteal phase. During the treatment phase a further five were excluded, two for protocol violation and three due to adverse effects, no details as to which arm of the crossover this occurred in
Free of selective reporting?	Yes	

Miner 2002a

Methods	Randomised , double blind, placebo controlled, 3 arm parallel group study (LPWDX1 versus LPWDX2 versus placebo). Refer to Miner 2002b for details of LPWDX2
Participants	Country: Australia, Europe and Mexico. Site: Multicentre in 30 centres. No details as to what or where these centres were Recruitment: Mean age LPWDX1 37.4±5.8 years, LPWDX2 36.1±5.2 years and placebo 37.4±5.4 years.Not stated where women were recruited from. Refer to Table of bias for details of attrition Inclusion: Women aged 18-45 years, regular menstrual cycles(23-35 days) were eligible. Meeting PMDD criteria in two screening cycles. Luteal scores average >/3.0 for each of the 5 DRSP symptoms corresponding to the items in DSM-IV criterion A, with 1>/ symptom corresponding to a DSM IV mood item; if follicular phase scores averaged <2.5 for each of these 5 DRSP symptoms; if mean scores for these 5 DRSP symptoms increased by >/50% from the follicular to the luteal phase; and if scores on the three functional DRSP items were >/4 on >/2 occasions during the luteal phase Exclusion: Axis 1 psychiatric disorder within previous 6 months (with exception of phobias). Women using hormonal contraceptives or who had used them in previous 3 months. Placebo responders in the single blind placebo run in
Interventions	Screening: Two cycles screening . Placebo run in: Single blind placebo run in Intervention: 3 cycles of treatment or placebo followed by another single blind placebo run out. Group 1 LPWD x2 Fluoxetine 90mg PO (n=86) versus Group 3 PLC placebo administered two times during luteal phase at 14 and 7 days before expected menses (n= 85). Timing of administration: administered at 14 and 7 days before expected menses

Miner 2002a (*Continued*)

	Summary measures: Mean data presented
Outcomes	Self completed electronic diary using the Daily Record of Severity of problems Scale (DRSP) for recording daily PMDD symptoms.Mood, physical and social functioning subtotalsTwo clinician rated and one patient rated scale.Rating Scale for PreMenstrual Tension (PMTS- C)CGI Severity score.PGI score
Notes	Study was supported by a grant from Forest Laboratories, New York Symptoms rated daily

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation schedule
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Yes	Double blind (patient and other not stated)
Incomplete outcome data addressed? All outcomes	Unclear	1204 women screened. Following single blind run in 257 were randomised
Free of selective reporting?	Yes	

Miner 2002b

Methods	Randomised , double blind, placebo controlled, 3 arm parallel group study (LPWDX1 versus LPWDX2 versus placebo). Refer to Miner 2002a for details of LPWDX1
Participants	Country: Australia, Europe and Mexico. Site: Multicentre in 30 centres. No details as to what or where these centres were Recruitment: Mean age LPWDX1 37.4±5.8 years, LPWDX2 36.1±5.2 years and Placebo 37.4±5.4 years.Not stated where women were recruited from. Refer to Table of bias for details of attrition Inclusion: Women aged 18-45 years, regular menstrual cycles(23-35 days) were eligible. Meeting PMDD criteria in two screening cycles. Luteal scores average >/3.0 for each of the 5 DRSP symptoms corresponding to the items in DSM-IV criterion A, with 1>/ symptom corresponding to a DSM IV mood item; if follicular phase scores averaged <2.5 for each of these 5 DRSP symptoms; if mean scores for these 5 DRSP symptoms increased by >/50% from the follicular to the luteal phase; and if scores on the three functional DRSP items were >/4 on >/2 occasions during the luteal phase Exclusion: Axis 1 psychiatric disorder within previous 6 months (with exception of phobias). Women using hormonal contraceptives or who had used them in previous 3 months. Placebo responders in the single blind placebo run in

Miner 2002b (*Continued*)

Interventions	Screening: Two cycles screening . Placebo run in: Single blind placebo run in Intervention: 3 cycles of treatment or placebo followed by another single blind placebo run out. Group 2 LPWD X1 placebo administered 1 time during the first week of the luteal phase, 14 days before expected menses and fluoxetine 90mg PO administered 7 days before expected menses (n=86) versus Group 3 PLC placebo administered two times during luteal phase at 14 and 7 days before expected menses (n=85) Timing of administration: As detailed above Summary measures: Mean data presented
Outcomes	Self completed electronic diary using the Daily Record of Severity of problems Scale (DRSP) for recording daily PMDD symptoms. Mood, physical and social functioning subtotals.Two clinician rated and one patient rated scale. Rating Scale for PreMenstrual Tension (PMTS- C) CGI Severity score. PGI score
Notes	Symptoms rated daily Study was supported by a grant from Forest Laboratories, New York

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation schedule
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Yes	Double blind (patient and other not stated)
Incomplete outcome data addressed? All outcomes	Unclear	1204 women screened. Following single blind run in 257 were randomised

Ozeren 1997

Methods	Randomised, double blind, placebo controlled 2 arm parallel trial
Participants	Country: Turkey Site: No details. Recruitment: Self referred factory workers. 440 women screened. 35 randomised and 30 completed. Refer to Table of bias for details of attrition.Mean age 30.6 +/- 7.48 years for treatment group and 31.7 +/- 7.42 years for placebo group Inclusion: Women aged 18-45. Meeting criteria for PMS being a luteal phase score at least twice that of the follicular phase score, and the luteal phase score to be at least 42 and the follicular phase score to be less than 40. Diagnosis confirmed using DSM-IV and DSM-3-R diagnostic criteria Exclusion: Those taking psychotropics, diuretics, antidepressants, anxiolytics, oral contraceptives, hormonal medications and those having major psychiatric disorders, pelvic

Ozeren 1997 (*Continued*)

	pathology and irregular menstrual cycles
Interventions	Screening: Three screening cycles Placebo run in: None Intervention: 20mg fluoxetine (n=18) daily PO for 3 cycles versus placebo (n=17) PO for 3 cycles Timing of administration: Medication taken in the morning. No details as to when in the menstrual cycle medication was commenced Summary measures: Mean data presented.
Outcomes	Calendar of Premenstrual Experiences
Notes	Daily symptom rating No details of ITT or power calculation No funding source stated

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation.
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Double blind, no details as to whom was blinded.
Incomplete outcome data addressed? All outcomes	Yes	440 women screened. 35 met diagnostic criteria. Five excluded during trial, two from the placebo group and three from the treatment group due to protocol violation or through intolerable adverse effects of fluoxetine
Free of selective reporting?	Yes	

Pearlstein 1997

Methods	Randomised placebo controlled, double blind, 3 parallel arms study (fluoxetine vs bupropion vs placebo)
Participants	Country: USA Site: Women treated in two PMS clinics. Recruitment: 44 women enrolled, 37 women randomised, 34 completed. Refer to Table of bias for details of attrition. Mean age 36.5±5 years Inclusion: Age 18 - 45 years, regular menstrual cycles (24 to 35 days), in good physical health in 6 months preceding study. A 30% increase in the premenstrual symptom average was required in at least 5 symptom categories as specified by PMDD criteria.

Pearlstein 1997 (*Continued*)

	Absence of significant follicular phase symptoms and a 30% or greater premenstrual increase in impairment of occupational, social, or interpersonal functioning was required on the basis of daily assessment Exclusion: Pregnancy, irregular menstruation, serious health problems, use of psychoactive or hormonal medications including oral contraceptive, current Axis 1 disorder (DSM-III-R), substance abuse or suicide risk in prior 6 months
Interventions	Screening: Two cycles of screening Placebo run in: Single blind placebo for one cycle Intervention: 20mg fluoxetine orally daily for 2 cycles (n=10)versus placebo administered orally daily for 2 cycles (n=12) Timing of administration: Medication taken daily throughout cycle Summary measures: Data presented for cycle 3
Outcomes	Hamilton Scale for Depression (HAM-D) Clinical Global Impression (CGI) Global Assessment Score (GAS) Daily Assessment Form (designed by group)
Notes	Daily symptom rating Funded by Eli-Lilly

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation at separate sites not centrally.
Allocation concealment?	Unclear	B - Unclear. No details of concealment
Blinding? All outcomes	Yes	Double blind. Subjects all took one white capsule in the morning and three red tablets each day in three-times-daily dosing. One of the physicians who rated patients was blind to medication but aware of the study design
Incomplete outcome data addressed? All outcomes	Yes	44 women enrolled, 37 women randomised, 34 completed. Three women were not randomised because they responded to the single blind placebo cycle, Two women experienced adverse side effects in single blind placebo cycle and failed to appear at end of single blind placebo cycle
Free of selective reporting?	Yes	

Pearlstein 2005 a

Methods	Randomised, double blind, placebo controlled 3 arm parallel trial. Paroxetine CR 25 mg versus 12.5 mg versus placebo (see Pearlstein 2005b for 12.5 mg data)
Participants	Country: USA and Canada Site: 47 outpatient centres . Recruitment: 1974 women screened, 371 randomised to Pearlstein a,b. 125 randomised to paroxetine 25mg and 82 completed; 125 randomised to placebo, 96 completed.Mean age paroxetine 25mg 36.5±4.87 years, mean age of placebo 35.8±5.79 years Inclusion: Women aged 18-45 years with regular menstrual cycles (22-35 days) and confirmed PMDD based on DSM-IV. Symptoms to have been present for at least nine out of previous twelve cycles over the previous year. Onset of severe premenstrual symptoms (as recorded on a daily basis) during the luteal phase was followed by symptom subsidence during the follicular phase based on four core symptoms (irritability, tension, affective lability and depressed mood). Required to demonstrate a 200% worsening on one core symptom or a 100% worsening on two or more symptoms during the luteal phase relative to the follicular phase. Baseline Clinical Global Impressions of Severity scale score >/3 Exclusion: Meeting DSM-IV criteria for other Axis 1 disorder except specific phobias in the previous six months, diagnosed with gynaecological or other clinically significant disease, clinically significant depressive symptomology during the follicular phase, suicide risk, taking medication for PMD, received previous adequate treatment or participated in a clinical trial for PMDD, breastfeeding or pregnant. Using oral or systemic contraception
Interventions	Screening: Two screening cycles Placebo run in: One cycle Intervention: Paroxetine 25mg taken orally in the morning throughout the cycle for three cycles versus placebo taken orally in the morning throughout the cycle for three cycles Timing of administration: No details as to which day of the cycle medication commenced. Placebo taken orally in the morning throughout the cycle for three cycles Summary measures: Treatment cycle 3 LOCF data
Outcomes	Visual Analogue Scale (VAS) recorded daily; Clinical Global Impressions of Severity scale (CGI-S); Sheehan Disability Scale (SDS)
Notes	Symptoms rated daily. Mean VAS score calculated by averaging the item score over the last five days of the luteal phase prior to menstruation Authors contacted, no response Funding GlaxoSmithKline

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation
Allocation concealment?	Unclear	B-unclear. No details of concealment

Pearlstein 2005 a (*Continued*)

Blinding? All outcomes	Unclear	Double blind, similar appearing medication, no details as to whom was blinded. Evidence that patients were blinded
Incomplete outcome data addressed? All outcomes	Yes	1974 women screened, 1212 eligible and 371 randomised. 125 randomised to 25mg paroxetine CR (120 ITT) and 82 completed (20 adverse events, 10 loss to follow up, 5 protocol deviation, 3 other reason) , 121 were randomised to 12.5mg paroxetine CR (115 ITT) and 89 completed (12 adverse events, 4 loss to follow up, 2 protocol deviation, 5 other reason, 3 lack of efficacy), 125 randomised to placebo (124 ITT), 96 completed (9 adverse events, 3 loss to follow up, 5 protocol deviation, 8 other reason, 3 lack of efficacy)
Free of selective reporting?	Yes	

Pearlstein 2005b

Methods	Randomised, double blind, placebo controlled 3 arm parallel trial. Paroxetine CR 25 mg versus 12.5 mg versus placebo (see Pearlstein 2005a for 25 mg data)
Participants	Country: USA and Canada Site: 47 outpatient centres . Recruitment: 1974 women screened, 371 randomised to Pearlstein a,b. 121 randomised to paroxetine 12.5mg and 89 completed; 125 randomised to placebo, 96 completed. Mean age paroxetine 12.5mg 36.4±5.82 years, mean age of placebo 35.8±5.79 years Inclusion: Women aged 18-45 years with regular menstrual cycles (22-35 days) and confirmed PMDD based on DSM-IV. Symptoms to have been present for at least nine out of previous twelve cycles over the previous year. Onset of severe premenstrual symptoms (as recorded on a daily basis) during the luteal phase was followed by symptom subsidence during the follicular phase based on four core symptoms (irritability, tension, affective lability and depressed mood). Required to demonstrate a 200% worsening on one core symptom or a 100% worsening on two or more symptoms during the luteal phase relative to the follicular phase. Baseline Clinical Global Impressions of Severity scale score >/3 Exclusion: Meeting DSM-IV criteria for other Axis 1 disorder except specific phobias in the previous six months, diagnosed with gynaecological or other clinically significant disease, clinically significant depressive symptomology during the follicular phase, suicide risk, taking medication for PMD, received previous adequate treatment or participated in a clinical trial for PMDD, breastfeeding or pregnant. Using oral or systemic contraception
Interventions	Screening: Two screening cycles Placebo run in: One cycle Intervention: Paroxetine 12.5mg taken orally in the morning throughout the cycle for three cycles versus placebo taken orally in the morning throughout the cycle for three

Pearlstein 2005b (*Continued*)

	cycles Timing of administration: No details as to which day of the cycle medication commenced Summary measures: Treatment cycle 3 LOCF data
Outcomes	Visual Analogue Scale (VAS) recorded daily; Clinical Global Impressions of Severity scale (CGI-S);Sheehan Disability Scale (SDS)
Notes	Symptoms rated daily. Mean VAS score calculated by averaging the item score over the last five days of the luteal phase prior to menstruation Authors contacted, no response. Funding GlaxoSmithKline.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Computer generated randomisation
Allocation concealment?	Unclear	B - unclear, no details as to concealment
Blinding? All outcomes	Yes	Double blind, similar appearing medication, no details as to whom was blinded. Evidence that patients were blinded
Incomplete outcome data addressed? All outcomes	Yes	1974 women screened, 1212 eligible and 371 randomised. 125 randomised to 25mg paroxetine CR (120 ITT) and 82 completed (20 adverse events, 10 loss to follow up, 5 protocol deviation, 3 other reason) , 121 were randomised to 12.5mg paroxetine CR (115 ITT) and 89 completed (12 adverse events, 4 loss to follow up, 2 protocol deviation, 5 other reason, 3 lack of efficacy), 125 randomised to placebo (124 ITT), 96 completed (9 adverse events, 3 loss to follow up, 5 protocol deviation, 8 other reason, 3 lack of efficacy)
Free of selective reporting?	Yes	

Steiner 1995 a

Methods	3 arm parallel trial (same placebo for both treatment groups, 20 mg and 60 mg) see Steiner 1995 (60 mg)
Participants	Country: Canada Site: Multicentre - 7 university affiliated clinics Recruitment: 405 women screened. 313 randomised to three conditions (refer to Steiner 1995b 60mg for third condition), 277 completed cycle 1 of phase 2 and were eligible for analysis.20mg: 102 randomised, 96 completed cycle 1placebo 53 randomised, 48 completed cycle 1. Refer to Table of bias for details of attrition.Mean age 36+/-5 years Inclusion: Women ages 18 to 45 years meeting diagnostic criteria for LLPDD with at least one year history of 5+ symptoms attributable to the disorder that began premenstrually and remitted post-menstrually. Severe enough to affect activities of daily living as assessed in screening cycles. Menstrual cycles ranging from 24 to 35 days Exclusion: Pregnant or lactating, taking oral contraceptive, had irregular menstrual cycles, had an unstable medical condition, a seizure disorder with a seizure within the last year, a record of multiple adverse drug reactions, known allergies to inhibitors of the reuptake of serotonin or a history of fluoxetine use. Other major psychiatric syndrome, expressed suicide ideation or intent, had used psychoactive medication or investigational drugs within two months prior to the study or were taking any other medication to treat premenstrual symptoms
Interventions	Screening: Two screening cycles Placebo run in: single blind placebo Intervention: 20mg fluoxetine taken orally versus placebo taken orally every day for 6 cycles in the morning Timing of administration: Treatment began on day1 of the third menstrual cycle Summary measures: Efficacy data used for all women completing at least one cycle of treatment
Outcomes	Observer and subject assessed visual analogue scale Prospective Record of the Impact and Severity of Menstrual Symptomology Side effects.
Notes	Withdrawals are number withdrawn after 6 cycles Analysable data for 1st cycle only Funded by Eli-Lilly

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - Unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind (no details as to whom was blinded)

Steiner 1995 a (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	405 women screened. 313 randomised to three conditions (refer to Steiner 1995b for third condition), 277 completed cycle 1 of phase 2 and were eligible for analysis. 33 withdrawals in Fluoxetine (20mg): side effects (11), lack of efficacy (4), loss to follow up (2), personal reasons (9), protocol violation (7). Placebo withdrawals = 53:in whole study. Side effects (8), lack of efficacy (27), loss to follow up (5), personal reasons (6), protocol violations (7)
Free of selective reporting?	Yes	

Steiner 1995b

Methods	3 arm parallel trial (same placebo for both treatment groups, 20mg and 60mg) see Steiner 1995 (20mg)
Participants	Country: Canada Site: Multicentre - 7 university affiliated clinics Recruitment: 405 women screened. 313 randomised to three conditions (refer to Steiner 1995a 20mg for third condition), 277 completed cycle 1 of phase 2 and were eligible for analysis. 60mg: 106 randomised, 86 completed cycle placebo 52 randomised, 47 completed cycle 1 Refer to Table of bias for details of attrition. Mean age 36±5 years Inclusion: women ages 18 to 45 years meeting diagnostic criteria for LLPDD with at least one year history of 5+ symptoms attributable to the disorder that began premenstrually and remitted post menstrually. Severe enough to affect activities of daily living as assessed in screening cycles. Menstrual cycles ranging from 24 to 35 days Exclusion: Pregnant or lactating, taking oral contraceptive, had irregular menstrual cycles, had an unstable medical condition, a seizure disorder with a seizure within the last year, a record of multiple adverse drug reactions, known allergies to inhibitors of the reuptake of serotonin or a history of fluoxetine use. Other major psychiatric syndrome, expressed suicide ideation or intent, had used psychoactive medication or investigational drugs within two months prior to the study or were taking any other medication to treat premenstrual symptoms
Interventions	Screening: Two screening cycles Placebo run in: single blind placebo for two cycles. Intervention: 60mg fluoxetine taken orally versus placebo taken orally every day for 6 cycles in the morning Timing of administration: Treatment began on day 1 of the third menstrual cycle Summary measures: Efficacy data used for all women completing at least one cycle of treatment
Outcomes	Observer and subject assessed visual analogue scale Prospective Record of the Impact and Severity of Menstrual Symptomology Side effects.

Steiner 1995b (*Continued*)

Notes	Withdrawals are number withdrawn after 6 cycles Analysable data for 1st cycle only Funded by Eli-Lilly

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind (no details as to whom was blinded)
Incomplete outcome data addressed? All outcomes	Yes	405 women screened. 313 randomised to three conditions (refer to Steiner 1995b 60mg for third condition), 277 completed cycle 1 of phase 2 and were eligible for analysis. 33 withdrawals in Fluoxetine (20mg) : side effects (11), lack of efficacy (4), loss to follow up (2), personal reasons (9), protocol violation (7). Placebo withdrawals = 53:in whole study. Side effects (8), lack of efficacy (27), loss to follow up (5), personal reasons (6), protocol violations (7)
Free of selective reporting?	Yes	

Steiner 2001

Methods	See Steiner 1995a,b
Participants	See Steiner 1995a,bThis paper reports on 320 women 104 allocated to fluoxetine 20 mg, 108 allocated to fluoxetine 60 mg and 108 allocated to placebo
Interventions	See Steiner 1995a,b
Outcomes	See Steiner 1995a,b
Notes	This study reports on the same sample as Steiner 1995. It focus' on physical symptoms. Some additional data was reported which has been included in Steiner 1995

Risk of bias

Item	Authors' judgement	Description

Steiner 2001 (*Continued*)

Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind (no details as to whom was blinded)
Incomplete outcome data addressed? All outcomes	Yes	See Steiner 1995a,b
Free of selective reporting?	Yes	

Steiner 2005 a

Methods	Randomised ,double blind, placebo controlled, fixed dose study
Participants	Country: International multicentre study. Site: Women attending outpatients department. Recruitment: Women recruited from outpatient department. Mean age paroxetine CR 12.5mg 35.9±6.01 years, placebo 36.9±5.51 years Refer to Table of bias for details of attrition Inclusion: Age 18-45, regular menstrual cycles (22-35 days), meeting DSM-IV criteria for PMDD. Having had condition for at least one year during which symptoms needed to have been present for nine out of twelve cycles. Needed to have baseline rating of at least 'mildly ill' according to the Clinical Global Impression severity of illness scale (CGI-S). Women required to demonstrate a 200% worsening on one core mood symptom or a 100% worsening on two or more of the core mood symptoms during the luteal phases of two or more reference cycles relative to their follicular phases score. Mean follicular phase score </20mm, mean luteal phase score >/40mm Exclusion: Meeting DSM-IV criteria for other Axis 1 disorders (except specific phobias) in the six months before screening, diagnosed with gynaecological or other clinically significant disease, had clinically significant depressive symptomatology during the follicular phase, suicide risk, taking medication that could interfere with PMDD symptoms or their assessment, using oral contraceptives, had previous treatment for PMDD, had participated in a trial for PMDD with SSRIs, were pregnant or breastfeeding
Interventions	Screening: Two to three screening cycles Placebo run in: Single blind placebo run-in taking medication from when they estimated they were 14 days before estimated due date of menses and to continue until start of menses. No medication taken during follicular phase Intervention: Paroxetine CR 12.5mg orally once daily in the morning during the luteal phases of the cycle for three cycles versus placebo orally once daily in the morning during the luteal phases of the cycle for three cycles Timing of administration: Requested to take medication once daily in the morning during the luteal phase Summary measures: Data summarised using LOCF for treatment cycle 3

Steiner 2005 a (*Continued*)

Outcomes	Visual Analogue Scale (VAS);Observer rated Premenstrual Tension Scale (PMTS-O); Global Assessment of Disease Severity (CGI-S); Global Assessment of Disease Improvement (CGI-I); Patient Global Evaluation (PGE); Sheehan Disability Scale (SDS); Adverse events
Notes	Daily symptom rating. Author contacted, no response. No details of funding

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind (no details as to whom was blinded)
Incomplete outcome data addressed? All outcomes	Yes	1615 women screened. 373 randomised 119 randomised to Paroxetine 25mg of which 87 completed (16 adverse events, 2 protocol violation, 3 loss to follow-up, 6 other reason, 2 lack of efficacy); 131 randomised to Paroxetine CR 12.5mg of which 104 completed the trial (13 adverse events, 4 protocol violation, 1 loss to follow up, 6 other reason, 2 lack of efficacy); 123 randomised to placebo of which 101 completed the trial (5 adverse events, 2 protocol violation, 6 other reason, 6 lack of efficacy)

Steiner 2005 b

Methods	Randomised ,double blind, placebo controlled, fixed dose study
Participants	Country: International multicentre study. Site: Women attending outpatients department. Recruitment: Women recruited from outpatient department. Mean age paroxetine CR 12.5mg 35.9±6.01 years, placebo 36.9±5.51 years. Refer to Table of bias for details of attrition Inclusion: Age 18-45, regular menstrual cycles (22-35 days), meeting DSM-IV criteria for PMDD. Having had condition for at least one year during which symptoms needed to have been present for nine out of twelve cycles. Needed to have baseline rating of at least 'mildly ill' according to the Clinical Global Impression severity of illness scale (CGI-S). Women required to demonstrate a 200% worsening on one core mood symptom or a 100% worsening on two or more of the core mood symptoms during the luteal phases

	of two or more reference cycles relative to their follicular phases score. Mean follicular phase score </20mm, mean luteal phase score >/40mm Exclusion: Meeting DSM-IV criteria for other Axis 1 disorders (except specific phobias) in the six months before screening, diagnosed with gynaecological or other clinically significant disease, had clinically significant depressive symptomatology during the follicular phase, suicide risk, taking medication that could interfere with PMDD symptoms or their assessment, using oral contraceptives, had previous treatment for PMDD, had participated in a trial for PMDD with SSRIs, were pregnant or breastfeeding
Interventions	Screening: Two to three screening cycles Placebo run in: Single blind placebo run-in taking medication from when they estimated they were 14 days before estimated due date of menses and to continue until start of menses. No medication taken during follicular phase Intervention: Paroxetine CR 25mg orally once daily in the morning during the luteal phases of the cycle for three cycles versus placebo orally once daily in the morning during the luteal phases of the cycle for three cycles Timing of administration: Requested to take medication once daily in the morning during the luteal phase Summary measures: Data summarised using LOCF for treatment cycle 3
Outcomes	Visual Analogue Scale (VAS); Observer rated Premenstrual Tension Scale (PMTS-O); Global Assessment of Disease Severity (CGI-S); Global Assessment of Disease Improvement (CGI-I); Patient Global Evaluation (PGE); Sheehan Disability Scale (SDS); Adverse events
Notes	Daily symptom rating. Author contacted, no response. No details of funding

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind (no details as to whom was blinded)
Incomplete outcome data addressed? All outcomes	Unclear	1615 women screened. 373 randomised 119 randomised to Paroxetine 25mg of which 87 completed (16 adverse events, 2 protocol violation, 3 loss to follow up, 6 other reason, 2 lack of efficacy); 131 randomised to Paroxetine CR 12.5mg of which 104 completed the trial (13 adverse events, 4 protocol violation, 1 loss to follow up, 6 other reason, 2 lack of efficacy); 123

		randomised to placebo of which 101 completed the trial (5 adverse events, 2 protocol violation, 6 other reason, 6 lack of efficacy)

Stone 1991

Methods	Randomised, double blind, placebo controlled 2 arm parallel trial
Participants	Country: USA Site: Based in PMS clinic. Recruitment: Women enrolled via self referral from newspaper advertisements. 152 completed two cycles of daily symptom rating (42 did not meet criteria of LLPDD). 110 women underwent further psychiatric evaluation. 71 of these were eligible to participate and 25 of these elected to participate and were randomised. the 46 who declined were unwilling to take medication or to be involved in a placebo controlled study. Refer to Table of bias for details of attrition.25 entered first cycle, 5 were eliminated from the study (refer to bias table) and the remaining 20 were randomised.Mean age 36 years (27 to 45). Mean age fluoxetine 36.6 years, mean age placebo group 35.4 years Inclusion: Met criteria of DSM-III-R diagnosis of LLPDD, physically healthy, and normal gynaecological examination. 30% increase in symptoms during the luteal phase of two cycles in at least five of the ten symptom categories listed in DSM-III-R. Average score of premenstrual week had to show 30% increase in severity over average score of postmenstrual week. At least one of the five positive symptoms had to be 'affective' Exclusion: No current major psychiatric disorder, pregnant, be receiving anti-depressants, anxiolytics, diuretics, hormones, neuroleptics or have irregular menstrual cycles
Interventions	Screening: Two screening cycles Placebo run in: Single blind placebo for first cycle. Intervention: 20mg fluoxetine (n=10) every day for 2 cycles versus placebo (n=10) taken daily for two cycles Timing of administration: Medication taken in the morning. No details as to what stage of the menstrual cycle medication commenced Summary measures: Mean final scores presented.
Outcomes	Daily Assessment Form (DAF); Global Assessment Scale (GAS); Adverse events
Notes	Daily symptom rating Funded by Eli-Lilly

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation.
Allocation concealment?	Unclear	B - Unclear. No details of concealment

Stone 1991 (*Continued*)

Blinding? All outcomes	Unclear	Double blind, no details as to whom was blinded.
Incomplete outcome data addressed? All outcomes	Yes	Five did not complete the protocol. One showed in improvement in the placebo run in, one withdrew due to side effects in placebo, one was withdrawn due to substance abuse and one was pregnant and one did not return after the first study cycle. The remaining 20 women were then randomised
Free of selective reporting?	Yes	

Su 1997

Methods	Randomised, double blind, placebo controlled, crossover trial
Participants	Country: USA Site: No details Recruitment: Self referred in response to local advertisements or referred by physicians. Nineteen randomised (17 completed). Refer to Table of bias for details of attrition. Mean age 36.5±5.4 years Inclusion: Absence of significant medical illness, absence of significant Axis 1 psychiatric illness, including alcohol and substance misuse. Not taking psychoactive medications, hormonal preparations (including oral contraceptives), mineral supplements, or non-steroidal anti-inflammatory medications within the past 6 months. Regular menstrual cycles (23-35 days). Confirmed diagnosis of PMS via a prospective daily 3 item VAS. >30% increase in mean negative mood symptoms, relative to the actual range of the analogue scale used, in the week before menses compared with the week after menses in at least two out of three cycles. Required to use barrier methods of contraception Exclusion: Appearance of significant mood symptoms during the follicular phase
Interventions	Screening: Three cycles of screening. Placebo run in: None Intervention: Crossover trial of 20mg fluoxetine every day cycle 1, 20-60mg every day for 2 further cycles (mean drug dose during cycle 3 was 29.9+/-10.6mg) versus placebo.At end of first arm there was one cycle washout period Timing of administration: Medication started on the first day of menses and continued for a full menstrual cycle Summary measures: Results of pre and post menstrual weeks were averaged for the three cycles in each condition in the paper.Composite scores calculated for mood symptoms and social impairment symptoms in paper
Outcomes	Weekly means of 16 item visual analogue scale (VAS) and 21 item daily rating form (DRF) during seven days before and seven days after menses. Beck Depression Inventory (BDI); State Trait Anxiety Inventory - State form (STAI); Rating Scale for Pre Menstrual Tension (PMTS self and PMTS observer); Physical symptom checklist; Adverse events

Su 1997 (*Continued*)

Notes	10 women given m-CPP (serotonin agonist) during follicular and luteal phase. Women who responded to m-CPP challenge responded to fluoxetine Unable to extract first arm data from paper. Daily symptom rating Fluoxetine provided by Eli-Lilly.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Yes	Double blind (patient and rater)
Incomplete outcome data addressed? All outcomes	Yes	Nineteen were enrolled in study and seventeen completed. Two women in treatment arm dropped out due to intolerable migraine headaches (n=1) and unrelated irregular menstrual bleeding (n=1) no details as to which arm of the crossover this occurred in
Free of selective reporting?	Yes	

Sundblad 1992

Methods	Randomised double blind 2 arm parallel study
Participants	Country: Sweden Site: No details Recruitment: 100 women recruited, 55 randomised 40 completed trial. Refer to Table of bias for details of attrition.Mean age 37.5 yearsWomen recruited via newspaper advertisements, followed by telephone and then structured interview Inclusion: Severe premenstrual irritability and/or dysphoria appearing regularly during the two weeks preceding menstrual bleeding and terminating a few days after the onset of menstruation. Meeting DSM-III-R criteria for LLPDD. >100% increase in either irritability or dysphoria (or both) during the premenstrual week as compared with the postmenstrual week, a mean premenstrual rating of irritability or dysphoria exceeding 20mm Exclusion: Previous or ongoing mental illness (apart from major depressive or dysthymic disorders, ongoing major depressive or dysthymic disorders, major depressive disorder or dysthymic disorder < 2 years from the time of the interview, ongoing medication for somatic or mental illness, use of oral contraceptives, ongoing alcohol abuse, ongoing somatic illness, irregular menstrual bleeding, planned pregnancy and <15 years of age

Sundblad 1992 (*Continued*)

Interventions	Screening: Screening for 2 cycles. Placebo run in: None. Intervention: Clomipramine increasing dose from 5mg to 50mg taken orally daily (25-75mg was minimum and maximum doses allowed) for 3 cyclesVersusPlacebo taken orally daily for 3 cycles.Timing of administration: Treatment started on the first day of menstrual bleedingSummary measures: Mean score data presented
Outcomes	Visual Analogue Scale (VAS) for irritability, dysphoria and bloating. Patient rated global assessment of improvement (enormously improved to enormously deteriorated). Side effects
Notes	Daily symptom rating Funding by Swedish Medical Research Council, and Ciba AB, Sweden

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Yes	Double blind (patients and investigators unaware of allocation until end of study)
Incomplete outcome data addressed? All outcomes	Yes	Double blind (patients and investigators unaware of allocation until end of study)
Free of selective reporting?	Yes	

Sundblad 1993

Methods	Randomised, double blind, placebo controlled 2 arm parallel study
Participants	Country: Sweden Site: No details Recruitment: 64 screened, 38 randomised, 29 completed. Refer to Table of bias for details of attrition.mean age clomipramine group was 40.4±1.5 years and the placebo group was 38.2±1.2 years.Women recruited via newspaper advertisements, followed by telephone and then structured interview Inclusion: Severe premenstrual irritability and/or dysphoria appearing regularly during the two weeks preceding menstrual bleeding and terminating a few days after the onset of menstruation. Meeting DSM-III-R criteria for LLPDD. >100% increase in either irritability or dysphoria (or both) during the premenstrual week as compared with the postmenstrual week, a mean premenstrual rating of irritability or dysphoria exceeding 20mm Exclusion: Previous or ongoing mental illness (apart from major depressive or dysthymic disorders, ongoing major depressive or dysthymic disorders, major depressive disorder

Sundblad 1993 (*Continued*)

	or dysthymic disorder < 2 years from the time of the interview, ongoing medication for somatic or mental illness, use of oral contraceptives, ongoing alcohol abuse, ongoing somatic illness, irregular menstrual bleeding, ongoing or planned pregnancy and <18 years of age, having previous treatment with antidepressants for premenstrual complaints
Interventions	Screening: Two screening cycles Placebo run in: None Intervention: Clomipramine increasing dose from 5mg to 50mg taken orally daily (25-75mg was minimum and maximum doses allowed) for 3 cycles during luteal phase only (n=22) Versus Placebo taken orally daily for 3 cycles during luteal phase only (n=16) Timing of administration: Treatment started at the estimated time of ovulation (fourteen days before expected menstruation) and continued until the start of menstruation Summary measures: Treatment cycle three data used
Outcomes	Visual analogue scale (VAS)Patient rated global assessment of improvement (enormously improved to enormously deteriorated).Side effects
Notes	Daily rating of symptoms Uneven allocation as some women had been randomised before they were excluded in the two reference cycles Funding by Swedish Medical Research Council,Swedish Society of Medicine and CIBA-GEIGY

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Yes	Double blind (patients and investigators unaware of allocation until end of study)
Incomplete outcome data addressed? All outcomes	Yes	Sixty four women recruited, thirty eight randomised. Twenty nine completed the trial. Two placebo patients dropped out, one for side effects and one for pregnancy. Seven clomipramine patients dropped out, six for side effects and one for pregnancy
Free of selective reporting?	Yes	

Veeninga 1990

Methods	Randomised double blind placebo controlled 2 arm parallel trial
Participants	Country: the Netherlands Site: No details Recruitment: Women were recruited by newspaper advertisements. 20 randomised 20 completed. Refer to Table of bias for details of attrition Inclusion:- women aged 18-45 years with regular menstrual cycles (24 to 31 days), not taking oral contraceptives or under treatment for menstrual problems and drug free for at least two months
Interventions	Screening: screening for two cycles. Placebo run in: None Intervention: 50mg fluvoxamine in week one increasing to 100 mg in week two and 150mg in week 3 and thereafter versus placebo every day for 2 cycles Timing of administration: Medication started in the first week of the menstrual cycle. No specific details Summary measures: Not clear.
Outcomes	Moos Menstrual Distress Questionnaire 90 item symptom checklist on d4, d12, d22, d26 of cycle
Notes	Symptoms recorded d4, d12, d22, d26 of cycle Funding not stated

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind no details
Incomplete outcome data addressed? All outcomes	Yes	20 women randomised. 20 completed
Free of selective reporting?	Yes	

Wikander 1998a

Methods	Randomised double blind placebo controlled 4 arm parallel trial. See Wikander 1998 (b) & (c). Common placebo group (20 randomised, 17 completed)
Participants	Country: Sweden Site: not stated Recruitment: 123 women recruited in total to 4 arm study. 78 received medication in

	the four arm study. 39 randomised, 35 completed this comparison of intermittent versus placebo arm. Women recruited via newspaper advertisements, followed by telephone and then structured interview. Mean age of citalopram intermittent was 37±1 and for placebo was 37±5 years. Refer to Table of bias for details of attrition Inclusion: Marked premenstrual irritability and/or dysphoria appearing regularly during the two weeks preceding menstrual bleeding and terminating a few days after the onset of menstruation. Criteria A, B, C and D for LLPDD in DSM-IV-R. Displaying cyclicity with respect to irritability and depressed mood during at least two cycles of prospective rating. >100% increase in either irritability or dysphoria (or both) during the premenstrual week as compared with the postmenstrual week, a mean premenstrual rating of irritability or dysphoria exceeding 20mm Exclusion: Previous or ongoing mental illness (apart from major depressive or dysthymic disorders, ongoing major depressive or dysthymic disorders, major depressive disorder or dysthymic disorder < 2 years from the time of the interview, ongoing medication for somatic or mental illness (with the exception of casual analgesics), use of oral contraceptives, ongoing alcohol abuse, ongoing somatic illness, irregular menstrual bleeding or a normal cycle length <25 or > 35 days, ongoing or planned pregnancy and <18 years of age, having previous treatment with antidepressants for premenstrual complaints
Interventions	Screening: Screening for 2 cycles Placebo run in: None Intervention: Group1: 10-30mg citalopram given orally for luteal phase for 3 cycles (n= 19)Versusplacebo given orally for luteal phase only for 3 cycles (n=20)Medication in 18 dosette packs, 6 for each cycle Timing of administration: Medication commenced on the first day of menses Summary measures: Data was analysed for endpoint data using LOCF
Outcomes	Visual analogue scale for irritability, depression, tension, anxiety, appetite, bloating, mastalgia. Side effects
Notes	Data on adverse events could not be extracted Funding by Swedish Medical Research Council, Soderstrom Konigska Nursing Home Foundation, Frederrik and Ingrid Thuring's Foundation, Knut and Alice Wallenberg's Foundation

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind, no details
Incomplete outcome data addressed? All outcomes	Yes	In total this four arm study enrolled 123 women. Seventy eight of them received medication. In the continuous dos-

Wikander 1998a (*Continued*)

		ing group two patients dropped out for side effects, in the semi-intermittent group 3 dropped out, two for side effects and 1 protocol violation; in the intermittent group one dropped out for side effects and three of the placebo group dropped out for side effects. Sixty nine subjects completed the trial
Free of selective reporting?	Yes	

Wikander 1998b

Methods	Randomised double blind placebo controlled 4 arm parallel trial. See Wikander 1998 (a) & (c).Common placebo group (20 randomised, 17 completed)
Participants	Country: Sweden Site: not stated Recruitment: 123 women recruited in total to 4 arm study. 78 received medication in the four arm study. 40 randomised, 34 completed this comparison of semi-intermittent versus placebo arm. Women recruited via newspaper advertisements, followed by telephone and then structured interview. Mean age of citalopram intermittent was 36+/-6 and for placebo was 37+/-5 years. Refer to Table of bias for details of attrition Inclusion: Marked premenstrual irritability and/or dysphoria appearing regularly during the two weeks preceding menstrual bleeding and terminating a few days after the onset of menstruation. Criteria A, B, C and D for LLPDD in DSM-IV-R. Displaying cyclicity with respect to irritability and depressed mood during at least two cycles of prospective rating. >100% increase in either irritability or dysphoria (or both) during the premenstrual week as compared with the postmenstrual week, a mean premenstrual rating of irritability or dysphoria exceeding 20mm Exclusion: Previous or ongoing mental illness (apart from major depressive or dysthymic disorders, ongoing major depressive or dysthymic disorders, major depressive disorder or dysthymic disorder < 2 years from the time of the interview, ongoing medication for somatic or mental illness (with the exception of casual analgesics), use of oral contraceptives, ongoing alcohol abuse, ongoing somatic illness, irregular menstrual bleeding or a normal cycle length <25 or > 35 days, ongoing or planned pregnancy and <18 years of age, having previous treatment with antidepressants for premenstrual complaints
Interventions	Screening: Screening for 2 cycles Placebo run in: None Intervention: Group2: 5mg citalopram follicular then 10-30mg citalopram luteal phase for three cycles (n=20) versus Placebo administered orally for three cycles (n=20) Medication in 18 dosette packs, 6 for each cycle Timing of administration: Medication commenced on the first day of menses Summary measures: Data was analysed for endpoint data using LOCF
Outcomes	Visual analogue scale for irritability, depression, tension, anxiety, appetite, bloating, mastalgia Side effects

Wikander 1998b (*Continued*)

Notes	Data on adverse events could not be extracted Funding by Swedish Medical Research Council, Soderstrom Konigska Nursing Home Foundation, Frederrik and Ingrid Thuring's Foundation, Knut and Alice Wallenberg's Foundation

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - Unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind, no details
Incomplete outcome data addressed? All outcomes	Yes	In total this four arm study enrolled 123 women. Seventy eight of them received medication. In the continuous dosing group two patients dropped out for side effects, in the semi-intermittent group 3 dropped out, two for side effects and 1 protocol violation; in the intermittent group one dropped out for side effects and three of the placebo group dropped out for side effects. Sixty nine subjects completed the trial
Free of selective reporting?	Yes	

Wikander 1998c

Methods	4 arm parallel trial See Wikander 1998 (1) & (2). Common placebo group (20 randomised, 17 completed)
Participants	Country: Sweden Site: Not stated Recruitment:123 women recruited in total to 4 arm study. 78 received medication in the four arm study. 39 randomised, 34 completed this comparison of continuous versus placebo arm. Women recruited via newspaper advertisements, followed by telephone and then structured interview. Mean age of citalopram intermittent was 36±6 and for placebo was 37±5 years. Refer to Table of bias for details of attrition Inclusion: Marked premenstrual irritability and/or dysphoria appearing regularly during the two weeks preceding menstrual bleeding and terminating a few days after the onset of menstruation. Criteria A, B, C and D for LLPDD in DSM-IV-R. Displaying cyclicity with respect to irritability and depressed mood during at least two cycles of prospective rating. >100% increase in either irritability or dysphoria (or both) during the premenstrual week as compared with the postmenstrual week, a mean premenstrual rating of

Wikander 1998c (*Continued*)

	irritability or dysphoria exceeding 20mm Exclusion: Previous or ongoing mental illness (apart from major depressive or dysthymic disorders, ongoing major depressive or dysthymic disorders, major depressive disorder or dysthymic disorder < 2 years from the time of the interview, ongoing medication for somatic or mental illness (with the exception of casual analgesics), use of oral contraceptives, ongoing alcohol abuse, ongoing somatic illness, irregular menstrual bleeding or a normal cycle length <25 or > 35 days, ongoing or planned pregnancy and <18 years of age, having previous treatment with antidepressants for premenstrual complaints
Interventions	Screening: Screening for 2 cycles Placebo run in: None Intervention: Group3: 10-30mg citalopram continuous for three cycles (n=19)Versus Placebo administered orally for three cycles (n=20)Medication in 18 dosette packs, 6 for each cycle Timing of administration: Medication commenced on the first day of menses Summary measures: Data was analysed for endpoint data using LOCF
Outcomes	Visual analogue scale for irritability, depression, tension, anxiety, appetite, bloating, mastalgia
Notes	Visual analogue scale for irritability, depression, tension, anxiety, appetite, bloating, mastalgia Side effects Funding by Swedish Medical Research Council, Soderstrom Konigska Nursing Home Foundation, Frederrik and Ingrid Thuring's Foundation, Knut and Alice Wallenberg's Foundation

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment
Blinding? All outcomes	Unclear	Double blind, no details
Incomplete outcome data addressed? All outcomes	Yes	In total this four arm study enrolled 123 women. Seventy eight of them received medication. In the continuous dosing group two patients dropped out for side effects, in the semi-intermittent group 3 dropped out, two for side effects and 1 protocol violation; in the intermittent group one dropped out for side effects and three of the placebo group dropped out for side effects. Sixty nine subjects completed the trial

Wikander 1998c (*Continued*)

Free of selective reporting?	Yes	

Wood 1992

Methods	Randomised, placebo controlled, crossover trial 2X3 cycles
Participants	Country: USA Site: Women recruited from a PMS clinic. Recruitment: Women were between the age of 33-42 years. 8 women randomised, 8 completed Inclusion: Regular menstrual cycles (26-32 days), ovulating, onset of premenstrual symptoms during the second half of the menstrual cycle with resolution within the first four days after the onset of menstruation Exclusion: Past or present psychiatric disorder, family history of depression in a first degree relative, significant medical or gynaecological disorders
Interventions	Screening: Screening for two to three cycles Placebo run in: No Intervention: 20mg fluoxetine every day for 3 cycles then crossover to placebo taken daily for 3 cycles Timing of administration: No details as to when in the cycle medication commenced Summary measures: Data pooled, unable to separate first arm data
Outcomes	Calender premenstrual Experiences, Profile of Mood States, Beck Depression Inventory, STATE-TRAIT Anxiety Inventory
Notes	Daily symptom rating Funding by National Institute of child health and human development

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised, crossover design. Order of randomisation based on a pre-selected randomisation list based on the sequential assignment of subject numbers
Allocation concealment?	Unclear	B - unclear. No details of concealment.
Blinding? All outcomes	Unclear	Double blind, no details.
Incomplete outcome data addressed? All outcomes	Yes	Eight women recruited.
Free of selective reporting?	Yes	

Yonkers 1997

Methods	Randomised, double blind, placebo controlled, 2 arm parallel trial
Participants	Country: USA Site: Twelve university affiliated psychiatric and gynaecological departments Recruitment: Women recruited by advertisement and referral. 447 screened, 243 randomised, 200 completed (99 treatment, 101 placebo). Refer to Table of bias for details of attrition.Mean age of sertraline group 36.8+/-4.8 (23-45), mean age of placebo group 36.5+/-5.0 (25-45) years Inclusion: Age range 24 to 45 years, regular menstrual cycles (24 to 36 days), more than two year history of PMDD Exclusion: Failure to confirm isolated luteal phase symptoms for at least two cycles based on daily symptom ratings, those meeting criteria for other, mood anxiety or eating disorder within previous 6 months, those with alcohol or other drug use or dependence within 12 months and those with a lifetime history of organic mental syndrome, psychotic disorder, or antisocial, schizotypal, or severe borderline personality disorder. Clinically symptomatic endometriosis, hysterectomy, perimenopausal status as determined by FSH >/20U/L, neurological disease or any severe or unstable general medical illness
Interventions	Screening: Two screening cycles Placebo run in: One single blind placebo treatment Intervention: 3 cycles of 50-150mg sertraline every day administered orally (n=121). Mean dosage across the three cycles was 79.1mg versus placebo administered orally daily for three cycles (n=122) Timing of administration: Treatment commenced on day 1 of menses and continued throughout cycle Summary measures: Review has used 'end point' data from paper which is the final visit for each patient
Outcomes	Daily Record of Severity of Problems (DRSP); Hamilton rating Scale for Depression (HRSD); Clinical Global Impression Scale (CGI-S) (CGI-I); Social Adjustment Scale (SAS); Patient Global Evaluation (PGE); Adverse events
Notes	Daily symptom rating Funded by Pfizer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation in blocks of four.
Allocation concealment?	Yes	A - Adequate. Randomisation occurred at a central location.
Incomplete outcome data addressed? All outcomes	Yes	447 women screened, 243 randomised. 121 received sertraline, there were 22 withdrawals (ineffective n=2, unavailable for follow up n=3, adverse event n=10, labora-

Yonkers 1997 (*Continued*)

		tory abnormality n=1, intercurrent illness n=2, poor compliance n=4), 122 women received placebo, there were 21 withdrawn (ineffective medication n= 6, unavailable for follow up n= 6, adverse event n=2, laboratory abnormality n=0, intercurrent illness n=1, poor compliance n=6)
Free of selective reporting?	Yes	

Young 1998

Methods	Randomised, double blind, crossover trial.
Participants	Country: USA Site: Walter Reed Army Medical Centre Recruitment: 50 women screened, 31 selected. Following two screening cycles 17 women randomised, 11 completed. Refer to Table of bias for details of attrition.Women recruited from medical centre who had responded to advertisements in local military newspapers and gynaecology clinics Inclusion: Age between 18 and 45 years. Meeting DSM-IV criteria. After screening cycles to have overall COPE score 30% greater during late luteal phase compared with follicular phase Exclusion: Any history of mental health treatment in previous 18 months, taking psychotropic medication. Diagnosis of active disease or pregnancy
Interventions	Screening: Two cycles screening with no medication. Placebo run in: None Intervention: 50mg sertraline day 15 to menses for 2 cycles versus placebo with one cycle washout Timing of administration: Commencing day 15 to the first day of menses Summary measures: Data from both arms combined.
Outcomes	Calender of Premenstrual Experiences (COPE) patient completed. Total scores and physical and behavioural sub-scores
Notes	Unable to extract data as not distinguishable by arm of study. Authors not contacted Independently funded

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details of randomisation
Allocation concealment?	Unclear	B - unclear. No details of concealment

Young 1998 (*Continued*)

Blinding? All outcomes	Yes	Double blind (physicians assessing women were blinded to treatment)
Incomplete outcome data addressed? All outcomes	Yes	Three women failed to complete study due to medication side effects (2x sertraline and 1x placebo. unclear as to which arm of the crossover this occurred in. One subject moved out of area and two discontinued for undetermined reasons

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alpay 2001	Not placebo controlled
Bellew 2002	Conference proceeding referring to full data published by Landen 2007
Brandenburg 1993	Open trial. Not placebo controlled
Cohen 2001	Conference abstract of data reported in full in Cohen 2002a,b
Cohen 2002	Conference abstract of data reported in full in Cohen 2004a,b
Cohen 2003	Conference abstract of data reported in full in Cohen 2004a,b
De la Gandara 1997	Open trial. Not placebo controlled
Diegoli 1998	Low quality [2] Jadad Score (Jadad 1996) [4] Authors quality score
Dillon 2000	This conference abstract refers to Steiner 2001 and is therefore reported in Steiner 1995a,b
Elks 1993	Open trial. Not placebo controlled
Flores Ramos 2003	randomised trial of intermittent and continuous citalopram. Not placebo controlled
Freeman 1996	Open trial. Not placebo controlled
Freeman 1998a	Conference abstract of Freeman 1996. Open trial. Not placebo controlled
Freeman 1998b	Conference abstract of Freeman 1996. Open trial. Not placebo controlled
Freeman 1999b	Open trial. Not placebo controlled

(*Continued*)

Freeman 2000	No extractable symptom data presented; only data on baseline postmenstrual symptoms
Freeman 2002	Open trial. Not placebo controlled
Freeman 2005	Randomised trial but not placebo controlled
Gee 2003	Conference abstract referring to data published in full by Steiner 2005a,b
Halbreich 2000a	Conference abstract, full data reported in Halbreich 2002
Halbreich 2000b	Conference abstract, full data reported in Halbreich 2002
Judge 2001	Conference abstract referring to full data reported by Cohen 2002
Koke 2001	This conference abstract refers to Steiner 2001 and is therefore reported in Steiner 1995a,b
Kornstein 2002	Conference abstract referring to full data reported by Kornstein 2006
Landen 2001	Conference proceedings reported in full in Landen 2007 (see included trials)
Landen 2002	Conference proceedings reported in full in Landen 2007 (see included trials)
Menkes 1992	Preliminary data from Menkes 1993
Miner 2002	Conference abstract referring to pooled data from Miner 2002 and Cohen 2002 reported in full in the included studies table
Nilsson 2000	This conference abstract refers to Steiner 2001 and is therefore reported in Steiner 1995a,b
Pearlstein 1994	Open trial. Not placebo controlled
Pearlstein 1998	Conference abstract of paper reported in full by Pearlstein 2000
Pearlstein 2000	No extractable symptom data presented; only data on psychosocial functioning
Pearlstein 2002	Conference abstract relating to full paper of Pearlstein 2005
Pearlstein 2003	Not RCT, retrospective analysis of Cohen (2002) and Miner (2002)
Pearlstein 2005	This paper refers to the population described in full by Halbreich 2002. It describes pre-treatment symptoms only of the sample population
Rickels 1990	Not blind, not randomised, placebo group from parallel trial
Steiner 1997b	Open trial. Not placebo controlled
Steiner 1999	Data reported in full in Steiner 1995a,b

(*Continued*)

Steiner 1999b	Data reported in full in Steiner 1995a,b
Steiner 1999c	Data reported in full in Steiner 1995a,b
Steiner 2000	Conference abstract, data reported in full in Steiner 1995a,b
Steiner 2000b	Conference abstract, data reported in full in Steiner 1995a,b
Steiner 2000c	Conference abstract, data reported in full in Steiner 2003; Steiner 1995a,b
Steiner 2001b	Conference abstract, data reported in full in Steiner 1995a,b
Steiner 2001c	Conference abstract, data reported in full in Steiner 1995a,b
Steiner 2001d	Conference abstract, data reported in full in Steiner 1995a,b
Steiner 2003	This paper reports on the sample described by Steiner 1995a,b. Only mean data for sub-study of functional work capacity reported using PMTS - self rated scale which was reported in full inn the above study. Data is reported graphically, no standard deviations
Stone 1990	Preliminary report of Stone 1991
Sunblad 1997	Open trial. Not placebo controlled
Trzepacz 2001a	This conference abstract refers to Steiner 2001 and is therefore reported in Steiner 1995a,b
Trzepacz 2001b	This conference abstract refers to Steiner 2001 and is therefore reported in Steiner 1995a,b
Yonkers 1996a	Open trial. Not placebo controlled
Yonkers 1996b	Preliminary report of Stone 1991
Yonkers 2005	This is a combination of data from Yonkers 1997 and Halbreich 2002. Not RCT
Yonkers 2006	Randomised crossover trial using paroxetine. However treatment was only administered for one cycle before crossover and one cycle after crossover. Study did not therefore meet review entry criteria
Young 1997	This conference abstract refers to the full paper Young 1998

DATA AND ANALYSES

Comparison 1. SSRI versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall symptoms	22	2294	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.68, -0.39]
1.1 Change scores	6	776	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.41, -0.11]
1.2 Absolute scores	16	1518	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-0.84, -0.50]
2 Behavioural premenstrual symptoms	15	1892	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.53, -0.30]
3 Physical premenstrual symptoms	14	1703	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.45, -0.22]
4 Functional symptoms	7	1002	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.46, -0.07]
5 Irritability	8	920	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.74, -0.40]
6 Specific SSRI	24		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 fluoxetine	8	827	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.88, -0.26]
6.2 Paroxetine	3	356	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.06, -0.60]
6.3 Citalopram	3	70	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-1.86, -0.69]
6.4 Sertraline	8	1049	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.56, -0.31]
6.5 fluvoxamine	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.55, 1.22]
6.6 clomipramine	1	28	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.40, 0.13]
7 Type of run-in	23		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Placebo run-in	15	1984	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.62, -0.34]
7.2 non placebo run-in	8	323	Std. Mean Difference (IV, Random, 95% CI)	-0.82 [-1.23, -0.41]
8 Luteal or continous administration	22		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Luteal phase only (intermittent) administration	11	1176	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.49, -0.21]
8.2 Continuous adminsitration	11	1107	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-0.92, -0.52]
9 Response to treatment	27	2731	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [2.43, 3.37]
10 Adverse events	23		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Nausea	21	2780	Odds Ratio (M-H, Fixed, 95% CI)	3.71 [2.75, 5.01]
10.2 Gastrointestinal irritability	1	44	Odds Ratio (M-H, Fixed, 95% CI)	8.08 [0.39, 166.27]
10.3 Insomnia/sleep disturbance	23	2842	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [1.46, 2.66]
10.4 Sexual dysfunction	7	546	Odds Ratio (M-H, Fixed, 95% CI)	4.25 [1.81, 9.99]
10.5 Headache	21	2548	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.93, 1.52]
10.6 Dizziness/vertigo	14	1760	Odds Ratio (M-H, Fixed, 95% CI)	2.76 [1.72, 4.44]
10.7 Fatigue/sedation	10	763	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [1.28, 3.17]
10.8 Decreased appetite	4	374	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.92, 5.14]
10.9 Decreased energy	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 8.33]
10.10 Anxiety	5	437	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.60, 3.31]
10.11 Breast tenderness	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 8.33]
10.12 Increased appetite	3	177	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.30, 5.19]
10.13 Tremor	6	994	Odds Ratio (M-H, Fixed, 95% CI)	7.31 [2.63, 20.31]
10.14 Somnolence/decreased concentration	9	1281	Odds Ratio (M-H, Fixed, 95% CI)	5.59 [2.92, 10.68]

10.15 Sweating	13	1604	Odds Ratio (M-H, Fixed, 95% CI)	3.22 [1.92, 5.42]
10.16 Visual disturbance	3	358	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [0.69, 5.17]
10.17 Dry mouth	12	1286	Odds Ratio (M-H, Fixed, 95% CI)	4.00 [2.41, 6.63]
10.18 Cardiovascular symptoms	4	380	Odds Ratio (M-H, Fixed, 95% CI)	5.14 [1.28, 20.61]
10.19 Yawning	5	717	Odds Ratio (M-H, Fixed, 95% CI)	4.55 [1.35, 15.26]
10.20 Asthenia	8	1299	Odds Ratio (M-H, Fixed, 95% CI)	3.46 [2.16, 5.55]
10.21 Decreased libido	14	2001	Odds Ratio (M-H, Fixed, 95% CI)	2.91 [1.84, 4.59]
10.22 Trauma	2	314	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.66, 6.32]
10.23 Dyspepsia	5	691	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.56, 3.67]
10.24 Respiratory disorder	8	1334	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.08]
10.25 Diarrhoea	13	1945	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [1.78, 5.16]
10.26 Sinusitis	8	1299	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.49, 1.52]
10.27 Constipation	6	589	Odds Ratio (M-H, Fixed, 95% CI)	2.77 [1.18, 6.50]
10.28 Parasthesia/numbness	1	44	Odds Ratio (M-H, Fixed, 95% CI)	5.49 [0.25, 121.18]
10.29 Rash	1	22	Odds Ratio (M-H, Fixed, 95% CI)	3.95 [0.14, 108.09]
10.30 Formication	1	29	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.11, 79.91]
10.31 Increased thirst	1	29	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 7.74]
10.32 Rhinitis	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.46, 2.07]
10.33 Pharyngitis	2	260	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.30, 3.50]
10.34 Back pain	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.22, 1.99]
10.35 Flu syndrome	2	260	Odds Ratio (M-H, Fixed, 95% CI)	2.65 [0.57, 12.37]
10.36 Pain	4	516	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.17, 1.44]
10.37 Accidental injury	2	260	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.02, 0.67]
10.38 Female genital disorders	2	359	Odds Ratio (M-H, Fixed, 95% CI)	3.57 [1.21, 10.49]
10.39 Vomiting	2	359	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.31, 5.98]
10.40 Infection	6	981	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.59]
10.41 Dysmenorrhoea	2	359	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.12]
11 Study withdrawal	32		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Withdrawal due to adverse event/s	27	3231	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [1.58, 2.83]
11.2 Withdrawal any reason	32	3486	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.22]

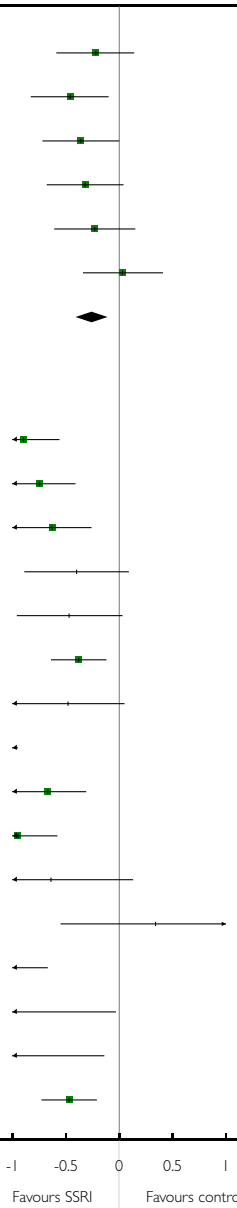
Analysis 1.1. Comparison 1 SSRI versus placebo, Outcome 1 Overall symptoms.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 1 Overall symptoms

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Change scores							
Cohen 2002a	86	-27.5 (20.1)	44	-23.2 (16.8)		5.6 %	-0.22 [-0.59, 0.14]
Cohen 2002b	86	-31.3 (17.6)	44	-23.2 (16.8)		5.6 %	-0.46 [-0.83, -0.10]
Kornstein 2006 a	91	-12.6 (11.5)	45	-8.8 (8.1)		5.7 %	-0.36 [-0.72, 0.00]
Kornstein 2006b	88	-12.1 (11.3)	45	-8.8 (8.1)		5.7 %	-0.32 [-0.68, 0.04]
Miner 2002a	84	-30.4 (19.7)	40	-25.9 (18.6)		5.5 %	-0.23 [-0.61, 0.15]
Miner 2002b	83	-25.3 (16.5)	40	-25.9 (18.6)		5.5 %	0.03 [-0.34, 0.41]
Subtotal (95% CI)	**518**		**258**			**33.6 %**	**-0.26 [-0.41, -0.11]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.98$, df = 5 (P = 0.55); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.45 (P = 0.00057)							
2 Absolute scores							
Cohen 2004 a	111	220 (161)	53	345 (63.7)		5.9 %	-0.90 [-1.25, -0.56]
Cohen 2004b	95	250 (149)	53	345 (63.7)		5.8 %	-0.75 [-1.10, -0.41]
Freeman 1999a	62	81 (60)	55	124 (75)		5.5 %	-0.63 [-1.01, -0.26]
Freeman 2004 a	48	79.4 (48.5)	25	98.8 (47.38)		4.4 %	-0.40 [-0.89, 0.09]
Freeman 2004b	45	76.8 (46.3)	25	98.8 (47.38)		4.3 %	-0.47 [-0.96, 0.03]
Halbreich 2002	119	46.5 (18.9)	110	54.9 (24.8)		6.9 %	-0.38 [-0.64, -0.12]
Jermain 1999	28	55 (53.9)	29	85 (68.7)		4.0 %	-0.48 [-1.01, 0.05]
Ozeren 1997	15	31.2 (8.2)	15	57.4 (18)		2.1 %	-1.82 [-2.69, -0.95]
Steiner 1995 a	96	32.4 (27.2)	48	51.1 (29.1)		5.7 %	-0.67 [-1.02, -0.31]
Steiner 1995b	86	26.6 (23.5)	48	51.1 (29.1)		5.6 %	-0.95 [-1.32, -0.58]
Sundblad 1993	14	15.75 (15.8)	14	29.92 (26.19)		2.5 %	-0.64 [-1.40, 0.13]
Veeninga 1990	10	1.12 (0.2)	10	1.05 (0.2)		2.0 %	0.34 [-0.55, 1.22]
Wikander 1998a	18	10 (3.67)	6	16.61 (3.67)		1.5 %	-1.74 [-2.81, -0.67]
Wikander 1998b	17	10 (3.39)	6	13.56 (3.39)		1.7 %	-1.01 [-2.00, -0.03]
Wikander 1998c	17	10 (3.39)	6	13.99 (3.39)		1.7 %	-1.13 [-2.13, -0.14]
Yonkers 1997	116	43.5 (19.1)	118	53.7 (24.1)		6.9 %	-0.47 [-0.73, -0.21]



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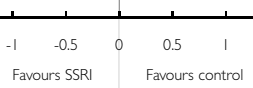
Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**897**		**621**			**66.4 %**	**-0.67 [-0.84, -0.50]**
Heterogeneity: Tau² = 0.05; Chi² = 29.93, df = 15 (P = 0.01); I² =50%							
Test for overall effect: Z = 7.89 (P < 0.00001)							
Total (95% CI)	**1415**		**879**			**100.0 %**	**-0.54 [-0.68, -0.39]**
Heterogeneity: Tau² = 0.06; Chi² = 49.08, df = 21 (P = 0.00049); I² =57%							
Test for overall effect: Z = 7.36 (P < 0.00001)							



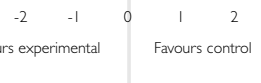
Analysis 1.2. Comparison 1 SSRI versus placebo, Outcome 2 Behavioural premenstrual symptoms.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 2 Behavioural premenstrual symptoms

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Arrendondo 1997	37	3.23 (5.66)	35	8.57 (11.24)		4.8 %	-0.60 [-1.07, -0.13]
Cohen 2002a	83	-13.4 (8.4)	43	-10.1 (7.3)		6.9 %	-0.41 [-0.78, -0.04]
Cohen 2002b	83	-14 (7.6)	43	-10.1 (7.3)		6.8 %	-0.52 [-0.89, -0.14]
Freeman 1999a	62	4.86 (5.84)	55	7.62 (6.7)		7.0 %	-0.44 [-0.81, -0.07]
Kornstein 2006 a	91	-4.3 (2.86)	45	-3.4 (2.01)		7.2 %	-0.34 [-0.70, 0.02]
Kornstein 2006b	88	-3.5 (3.75)	45	-3.4 (2.01)		7.2 %	-0.03 [-0.39, 0.33]
Miner 2002a	84	-14.5 (8.2)	40	-11.6 (7.9)		6.7 %	-0.36 [-0.73, 0.02]
Miner 2002b	83	-11.8 (7.7)	40	-11.6 (7.9)		6.7 %	-0.03 [-0.40, 0.35]
Pearlstein 2005 a	78	16.9 (19.36)	48	27.8 (23.12)		7.0 %	-0.52 [-0.88, -0.15]
Pearlstein 2005b	92	20.1 (23.1)	48	27.8 (23.12)		7.4 %	-0.33 [-0.68, 0.02]
Steiner 2005 a	130	-32 (22.8)	60	-24 (15.5)		8.7 %	-0.38 [-0.69, -0.07]
Steiner 2005 b	116	-35 (21.5)	60	-24 (15.5)		8.4 %	-0.56 [-0.87, -0.24]
Sundblad 1992	20	8 (4.5)	20	36 (26.8)		2.5 %	-1.43 [-2.13, -0.73]



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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Sundblad 1993	15	11.67 (9.7)	14	31 (28.7)		2.1 %	-0.89 [-1.66, -0.12]
Yonkers 1997	116	7.4 (5.7)	118	9.8 (5.2)		10.6 %	-0.44 [-0.70, -0.18]
Total (95% CI)	**1178**		**714**			**100.0 %**	**-0.42 [-0.53, -0.30]**

Heterogeneity: Tau² = 0.02; Chi² = 20.45, df = 14 (P = 0.12); I² =32%

Test for overall effect: Z = 6.95 (P < 0.00001)

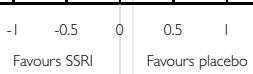
Analysis 1.3. Comparison 1 SSRI versus placebo, Outcome 3 Physical premenstrual symptoms.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 3 Physical premenstrual symptoms

Study or subgroup	SSRI N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Cohen 2002a	83	-3 (3.7)	43	-3 (3.1)		7.6 %	0.0 [-0.37, 0.37]
Cohen 2002b	83	-4.7 (3.2)	43	-3 (3.1)		7.4 %	-0.53 [-0.91, -0.16]
Freeman 1999a	62	12 (11)	55	17 (13)		7.6 %	-0.41 [-0.78, -0.05]
Halbreich 2002	112	8.6 (3.7)	107	9.1 (3.8)		12.1 %	-0.13 [-0.40, 0.13]
Kornstein 2006 a	91	-1.7 (1.9)	45	-1.3 (1.3)		7.9 %	-0.23 [-0.59, 0.13]
Kornstein 2006b	88	-1.7 (1.9)	45	-1.3 (1.3)		7.8 %	-0.23 [-0.59, 0.13]
Miner 2002a	84	-3.8 (4.2)	40	-3 (3.7)		7.3 %	-0.20 [-0.57, 0.18]
Miner 2002b	83	-3.4 (3.2)	40	-3 (3.7)		7.3 %	-0.12 [-0.50, 0.26]
Pearlstein 1997	10	45 (35)	12	92 (45)		1.5 %	-1.11 [-2.02, -0.19]
Steiner 1995 a	95	26.7 (20.74)	47	39.2 (21.4)		8.0 %	-0.59 [-0.95, -0.24]
Steiner 1995b	85	27.2 (21.57)	47	39.2 (21.4)		7.8 %	-0.55 [-0.92, -0.19]
Sundblad 1992	20	16 (22.4)	20	29 (26.8)		3.0 %	-0.52 [-1.15, 0.12]
Sundblad 1993	15	19.83 (21.93)	14	28.83 (23.63)		2.3 %	-0.38 [-1.12, 0.35]
Yonkers 1997	116	16.7 (7.3)	118	20.6 (9.4)		12.5 %	-0.46 [-0.72, -0.20]



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Study or subgroup	SSRI N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Total (95% CI)	**1027**		**676**			**100.0 %**	**-0.34 [-0.45, -0.22]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 16.52$, df = 13 (P = 0.22); $I^2 = 21\%$

Test for overall effect: Z = 5.73 (P < 0.00001)

Analysis 1.4. Comparison 1 SSRI versus placebo, Outcome 4 Functional symptoms.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 4 Functional symptoms

Study or subgroup	SSRIs N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Cohen 2002a	83	-4.9 (3.4)	43	-3.9 (2.9)		13.6 %	-0.31 [-0.68, 0.06]
Cohen 2002b	83	-5.1 (3.2)	43	-3.9 (2.9)		13.6 %	-0.38 [-0.76, -0.01]
Kornstein 2006 a	91	-0.3 (0.95)	45	-0.2 (0.67)		14.1 %	-0.11 [-0.47, 0.24]
Kornstein 2006b	88	-0.3 (0.94)	45	-0.2 (0.67)		14.0 %	-0.12 [-0.48, 0.24]
Miner 2002a	84	-5.3 (3.3)	40	-4.5 (3.3)		13.4 %	-0.24 [-0.62, 0.14]
Miner 2002b	83	-4.3 (3)	40	-4.5 (3.3)		13.4 %	0.06 [-0.31, 0.44]
Yonkers 1997	116	1.8 (0.4)	118	2.1 (0.5)		18.0 %	-0.66 [-0.92, -0.40]
Total (95% CI)	**628**		**374**			**100.0 %**	**-0.27 [-0.46, -0.07]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 13.09$, df = 6 (P = 0.04); $I^2 = 54\%$

Test for overall effect: Z = 2.69 (P = 0.0071)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 SSRI versus placebo, Outcome 5 Irritability.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

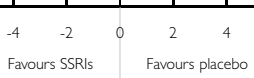
Comparison: 1 SSRI versus placebo

Outcome: 5 Irritability

Study or subgroup	SSRIs N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Cohen 2002a	83	-3.6 (2.3)	43	-2.7 (1.9)		14.4 %	-0.41 [-0.78, -0.04]
Cohen 2002b	83	-3.7 (2.1)	43	-2.7 (1.9)		14.3 %	-0.49 [-0.86, -0.12]
Freeman 1999a	62	4.8 (5.6)	55	9.1 (6.6)		14.2 %	-0.70 [-1.08, -0.33]
Halbreich 2002	119	3.9 (2)	107	5.2 (2.6)		21.7 %	-0.56 [-0.83, -0.30]
Pearlstein 1997	10	94 (97)	12	102 (70)		3.7 %	-0.09 [-0.93, 0.75]
Sundblad 1992	20	9 (4.5)	20	39 (31.3)		5.3 %	-1.32 [-2.01, -0.62]
Sundblad 1993	15	15 (9.7)	14	38 (26.2)		4.1 %	-1.15 [-1.94, -0.35]
Yonkers 1997	116	4.2 (1.9)	118	5.2 (2.4)		22.3 %	-0.46 [-0.72, -0.20]
Total (95% CI)	**508**		**412**			**100.0 %**	**-0.57 [-0.74, -0.40]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.76$, df = 7 (P = 0.20); $I^2 = 28\%$

Test for overall effect: Z = 6.65 (P < 0.00001)



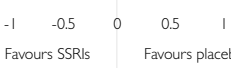
Analysis 1.6. Comparison 1 SSRI versus placebo, Outcome 6 Specific SSRI.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 6 Specific SSRI

Study or subgroup	SSRI N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 fluoxetine							
Cohen 2002a	83	-27.5 (20.1)	43	-23.2 (16.8)		15.0 %	-0.22 [-0.59, 0.14]
Cohen 2002b	83	-31.3 (17.6)	43	-23.2 (16.8)		14.9 %	-0.46 [-0.84, -0.09]
Miner 2002a	84	-30.4 (19.7)	40	-25.9 (18.6)		14.7 %	-0.23 [-0.61, 0.15]
Miner 2002b	83	-25.3 (16.3)	40	-25.9 (18.6)		14.8 %	0.03 [-0.34, 0.41]
Ozeren 1997	15	31.2 (8.2)	15	57.4 (18)		5.5 %	-1.82 [-2.69, -0.95]
Steiner 1995 a	96	32.4 (27.2)	48	51.1 (29.1)		15.4 %	-0.67 [-1.02, -0.31]
Steiner 1995b	86	26.6 (23.5)	48	51.1 (29.1)		14.9 %	-0.95 [-1.32, -0.58]
Stone 1991	10	67.5 (11.96)	10	81.3 (11.96)		4.7 %	-1.11 [-2.06, -0.15]
Subtotal (95% CI)	**540**		**287**			**100.0 %**	**-0.57 [-0.88, -0.26]**
Heterogeneity: Tau² = 0.14; Chi² = 28.69, df = 7 (P = 0.00016); I² =76%							
Test for overall effect: Z = 3.56 (P = 0.00037)							
2 Paroxetine							
Cohen 2004 a	111	220 (161)	53	345 (63.7)		39.2 %	-0.90 [-1.25, -0.56]
Cohen 2004b	95	250 (149)	53	345 (63.7)		38.8 %	-0.75 [-1.10, -0.41]
Eriksson 1995	22	7.38 (11.9)	22	26.8 (30.68)		22.1 %	-0.82 [-1.44, -0.20]
Subtotal (95% CI)	**228**		**128**			**100.0 %**	**-0.83 [-1.06, -0.60]**
Heterogeneity: Tau² = 0.0; Chi² = 0.37, df = 2 (P = 0.83); I² =0.0%							
Test for overall effect: Z = 7.17 (P < 0.00001)							
3 Citalopram							
Wikander 1998a	18	10 (3.67)	6	16.61 (3.67)		30.6 %	-1.74 [-2.81, -0.67]
Wikander 1998b	17	10 (3.39)	6	13.56 (3.39)		35.1 %	-1.01 [-2.00, -0.03]
Wikander 1998c	17	10 (3.39)	6	13.99 (3.39)		34.3 %	-1.13 [-2.13, -0.14]
Subtotal (95% CI)	**52**		**18**			**100.0 %**	**-1.27 [-1.86, -0.69]**
Heterogeneity: Tau² = 0.0; Chi² = 1.07, df = 2 (P = 0.58); I² =0.0%							
Test for overall effect: Z = 4.26 (P = 0.000021)							
4 Sertraline							
Freeman 1999a	62	81 (60)	55	124 (75)		12.8 %	-0.63 [-1.01, -0.26]
Freeman 2004 a	48	79.4 (48.5)	25	98.8 (47.38)		10.0 %	-0.40 [-0.89, 0.09]



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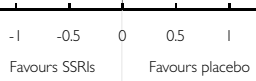
Study or subgroup	SSRI N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Freeman 2004b	45	76.8 (46.3)	25	98.8 (47.38)		9.9 %	-0.47 [-0.96, 0.03]
Halbreich 2002	119	46.5 (18.9)	110	54.9 (24.8)		15.9 %	-0.38 [-0.64, -0.12]
Jermain 1999	28	55 (53.9)	29	85 (68.7)		9.2 %	-0.48 [-1.01, 0.05]
Kornstein 2006 a	91	-12.6 (11.5)	45	-8.8 (8.1)		13.1 %	-0.36 [-0.72, 0.00]
Kornstein 2006b	88	-12.1 (11.3)	45	-8.8 (8.1)		13.1 %	-0.32 [-0.68, 0.04]
Yonkers 1997	116	43.5 (19.1)	118	53.7 (24.1)		15.9 %	-0.47 [-0.73, -0.21]
Subtotal (95% CI)	**597**		**452**			**100.0 %**	**-0.43 [-0.56, -0.31]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.94$, df = 7 (P = 0.96); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.76 (P < 0.00001)							
5 fluvoxamine							
Veeninga 1990	10	1.12 (0.2)	10	1.05 (0.2)		100.0 %	0.34 [-0.55, 1.22]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**0.34 [-0.55, 1.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.74 (P = 0.46)							
6 clomipramine							
Sundblad 1993	14	15.75 (15.8)	14	29.92 (26.19)		100.0 %	-0.64 [-1.40, 0.13]
Subtotal (95% CI)	**14**		**14**			**100.0 %**	**-0.64 [-1.40, 0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.64 (P = 0.10)							



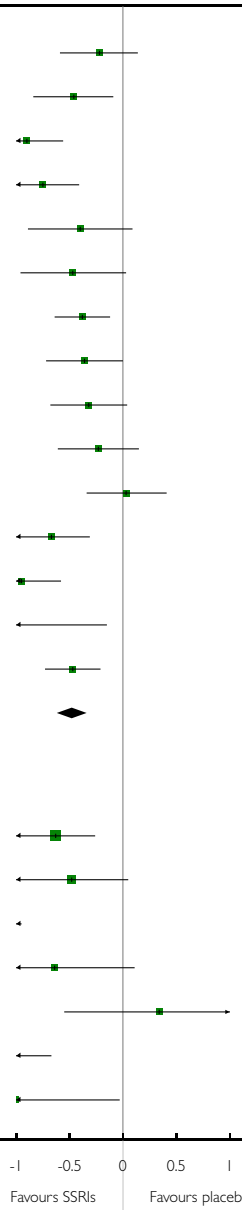
Analysis 1.7. Comparison 1 SSRI versus placebo, Outcome 7 Type of run-in.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 7 Type of run-in

Study or subgroup	SSRIs N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Placebo run-in							
Cohen 2002a	83	-27.5 (20.1)	43	-23.2 (16.8)		6.9 %	-0.22 [-0.59, 0.14]
Cohen 2002b	83	-31.3 (17.6)	43	-23.2 (16.8)		6.9 %	-0.46 [-0.84, -0.09]
Cohen 2004 a	111	220 (161)	53	345 (63.7)		7.3 %	-0.90 [-1.25, -0.56]
Cohen 2004b	95	250 (149.2)	53	345 (63.7)		7.2 %	-0.75 [-1.10, -0.41]
Freeman 2004 a	48	79.4 (48.5)	25	98.8 (47.38)		5.4 %	-0.40 [-0.89, 0.09]
Freeman 2004b	45	76.8 (46.3)	25	98.8 (47.38)		5.3 %	-0.47 [-0.96, 0.03]
Halbreich 2002	119	46.5 (18.9)	110	54.9 (24.8)		8.5 %	-0.38 [-0.64, -0.12]
Kornstein 2006 a	91	-12.6 (11.5)	45	-8.8 (8.1)		7.1 %	-0.36 [-0.72, 0.00]
Kornstein 2006b	88	-12.1 (11.3)	45	-8.8 (8.1)		7.0 %	-0.32 [-0.68, 0.04]
Miner 2002a	84	-30.4 (19.7)	40	-25.9 (18.6)		6.8 %	-0.23 [-0.61, 0.15]
Miner 2002b	83	-25.3 (16.5)	40	-25.9 (18.6)		6.8 %	0.03 [-0.34, 0.41]
Steiner 1995 a	96	32.4 (27.2)	48	51.1 (29.1)		7.1 %	-0.67 [-1.02, -0.31]
Steiner 1995b	86	26.6 (23.5)	48	51.1 (29.1)		6.9 %	-0.95 [-1.32, -0.58]
Stone 1991	10	67.5 (11.96)	10	81.3 (11.96)		2.2 %	-1.11 [-2.06, -0.15]
Yonkers 1997	116	43.5 (19.1)	118	53.7 (24.1)		8.5 %	-0.47 [-0.73, -0.21]
Subtotal (95% CI)	**1238**		**746**			**100.0 %**	**-0.48 [-0.62, -0.34]**
Heterogeneity: Tau² = 0.04; Chi² = 29.71, df = 14 (P = 0.01); I² =53%							
Test for overall effect: Z = 6.76 (P < 0.00001)							
2 non placebo run-in							
Freeman 1999a	62	81 (60)	55	124 (75)		26.3 %	-0.63 [-1.01, -0.26]
Jermain 1999	28	55 (53.9)	29	85 (68.7)		19.1 %	-0.48 [-1.01, 0.05]
Ozeren 1997	15	31.2 (8.2)	15	57.4 (18)		9.8 %	-1.82 [-2.69, -0.95]
Sundblad 1993	15	15.75 (15.8)	14	29.92 (26.19)		12.2 %	-0.64 [-1.39, 0.11]
Veeninga 1990	10	1.12 (0.2)	10	1.05 (0.2)		9.6 %	0.34 [-0.55, 1.22]
Wikander 1998a	18	10 (3.67)	6	16.61 (3.67)		7.0 %	-1.74 [-2.81, -0.67]
Wikander 1998b	17	10 (3.39)	6	13.56 (3.39)		8.1 %	-1.01 [-2.00, -0.03]



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Study or subgroup	SSRIs N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Wikander 1998c	17	10 (3.39)	6	13.99 (3.39)		7.9 %	-1.13 [-2.13, -0.14]
Subtotal (95% CI)	**182**		**141**			**100.0 %**	**-0.82 [-1.23, -0.41]**

Heterogeneity: Tau² = 0.19; Chi² = 17.19, df = 7 (P = 0.02); I² =59%

Test for overall effect: Z = 3.93 (P = 0.000086)

Analysis 1.8. Comparison 1 SSRI versus placebo, Outcome 8 Luteal or continous administration.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 8 Luteal or continous administration

Study or subgroup	SSRIs N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Luteal phase only (intermittent) administration							
Cohen 2002a	83	-27.5 (20.1)	43	-23.2 (16.8)		10.6 %	-0.22 [-0.59, 0.14]
Cohen 2002b	83	-31.3 (17.6)	43	-23.2 (16.8)		10.5 %	-0.46 [-0.84, -0.09]
Freeman 2004b	45	76.8 (46.3)	25	98.8 (47.38)		8.2 %	-0.47 [-0.96, 0.03]
Halbreich 2002	119	46.5 (18.9)	110	54.9 (24.8)		13.0 %	-0.38 [-0.64, -0.12]
Jermain 1999	28	55 (53.9)	29	85 (68.7)		7.7 %	-0.48 [-1.01, 0.05]
Kornstein 2006 a	91	-12.6 (11.5)	45	-8.8 (8.1)		10.8 %	-0.36 [-0.72, 0.00]
Kornstein 2006b	88	-12.1 (11.3)	45	-8.8 (8.1)		10.8 %	-0.32 [-0.68, 0.04]
Miner 2002a	84	-30.4 (19.7)	40	-25.9 (18.6)		10.4 %	-0.23 [-0.61, 0.15]
Miner 2002b	83	-25.3 (16.5)	40	-25.9 (18.6)		10.4 %	0.03 [-0.34, 0.41]
Sundblad 1993	14	15.75 (15.8)	14	29.92 (26.19)		4.8 %	-0.64 [-1.40, 0.13]
Wikander 1998a	18	10 (3.67)	6	16.61 (3.67)		2.8 %	-1.74 [-2.81, -0.67]
Subtotal (95% CI)	**736**		**440**			**100.0 %**	**-0.35 [-0.49, -0.21]**

Heterogeneity: Tau² = 0.01; Chi² = 12.71, df = 10 (P = 0.24); I² =21%

Test for overall effect: Z = 4.84 (P < 0.00001)

2 Continuous adminsitration

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Study or subgroup	SSRIs N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Cohen 2004 a	111	220 (161)	53	345 (63.7)		12.4 %	-0.90 [-1.25, -0.56]
Cohen 2004b	95	250 (149)	53	345 (63.7)		12.3 %	-0.75 [-1.10, -0.41]
Freeman 1999a	62	81 (60)	55	124 (75)		11.7 %	-0.63 [-1.01, -0.26]
Freeman 2004 a	48	79.4 (48.5)	25	98.8 (47.38)		9.2 %	-0.40 [-0.89, 0.09]
Ozeren 1997	15	31.2 (8.2)	15	57.4 (18)		4.4 %	-1.82 [-2.69, -0.95]
Steiner 1995 a	96	32.4 (27.2)	48	51.1 (29.1)		12.1 %	-0.67 [-1.02, -0.31]
Steiner 1995b	86	26.6 (23.5)	48	51.1 (29.1)		11.7 %	-0.95 [-1.32, -0.58]
Stone 1991	10	67.5 (11.96)	10	81.3 (11.96)		3.8 %	-1.11 [-2.06, -0.15]
Veeninga 1990	10	1.12 (0.2)	10	1.05 (0.2)		4.3 %	0.34 [-0.55, 1.22]
Wikander 1998c	17	10 (3.39)	6	13.99 (3.39)		3.5 %	-1.13 [-2.13, -0.14]
Yonkers 1997	116	43.5 (19.1)	118	53.7 (24.1)		14.5 %	-0.47 [-0.73, -0.21]
Subtotal (95% CI)	**666**		**441**			**100.0 %**	**-0.72 [-0.92, -0.52]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 20.99$, df = 10 (P = 0.02); $I^2 = 52\%$

Test for overall effect: Z = 7.06 (P < 0.00001)

Analysis 1.9. Comparison 1 SSRI versus placebo, Outcome 9 Response to treatment.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 9 Response to treatment

Study or subgroup	SSRIs n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Cohen 2004 a	67/111	24/54		7.5 %	1.90 [0.99, 3.67]
Cohen 2004b	56/95	24/54		7.4 %	1.79 [0.91, 3.52]
Crnobaric 1998	10/14	3/11		0.6 %	6.67 [1.14, 38.83]
Eriksson 1995	20/22	9/22		0.5 %	14.44 [2.68, 77.80]
Freeman 1999a	38/62	19/55		4.6 %	3.00 [1.41, 6.38]
Freeman 2004 a	30/48	9/25		2.6 %	2.96 [1.09, 8.09]
Freeman 2004b	23/45	9/25		3.3 %	1.86 [0.68, 5.07]
Halbreich 2002	69/119	49/109		12.6 %	1.69 [1.00, 2.85]
Kornstein 2006 a	43/91	12/45		5.0 %	2.46 [1.13, 5.37]
Kornstein 2006b	37/88	12/45		5.4 %	2.00 [0.91, 4.37]
Lnden 2007 a	37/67	7/28		2.6 %	3.70 [1.39, 9.87]
Lnden 2007b	44/53	7/28		0.9 %	14.67 [4.80, 44.78]
Ozeren 1997	12/15	4/15		0.5 %	11.00 [2.00, 60.57]
Pearlstein 1997	10/10	2/12		0.1 %	88.20 [3.76, 2067.63]
Pearlstein 2005 a	80/105	29/59		5.2 %	3.31 [1.68, 6.53]
Pearlstein 2005b	69/103	29/59		7.1 %	2.10 [1.09, 4.04]
Steiner 1995 a	50/96	11/48		4.1 %	3.66 [1.67, 8.00]
Steiner 1995b	45/86	11/48		3.9 %	3.69 [1.67, 8.18]
Steiner 2005 a	74/130	26/60		9.0 %	1.73 [0.93, 3.20]
Steiner 2005 b	79/116	26/60		6.4 %	2.79 [1.47, 5.31]
Stone 1991	9/10	2/10		0.1 %	36.00 [2.72, 476.28]
Sundblad 1992	20/20	10/20		0.1 %	41.00 [2.18, 770.08]
Sundblad 1993	15/15	10/14		0.2 %	13.29 [0.65, 273.59]
Wikander 1998a	17/18	3/6		0.1 %	17.00 [1.30, 223.14]
Wikander 1998b	12/17	3/6		0.8 %	2.40 [0.36, 16.21]
Wikander 1998c	13/17	3/6		0.6 %	3.25 [0.46, 22.93]

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Study or subgroup	SSRIs n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Yonkers 1997	72/116	40/118		8.8 %	3.19 [1.87, 5.45]
Total (95% CI)	**1689**	**1042**	♦	**100.0 %**	**2.86 [2.43, 3.37]**

Total events: 1051 (SSRIs), 393 (placebo)
Heterogeneity: Chi^2 = 43.01, df = 26 (P = 0.02); I^2 =40%
Test for overall effect: Z = 12.57 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 SSRI versus placebo, Outcome 10 Adverse events.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 10 Adverse events

Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Nausea					
Cohen 2002a	7/86	2/44		4.4 %	1.86 [0.37, 9.36]
Cohen 2002b	8/86	2/44		4.3 %	2.15 [0.44, 10.61]
Cohen 2004 a	10/111	1/54		2.2 %	5.25 [0.65, 42.10]
Cohen 2004b	8/95	1/54		2.1 %	4.87 [0.59, 40.07]
Eriksson 1995	2/22	0/22		0.8 %	5.49 [0.25, 121.18]
Freeman 1999a	15/62	4/55		5.8 %	4.07 [1.26, 13.14]
Halbreich 2002	15/119	3/110		4.9 %	5.14 [1.45, 18.29]
Kornstein 2006 a	10/98	3/50		6.4 %	1.78 [0.47, 6.78]
Kornstein 2006b	21/97	3/50		5.6 %	4.33 [1.22, 15.31]
Lnden 2007 a	30/59	5/29		5.9 %	4.97 [1.67, 14.77]
Lnden 2007b	26/60	5/29		6.9 %	3.67 [1.23, 10.92]
Miner 2002a	13/86	1/42		2.0 %	7.30 [0.92, 57.84]

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Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Miner 2002b	12/86	1/42		2.1 %	6.65 [0.83, 52.97]
Pearlstein 2005 a	35/120	6/62		10.1 %	3.84 [1.52, 9.73]
Pearlstein 2005b	18/115	6/62		11.8 %	1.73 [0.65, 4.62]
Steiner 1995 a	14/102	4/53		8.2 %	1.95 [0.61, 6.25]
Steiner 1995b	25/106	4/53		7.3 %	3.78 [1.24, 11.51]
Steiner 2005 a	16/130	1/60		2.2 %	8.28 [1.07, 63.98]
Steiner 2005 b	27/116	1/60		1.8 %	17.90 [2.37, 135.32]
Stone 1991	0/10	1/10		2.6 %	0.30 [0.01, 8.33]
Sundblad 1993	4/15	2/14		2.7 %	2.18 [0.33, 14.36]
Subtotal (95% CI)	**1781**	**999**		**100.0 %**	**3.71 [2.75, 5.01]**
Total events: 316 (SSRIs), 56 (Placebo)					
Heterogeneity: Chi^2 = 12.78, df = 20 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 8.55 (P < 0.00001)					
2 Gastrointestinal irritability					
Eriksson 1995	3/22	0/22		100.0 %	8.08 [0.39, 166.27]
Subtotal (95% CI)	**22**	**22**		**100.0 %**	**8.08 [0.39, 166.27]**
Total events: 3 (SSRIs), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					
3 Insomnia/sleep disturbance					
Cohen 2002a	9/86	2/44		3.5 %	2.45 [0.51, 11.89]
Cohen 2002b	9/86	2/44		3.5 %	2.45 [0.51, 11.89]
Cohen 2004 a	6/111	2/54		3.8 %	1.49 [0.29, 7.62]
Cohen 2004b	5/95	2/54		3.6 %	1.44 [0.27, 7.71]
Eriksson 1995	2/22	1/22		1.4 %	2.10 [0.18, 25.01]
Freeman 1999a	12/62	6/55		7.6 %	1.96 [0.68, 5.64]
Halbreich 2002	14/119	11/110		15.0 %	1.20 [0.52, 2.77]
Kornstein 2006 a	14/98	4/50		6.8 %	1.92 [0.60, 6.16]
Kornstein 2006b	20/97	5/50		7.8 %	2.34 [0.82, 6.66]
Lnden 2007 a	5/59	5/29		9.1 %	0.44 [0.12, 1.68]
Lnden 2007b	6/60	5/29		9.0 %	0.53 [0.15, 1.92]
Miner 2002a	9/86	1/42		1.8 %	4.79 [0.59, 39.15]
Miner 2002b	6/86	1/42		1.9 %	3.08 [0.36, 26.40]
Pearlstein 1997	1/10	0/12		0.6 %	3.95 [0.14, 108.09]

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Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Pearlstein 2005 a	11/120	1/62		1.8 %	6.16 [0.78, 48.83]
Pearlstein 2005b	7/115	1/62		1.8 %	3.95 [0.48, 32.90]
Steiner 1995 a	10/102	4/53		7.1 %	1.33 [0.40, 4.47]
Steiner 1995b	28/106	4/53		5.8 %	4.40 [1.45, 13.30]
Steiner 2005 a	13/130	1/60		1.8 %	6.56 [0.84, 51.33]
Steiner 2005 b	4/116	1/60		1.9 %	2.11 [0.23, 19.28]
Stone 1991	2/10	2/10		2.4 %	1.00 [0.11, 8.95]
Sundblad 1992	2/20	0/20		0.7 %	5.54 [0.25, 123.08]
Sundblad 1993	1/15	1/14		1.4 %	0.93 [0.05, 16.42]
Subtotal (95% CI)	**1811**	**1031**		**100.0 %**	**1.97 [1.46, 2.66]**
Total events: 196 (SSRIs), 62 (Placebo)					
Heterogeneity: Chi^2 = 18.07, df = 22 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 4.42 (P < 0.00001)					
4 Sexual dysfunction					
Cohen 2004 a	13/111	0/54		8.9 %	14.94 [0.87, 256.21]
Cohen 2004b	7/95	0/54		8.8 %	9.24 [0.52, 164.97]
Eriksson 1995	5/22	0/22		5.7 %	14.14 [0.73, 273.39]
Freeman 1999a	6/62	3/55		43.2 %	1.86 [0.44, 7.81]
Pearlstein 1997	0/10	1/12		19.8 %	0.37 [0.01, 9.98]
Stone 1991	1/10	0/10		6.5 %	3.32 [0.12, 91.60]
Sundblad 1993	1/15	0/14		7.0 %	3.00 [0.11, 79.91]
Subtotal (95% CI)	**325**	**221**		**100.0 %**	**4.25 [1.81, 9.99]**
Total events: 33 (SSRIs), 4 (Placebo)					
Heterogeneity: Chi^2 = 5.12, df = 6 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 3.33 (P = 0.00088)					
5 Headache					
Cohen 2002a	15/86	6/44		5.4 %	1.34 [0.48, 3.73]
Cohen 2002b	13/86	6/44		5.6 %	1.13 [0.40, 3.20]
Cohen 2004 a	13/111	6/54		5.9 %	1.06 [0.38, 2.96]
Cohen 2004b	9/95	6/54		5.7 %	0.84 [0.28, 2.49]
Eriksson 1995	3/22	4/22		2.9 %	0.71 [0.14, 3.63]
Freeman 1999a	9/62	7/55		5.3 %	1.16 [0.40, 3.37]
Halbreich 2002	18/119	9/110		6.6 %	2.00 [0.86, 4.66]
Kornstein 2006 a	13/98	4/50		3.8 %	1.76 [0.54, 5.70]

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Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kornstein 2006b	6/97	4/50		4.1 %	0.76 [0.20, 2.82]
Lnden 2007 a	9/59	8/29		7.5 %	0.47 [0.16, 1.39]
Lnden 2007b	15/60	8/29		6.7 %	0.88 [0.32, 2.38]
Miner 2002a	11/86	4/52		3.6 %	1.76 [0.53, 5.85]
Miner 2002b	11/86	4/52		3.6 %	1.76 [0.53, 5.85]
Pearlstein 1997	0/10	1/12		1.1 %	0.37 [0.01, 9.98]
Pearlstein 2005 a	17/120	8/62		7.5 %	1.11 [0.45, 2.75]
Pearlstein 2005b	17/115	8/62		7.4 %	1.17 [0.47, 2.89]
Steiner 2005 a	16/130	7/60		7.0 %	1.06 [0.41, 2.74]
Steiner 2005 b	18/116	7/60		6.5 %	1.39 [0.55, 3.54]
Stone 1991	0/10	2/10		2.0 %	0.16 [0.01, 3.85]
Sundblad 1992	7/20	2/20		1.1 %	4.85 [0.86, 27.22]
Sundblad 1993	2/15	1/14		0.7 %	2.00 [0.16, 24.87]
Subtotal (95% CI)	**1603**	**945**		**100.0 %**	**1.19 [0.93, 1.52]**
Total events: 222 (SSRIs), 112 (Placebo)					
Heterogeneity: Chi^2 = 12.10, df = 20 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.38 (P = 0.17)					
6 Dizziness/vertigo					
Cohen 2004 a	3/111	2/54		10.5 %	0.72 [0.12, 4.46]
Cohen 2004b	5/95	2/54		9.7 %	1.44 [0.27, 7.71]
Eriksson 1995	1/22	0/22		1.9 %	3.14 [0.12, 81.35]
Freeman 1999a	6/62	2/55		7.6 %	2.84 [0.55, 14.69]
Lnden 2007 a	8/59	2/29		9.3 %	2.12 [0.42, 10.68]
Lnden 2007b	8/60	2/29		9.3 %	2.08 [0.41, 10.47]
Pearlstein 2005 a	11/120	2/62		9.6 %	3.03 [0.65, 14.11]
Pearlstein 2005b	4/115	2/62		10.0 %	1.08 [0.19, 6.07]
Steiner 1995 a	8/102	1/53		4.8 %	4.43 [0.54, 36.37]
Steiner 1995b	15/106	1/53		4.6 %	8.57 [1.10, 66.76]
Steiner 2005 a	7/130	2/60		10.3 %	1.65 [0.33, 8.19]
Steiner 2005 b	8/116	2/60		9.8 %	2.15 [0.44, 10.45]
Sundblad 1992	7/20	0/20		1.3 %	22.78 [1.20, 432.58]
Sundblad 1993	5/15	0/14		1.4 %	15.19 [0.75, 305.73]
Subtotal (95% CI)	**1133**	**627**		**100.0 %**	**2.76 [1.72, 4.44]**

0.01 0.1 1 10 100

Favours placebo Favours SSRIs

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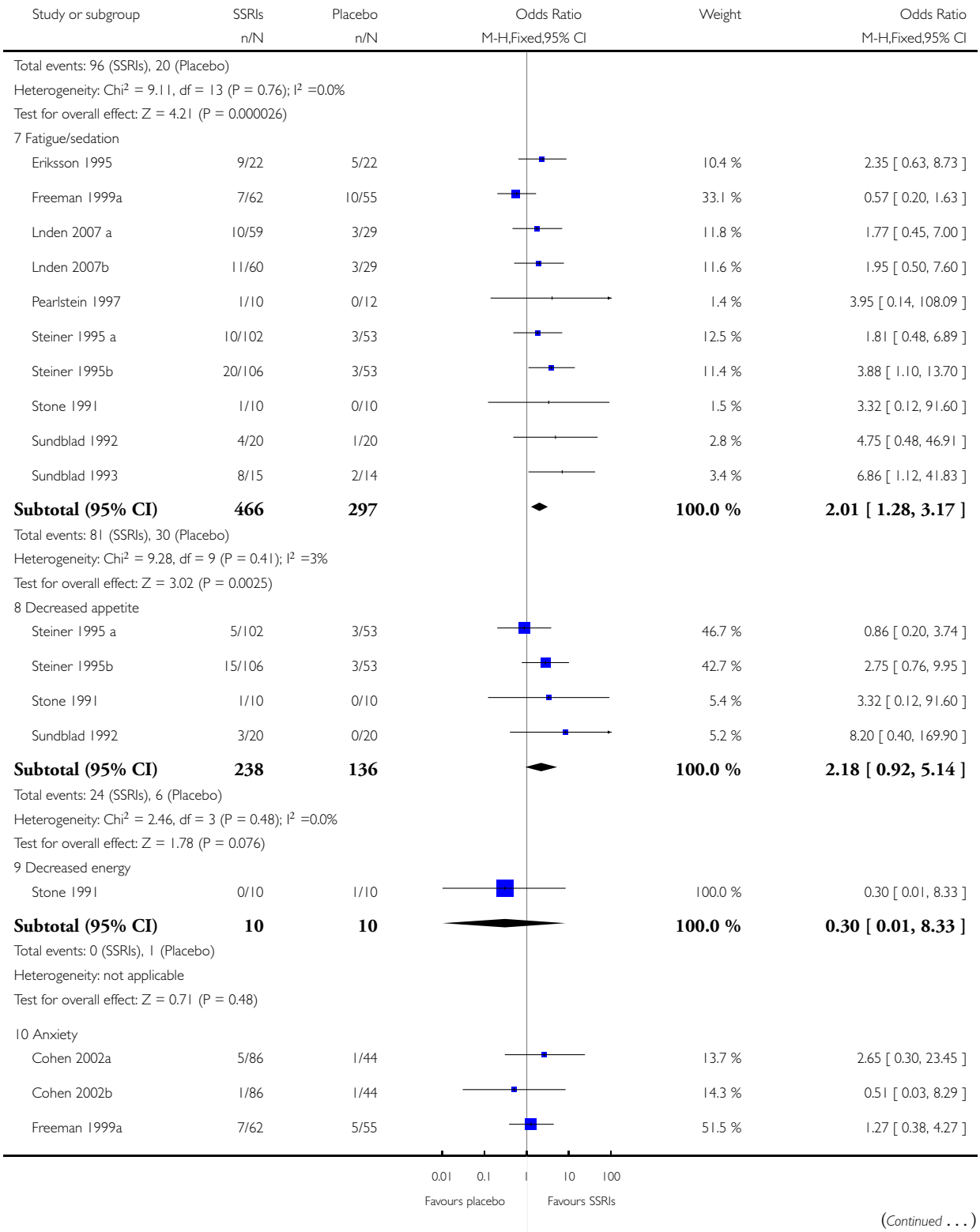

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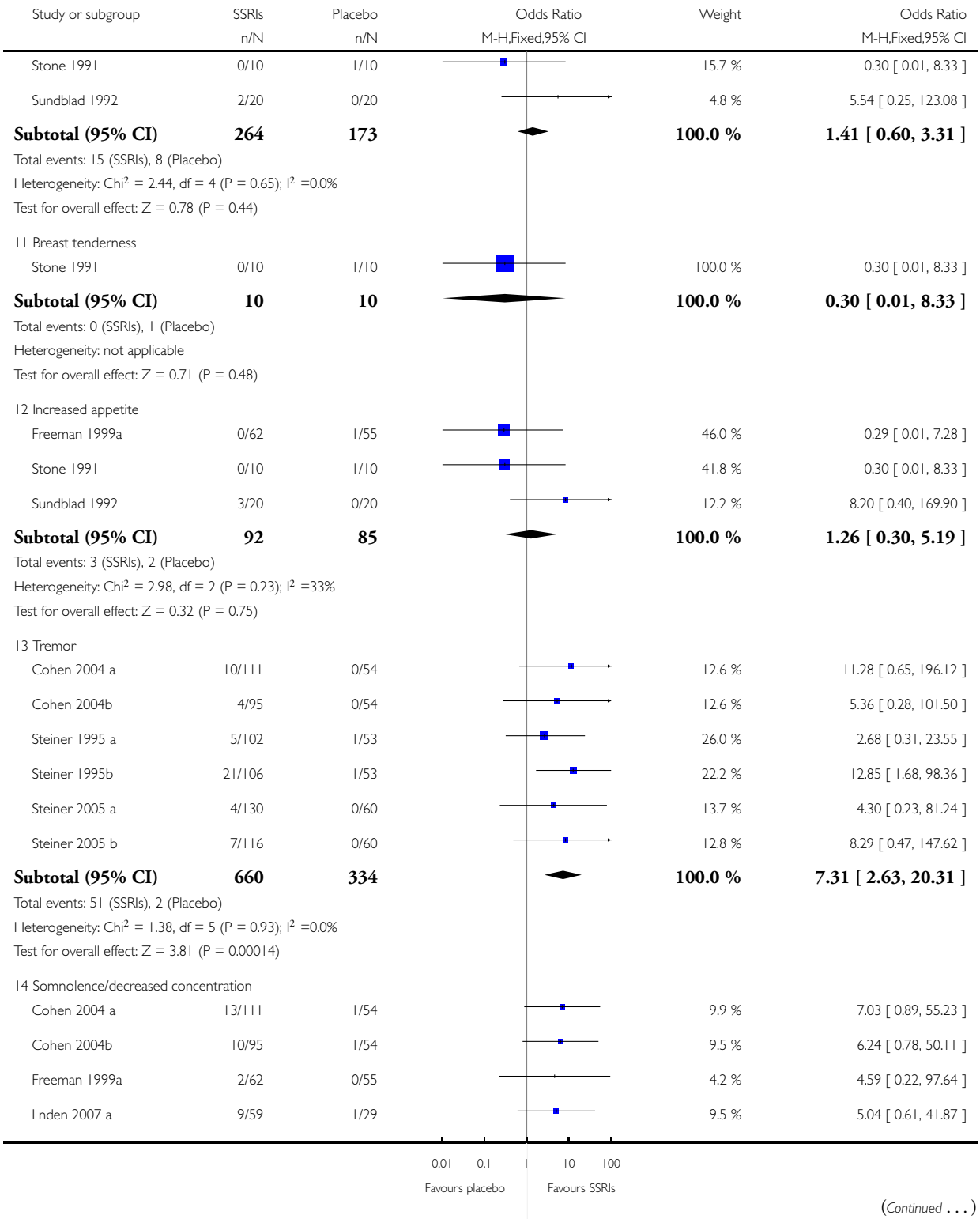

Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Stone 1991	0/10	1/10		15.7 %	0.30 [0.01, 8.33]
Sundblad 1992	2/20	0/20		4.8 %	5.54 [0.25, 123.08]
Subtotal (95% CI)	**264**	**173**		**100.0 %**	**1.41 [0.60, 3.31]**
Total events: 15 (SSRIs), 8 (Placebo)					
Heterogeneity: Chi² = 2.44, df = 4 (P = 0.65); I² =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
11 Breast tenderness					
Stone 1991	0/10	1/10		100.0 %	0.30 [0.01, 8.33]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**0.30 [0.01, 8.33]**
Total events: 0 (SSRIs), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
12 Increased appetite					
Freeman 1999a	0/62	1/55		46.0 %	0.29 [0.01, 7.28]
Stone 1991	0/10	1/10		41.8 %	0.30 [0.01, 8.33]
Sundblad 1992	3/20	0/20		12.2 %	8.20 [0.40, 169.90]
Subtotal (95% CI)	**92**	**85**		**100.0 %**	**1.26 [0.30, 5.19]**
Total events: 3 (SSRIs), 2 (Placebo)					
Heterogeneity: Chi² = 2.98, df = 2 (P = 0.23); I² =33%					
Test for overall effect: Z = 0.32 (P = 0.75)					
13 Tremor					
Cohen 2004 a	10/111	0/54		12.6 %	11.28 [0.65, 196.12]
Cohen 2004b	4/95	0/54		12.6 %	5.36 [0.28, 101.50]
Steiner 1995 a	5/102	1/53		26.0 %	2.68 [0.31, 23.55]
Steiner 1995b	21/106	1/53		22.2 %	12.85 [1.68, 98.36]
Steiner 2005 a	4/130	0/60		13.7 %	4.30 [0.23, 81.24]
Steiner 2005 b	7/116	0/60		12.8 %	8.29 [0.47, 147.62]
Subtotal (95% CI)	**660**	**334**		**100.0 %**	**7.31 [2.63, 20.31]**
Total events: 51 (SSRIs), 2 (Placebo)					
Heterogeneity: Chi² = 1.38, df = 5 (P = 0.93); I² =0.0%					
Test for overall effect: Z = 3.81 (P = 0.00014)					
14 Somnolence/decreased concentration					
Cohen 2004 a	13/111	1/54		9.9 %	7.03 [0.89, 55.23]
Cohen 2004b	10/95	1/54		9.5 %	6.24 [0.78, 50.11]
Freeman 1999a	2/62	0/55		4.2 %	4.59 [0.22, 97.64]
Lnden 2007 a	9/59	1/29		9.5 %	5.04 [0.61, 41.87]

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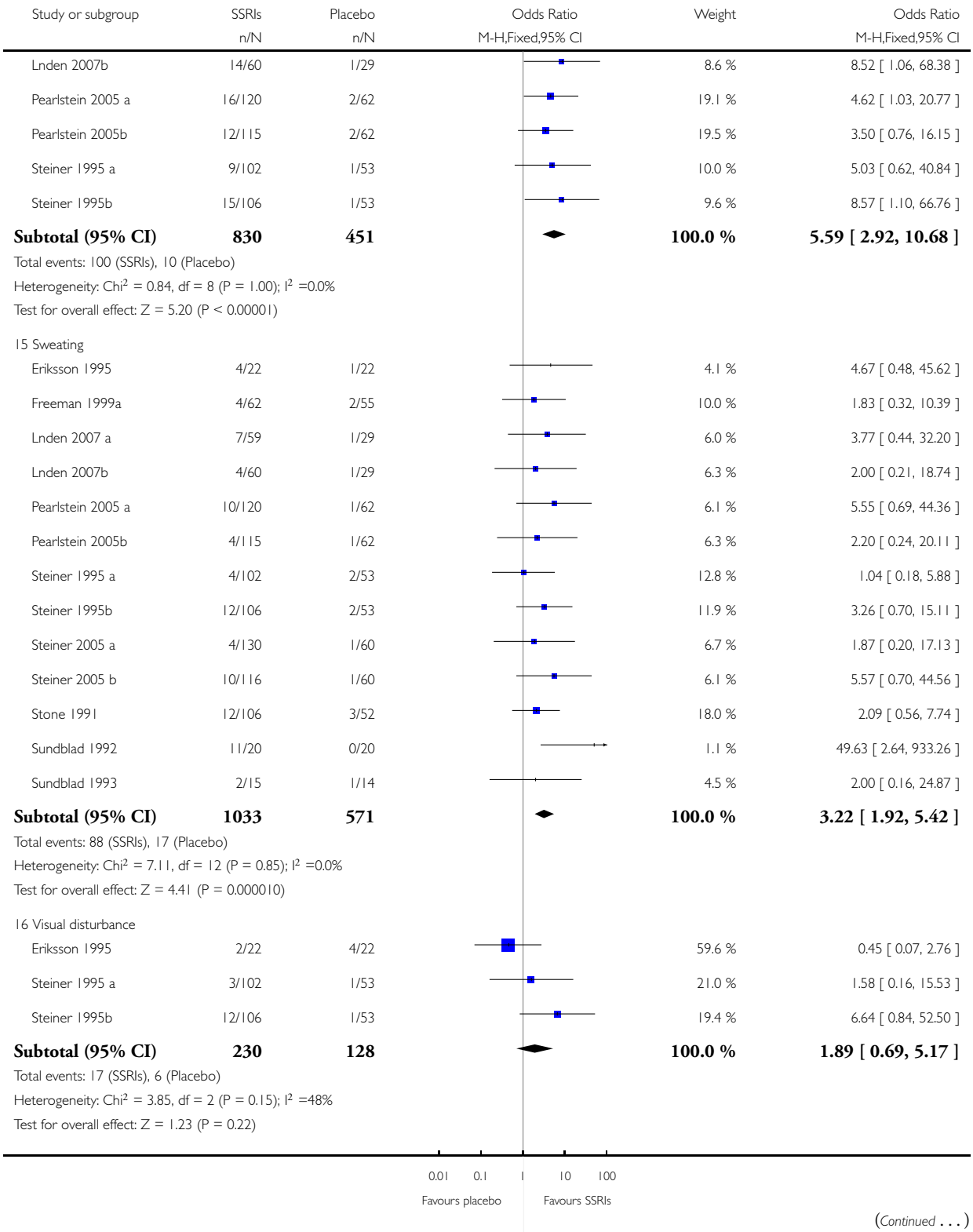

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Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
17 Dry mouth					
Cohen 2004 a	8/111	1/54		6.8 %	4.12 [0.50, 33.79]
Cohen 2004b	2/95	1/54		6.8 %	1.14 [0.10, 12.87]
Eriksson 1995	4/22	2/22		8.9 %	2.22 [0.36, 13.62]
Freeman 1999a	13/62	4/55		18.3 %	3.38 [1.03, 11.09]
Halbreich 2002	12/119	3/110		15.3 %	4.00 [1.10, 14.58]
Lnden 2007 a	4/59	0/29		3.4 %	4.78 [0.25, 91.92]
Lnden 2007b	6/60	0/29		3.3 %	7.04 [0.38, 129.32]
Pearlstein 1997	0/10	1/12		7.2 %	0.37 [0.01, 9.98]
Steiner 1995 a	4/102	2/53		13.8 %	1.04 [0.18, 5.88]
Steiner 1995b	11/106	2/53		13.0 %	2.95 [0.63, 13.84]
Sundblad 1992	15/20	1/20		1.4 %	57.00 [6.00, 541.47]
Sundblad 1993	10/15	1/14		1.9 %	26.00 [2.61, 259.29]
Subtotal (95% CI)	**781**	**505**		**100.0 %**	**4.00 [2.41, 6.63]**
Total events: 89 (SSRIs), 18 (Placebo)					
Heterogeneity: Chi² = 14.05, df = 11 (P = 0.23); I² =22%					
Test for overall effect: Z = 5.38 (P < 0.00001)					
18 Cardiovascular symptoms					
Eriksson 1995	1/22	1/22		37.1 %	1.00 [0.06, 17.07]
Pearlstein 1997	1/10	0/12		15.4 %	3.95 [0.14, 108.09]
Steiner 1995 a	11/106	0/53		23.1 %	12.88 [0.74, 223.00]
Steiner 1995b	4/102	0/53		24.4 %	4.89 [0.26, 92.53]
Subtotal (95% CI)	**240**	**140**		**100.0 %**	**5.14 [1.28, 20.61]**
Total events: 17 (SSRIs), 1 (Placebo)					
Heterogeneity: Chi² = 1.70, df = 3 (P = 0.64); I² =0.0%					
Test for overall effect: Z = 2.31 (P = 0.021)					
19 Yawning					
Eriksson 1995	4/22	0/22		11.3 %	10.95 [0.55, 216.75]
Pearlstein 2005 a	7/120	0/62		17.3 %	8.26 [0.46, 147.04]
Pearlstein 2005b	2/115	1/62		35.8 %	1.08 [0.10, 12.15]
Steiner 1995 a	1/102	0/53		18.1 %	1.58 [0.06, 39.49]
Steiner 1995b	6/106	0/53		17.5 %	6.92 [0.38, 125.21]
Subtotal (95% CI)	**465**	**252**		**100.0 %**	**4.55 [1.35, 15.26]**
Total events: 20 (SSRIs), 1 (Placebo)					
Heterogeneity: Chi² = 2.35, df = 4 (P = 0.67); I² =0.0%					

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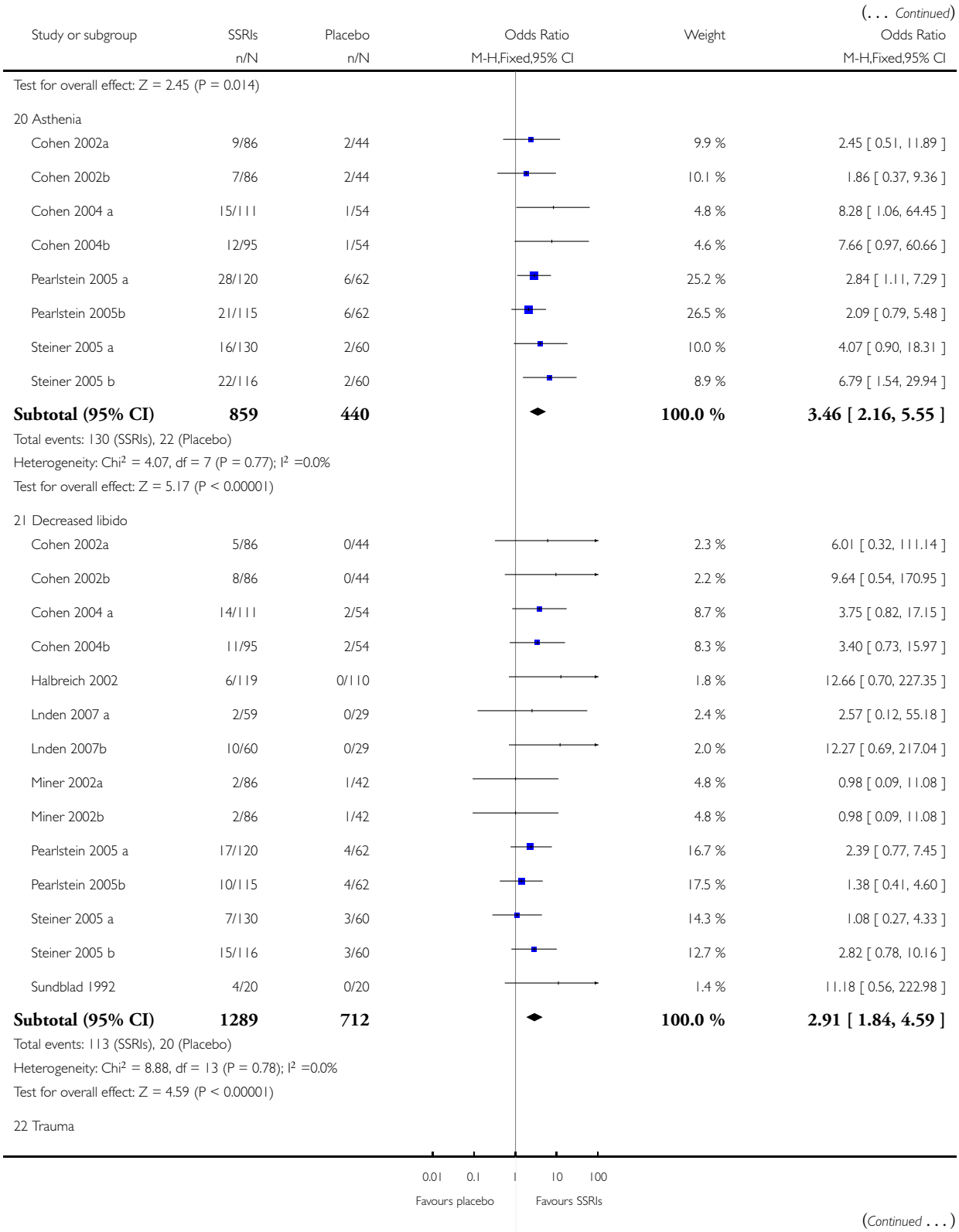

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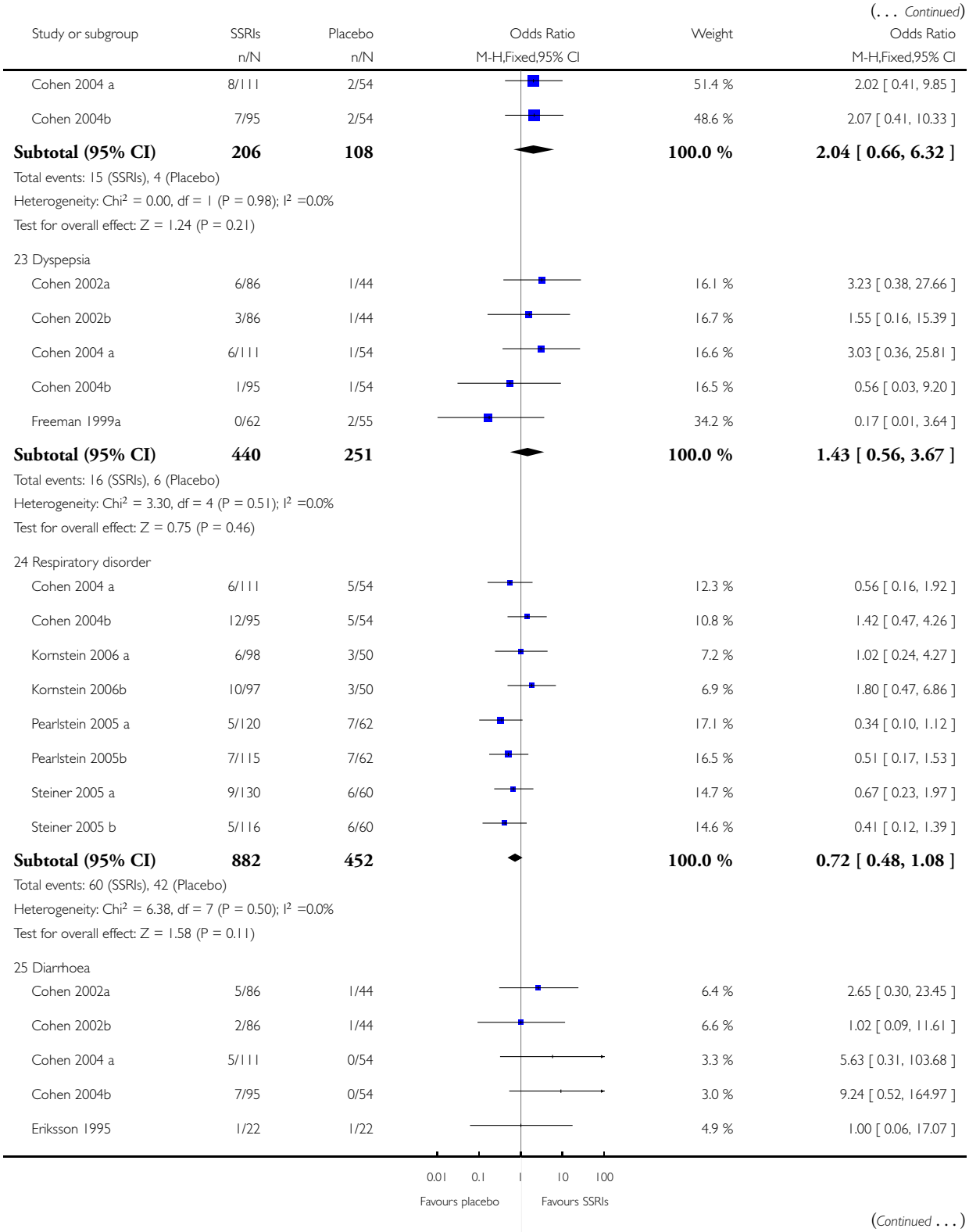

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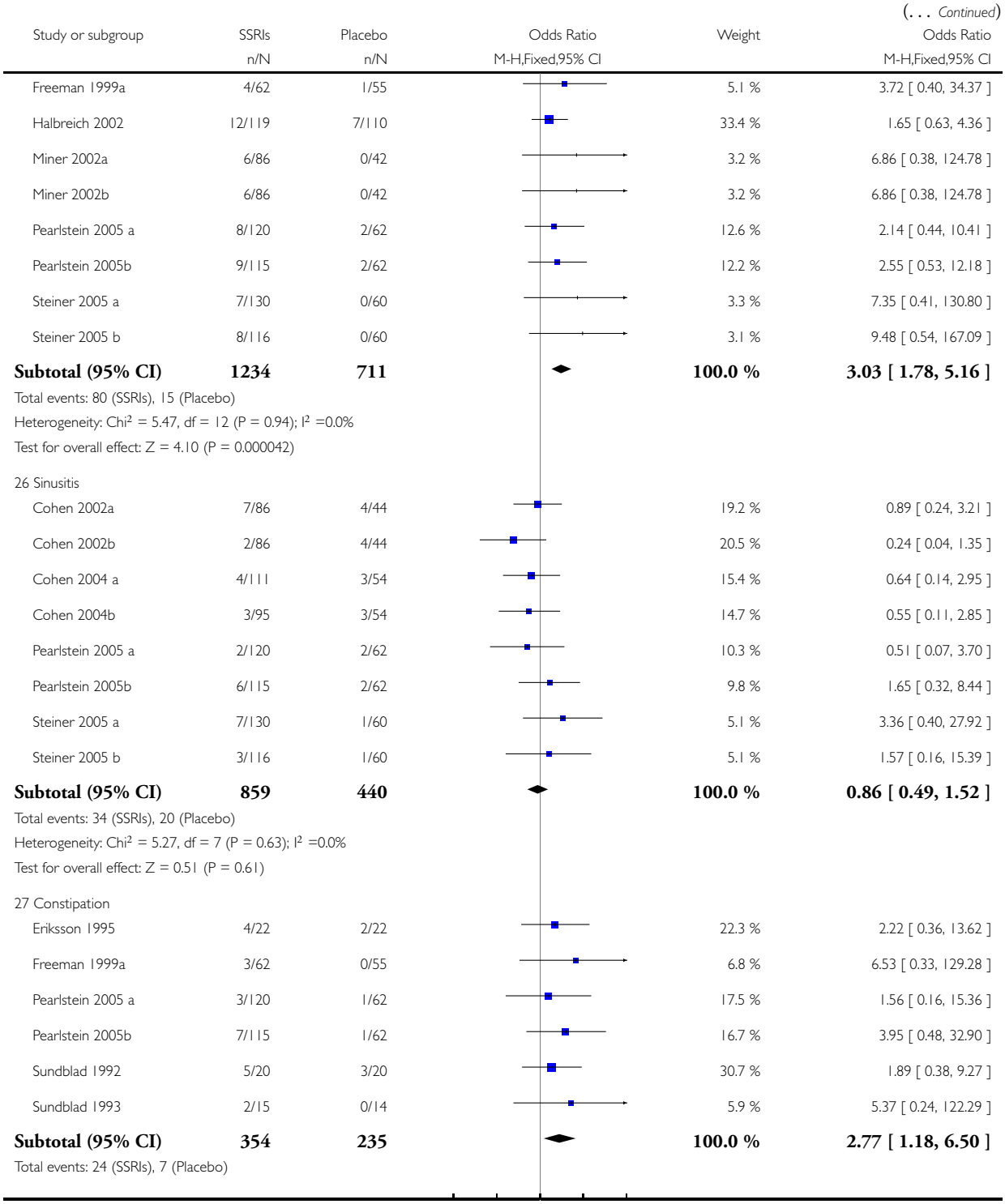

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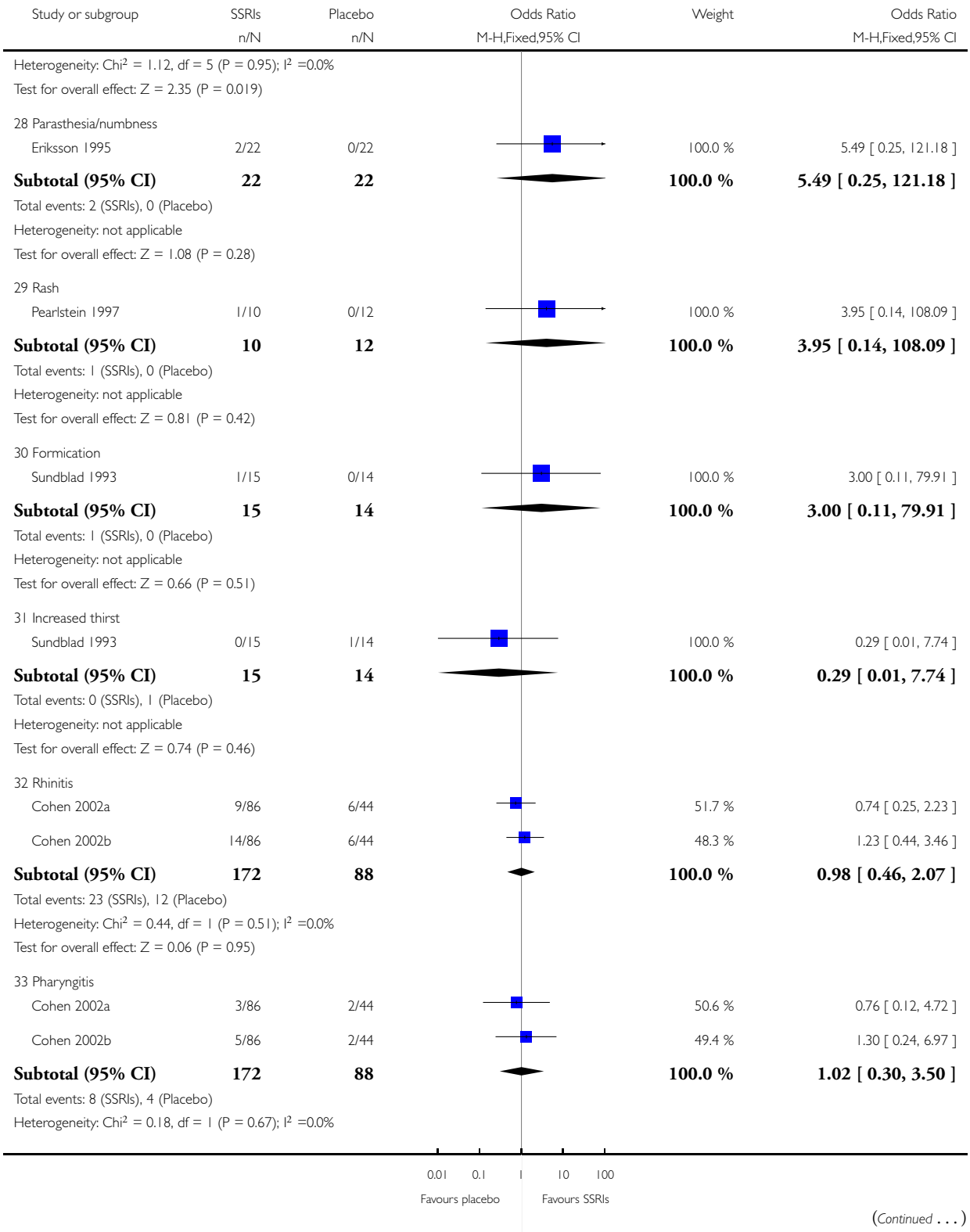

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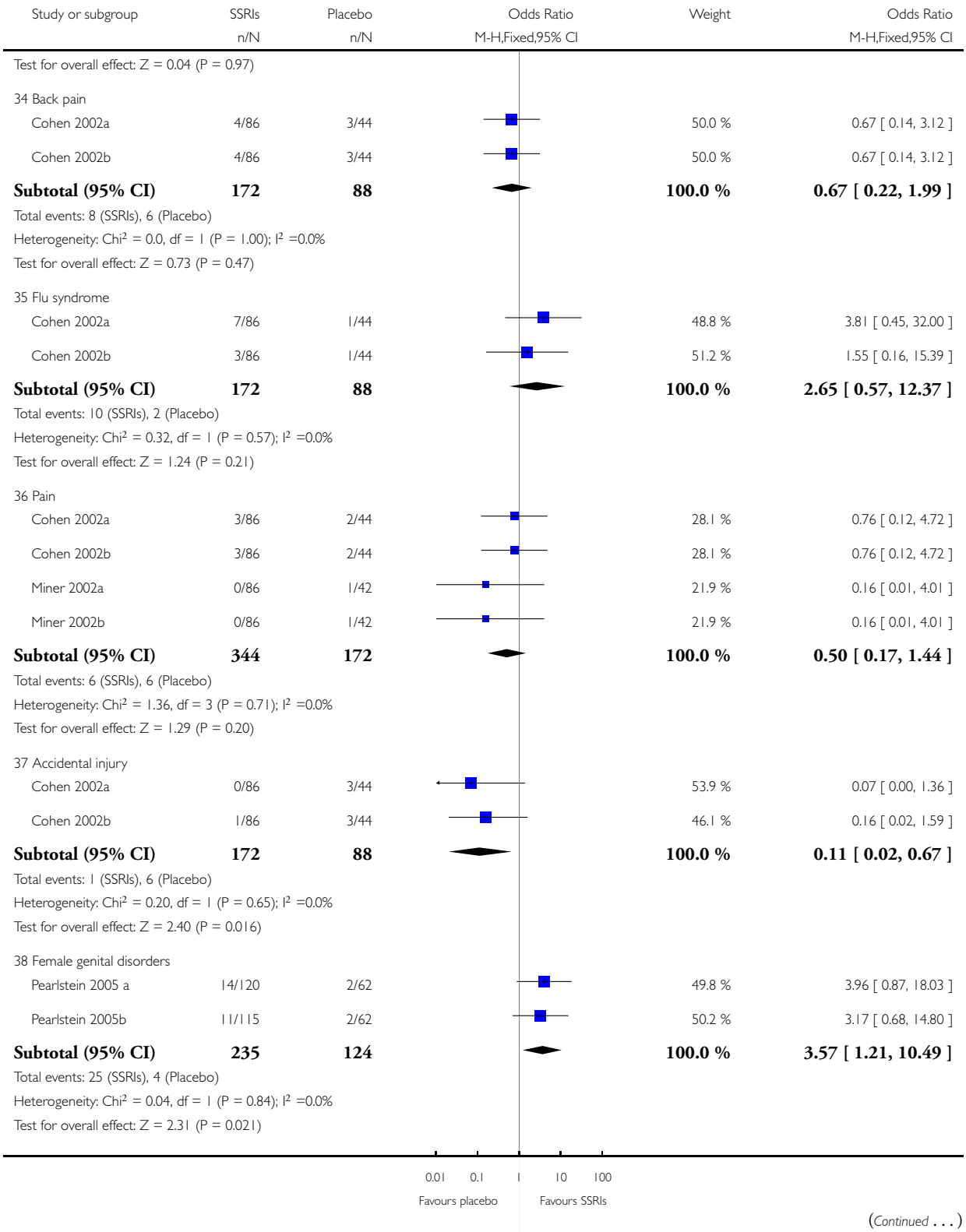

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Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
39 Vomiting					
Pearlstein 2005 a	6/120	1/62		39.3 %	3.21 [0.38, 27.28]
Pearlstein 2005b	0/115	1/62		60.7 %	0.18 [0.01, 4.42]
Subtotal (95% CI)	**235**	**124**		**100.0 %**	**1.37 [0.31, 5.98]**
Total events: 6 (SSRIs), 2 (Placebo)					
Heterogeneity: Chi^2 = 2.16, df = 1 (P = 0.14); I^2 =54%					
Test for overall effect: Z = 0.42 (P = 0.68)					
40 Infection					
Miner 2002a	0/86	3/42		19.8 %	0.07 [0.00, 1.29]
Miner 2002b	3/86	3/42		16.5 %	0.47 [0.09, 2.43]
Pearlstein 2005 a	5/120	2/62		10.7 %	1.30 [0.25, 6.92]
Pearlstein 2005b	9/115	2/62		10.2 %	2.55 [0.53, 12.18]
Steiner 2005 a	5/130	4/60		22.3 %	0.56 [0.14, 2.16]
Steiner 2005 b	10/116	4/60		20.5 %	1.32 [0.40, 4.40]
Subtotal (95% CI)	**653**	**328**		**100.0 %**	**0.88 [0.49, 1.59]**
Total events: 32 (SSRIs), 18 (Placebo)					
Heterogeneity: Chi^2 = 6.32, df = 5 (P = 0.28); I^2 =21%					
Test for overall effect: Z = 0.41 (P = 0.68)					
41 Dysmenorrhoea					
Pearlstein 2005 a	3/120	4/62		50.4 %	0.37 [0.08, 1.72]
Pearlstein 2005b	3/115	4/62		49.6 %	0.39 [0.08, 1.79]
Subtotal (95% CI)	**235**	**124**		**100.0 %**	**0.38 [0.13, 1.12]**
Total events: 6 (SSRIs), 8 (Placebo)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 1.75 (P = 0.080)					

Analysis 1.11. Comparison 1 SSRI versus placebo, Outcome 11 Study withdrawal.

Review: Selective serotonin reuptake inhibitors for premenstrual syndrome

Comparison: 1 SSRI versus placebo

Outcome: 11 Study withdrawal

Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Withdrawal due to adverse event/s				
Cohen 2002a	2/86	1/44		1.02 [0.09, 11.61]
Cohen 2002b	4/86	1/44		2.10 [0.23, 19.35]
Cohen 2004 a	15/111	4/54		1.95 [0.62, 6.20]
Cohen 2004b	9/95	4/54		1.31 [0.38, 4.47]
Eriksson 1995	3/27	2/26		1.50 [0.23, 9.80]
Freeman 2004 a	7/56	1/28		3.86 [0.45, 33.02]
Freeman 2004b	5/56	1/28		2.65 [0.29, 23.82]
Halbreich 2002	11/119	1/110		11.10 [1.41, 87.48]
Kornstein 2006 a	7/98	4/50		0.88 [0.25, 3.18]
Kornstein 2006b	10/97	4/50		1.32 [0.39, 4.45]
Lnden 2007 a	3/59	1/29		1.50 [0.15, 15.08]
Lnden 2007b	5/60	1/29		2.55 [0.28, 22.85]
Miner 2002a	1/84	1/42		0.49 [0.03, 8.10]
Miner 2002b	2/83	1/42		1.01 [0.09, 11.50]
Ozeren 1997	2/18	0/17		5.30 [0.24, 118.89]
Pearlstein 2005 a	20/120	5/62		2.28 [0.81, 6.40]
Pearlstein 2005b	12/115	5/62		1.33 [0.45, 3.96]
Steiner 1995 a	11/102	4/53		1.48 [0.45, 4.90]
Steiner 1995b	35/106	4/53		6.04 [2.02, 18.08]
Steiner 2005 a	13/130	3/62		2.19 [0.60, 7.97]
Steiner 2005 b	16/119	3/62		3.06 [0.85, 10.92]
Sundblad 1992	4/26	5/29		0.87 [0.21, 3.67]
Sundblad 1993	6/22	1/16		5.63 [0.60, 52.37]
Wikander 1998a	1/19	1/6		0.28 [0.01, 5.27]
Wikander 1998b	2/20	1/6		0.56 [0.04, 7.46]

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Study or subgroup	SSRIs n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Wikander 1998c	2/19	1/6		0.59 [0.04, 7.91]
Yonkers 1997	10/116	2/118		5.47 [1.17, 25.55]
Subtotal (95% CI)	**2049**	**1182**	◆	**2.11 [1.58, 2.83]**
Total events: 218 (SSRIs), 62 (Placebo)				
Heterogeneity: Chi^2 = 20.43, df = 26 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 5.01 (P < 0.00001)				
2 Withdrawal any reason				
Cohen 2002a	9/86	7/44		0.62 [0.21, 1.79]
Cohen 2002b	22/86	7/44		1.82 [0.71, 4.66]
Cohen 2004 a	39/111	14/54		1.55 [0.75, 3.19]
Cohen 2004b	25/95	14/54		1.02 [0.48, 2.18]
Crnobaric 1998	0/14	0/11		0.0 [0.0, 0.0]
Eriksson 1995	5/27	4/26		1.25 [0.30, 5.28]
Freeman 1999a	13/66	15/59		0.72 [0.31, 1.67]
Freeman 2004 a	16/56	6/28		1.47 [0.50, 4.29]
Freeman 2004b	21/56	6/28		2.20 [0.77, 6.30]
Halbreich 2002	27/119	33/110		0.68 [0.38, 1.24]
Jermain 1999	9/28	5/29		2.27 [0.65, 7.92]
Kornstein 2006 a	24/98	11/50		1.15 [0.51, 2.59]
Kornstein 2006b	20/97	11/50		0.92 [0.40, 2.11]
Lnden 2007 a	9/59	4/29		1.13 [0.32, 4.01]
Lnden 2007b	6/60	4/29		0.69 [0.18, 2.68]
Miner 2002a	2/86	3/43		0.32 [0.05, 1.98]
Miner 2002b	3/86	3/43		0.48 [0.09, 2.49]
Ozeren 1997	3/18	2/17		1.50 [0.22, 10.30]
Pearlstein 2005 a	38/120	14/62		1.59 [0.78, 3.23]
Pearlstein 2005b	26/115	14/62		1.00 [0.48, 2.10]
Steiner 1995 a	33/102	27/53		0.46 [0.23, 0.91]
Steiner 1995b	47/106	27/53		0.77 [0.40, 1.49]
Steiner 2005 a	26/131	10/62		1.29 [0.58, 2.87]
Steiner 2005 b	29/119	10/62		1.68 [0.76, 3.71]
Stone 1991	0/10	0/10		0.0 [0.0, 0.0]
Sundblad 1992	6/26	9/29		0.67 [0.20, 2.22]

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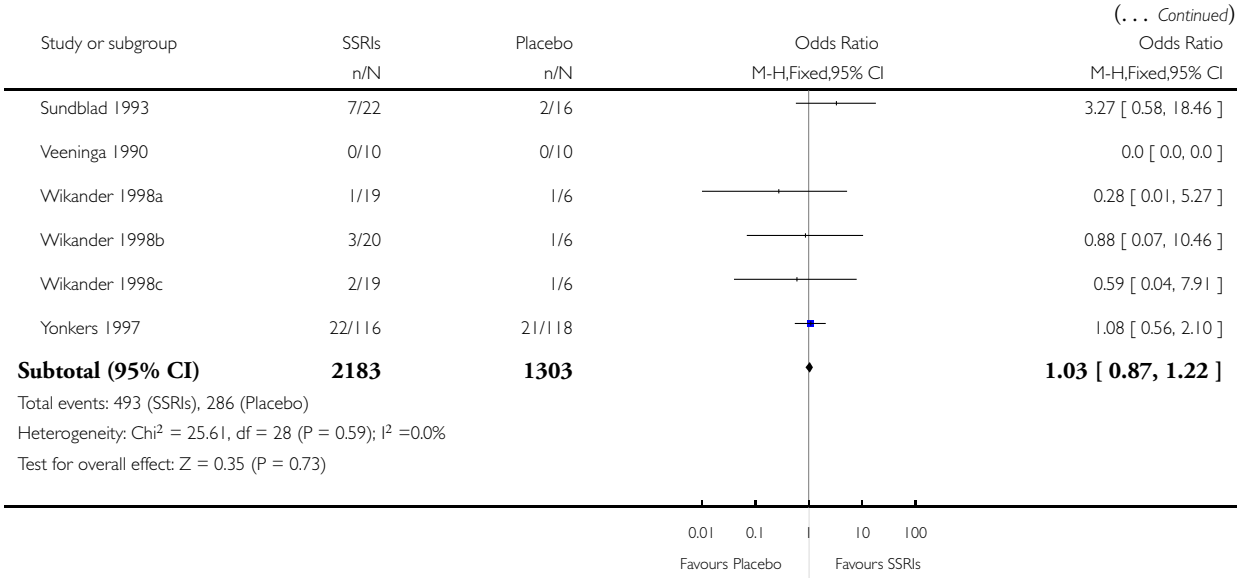

ADDITIONAL TABLES

Table 1. Outcome measures utilised by included studies

Outcome Measure	Studies	Description
Daily Symptom Report	Kornstein 2006a,b	17 common PMS symptoms self rated daily on a 5-point scale (from 0=none to 4=severe/overwhelming/unable to function). Mood (anxiety, irritability, depression, nervous tension, mood swing, feeling out of control); Behavioural (poor coordination, insomnia, confusion/poor concentration, headache, crying, fatigue); Pain (aches, cramps, breast tenderness); Physical symptoms (food cravings, swelling); Distress
Clinical Global Impression Severity of Illness (CGI-S)	Freeman 1999, Kornstein 2006; Pearlstein 2005a,b; Miner 2002a,b; Steiner 2005 a,b; Yonkers 1997; Cohen 2004a,b; Freeman, 1999Freeman, 1999, Halbreich 2002, Pearlstein 1997, Yonkers 2006	Clinician rated. 7-point scale (1= not ill to 7 = extremely ill)
Clinical Global Improvement (CGI-I)	Kornstein 2006a,b, Landen 2007a,b; Crnobaric 1998; Miner 2002a,b; Steiner 2005 a,b; Menkes 1993; Yonkers 1997; Cohen 2004a,b; Halbreich 1997, Freeman,	Clinician rated. 7-point scale (1= very much better to 7 = very much worse)

Table 1. Outcome measures utilised by included studies (*Continued*)

	1999, Halbreich 2002, Yonkers 2006	
Patient Global Evaluation (PGE)	Kornstein 2006a,b, Landen 2007a,b; Steiner 2005 a,b; Yonkers 1997, Halbreich 2002	Self rated 7-point ordinal scale (from 1 = very much improved to 7 = very much worse) that rates the degree of overall improvement in PMS symptoms compared with pre-treatment baseline. Assessments were based on the past week
Quality of Life Enjoyment and Satisfaction Scale	Kornstein 2006a,b, Halbreich 2002	Self rated 5 point ordinal scale 1 = very poor to 5 = very good. A total score computed by adding the first 14 items, dividing by 70 (maximum total score) and multiplying by 100
Social Adjustment Scale Self Report (SAS-SR)	Kornstein 2006a,b; Yonkers 1997, Halbreich 2002	Self rated 55-item scale assessing work and or housework, interpersonal relationships, and social and leisure activities during the previous week
Calender of Premenstrual Experience (COPE)	Young 1998, Crnobaric 1998; Ozeren 1997; Jermain 1999; Wood 1992	Self rated 22 symptoms grouped into behavioural (14 symptoms,) and physical (8 symptoms) categories. Symptoms rated daily from 0 (none) to 3 (severe)
Visual Analogue Scale (VAS)	Menkes 1993	0-100mm for irritability, depressed mood, increased appetite/carbohydrate cravings, breast tenderness and bloating. 0 = no complaints to 100 = maximum complaints
Visual Analogue Scale (VAS)	Menkes 1992	0-100mm for irritability, depressed mood, increased appetite/carbohydrate cravings, breast tenderness and bloating. 0 = no complaints to 100 = maximum complaints
Visual Analogue Scale (VAS)	Landen 2007a,b	0-100mm, no details as to symptoms included in scale.
Visual Analogue Scale (VAS)	Steiner 1995a,b; 2001	0-100mm for tension, irritability and dysphoria with 0 being no symptoms and 100 being severe or extreme symptoms. The mean of the three scales was used determine the total psychological - symptom score
Visual Analogue Scale (VAS)	Pearlstein 2005a,b; Steiner 2005 a,b; Cohen 2004a,b;	0-100mm with 0 being 'not at all' and 100 being 'extreme'. Eleven symptoms were recorded irritability, tension, affective lability, depressed mood, decreased interest, difficulty concentrating, lack of energy,

Table 1. Outcome measures utilised by included studies (*Continued*)

		change in appetite, change in sleep pattern, feeling out of control and physical symptoms. VAS Mood is a composite score of irritability, tension, depressed mood and affective lability
Visual Analogue Scale (VAS)	Su 1997	A 16-item extended version of the VAS scale.
Visual Analogue Scale (VAS)	Wikander a,b,c 1998; Eriksson 1995	0-100mm scale with 0 = no complaints and 100 = maximal complaints. Symptoms include irritability, depressed mood, tension, anxiety, increased appetite, bloating, breast tenderness
Premenstrual tension scale (PMTS) - observer and self rated	Landen 2007a,b; Steiner 1995a,b; 2001; Miner 2002a,b; Steiner 2005 a,b;Cohen 2002a,b; Su 1997; Yonkers 2006	36-item scale completed by patient and 10-item scale completed by therapist/clinician. Both scales rate premenstrual symptoms on a given day and the score can range from 0 to 36 indicating all symptoms present and severe
Sheehan Disability Scale (SDS)	Landen 2007a,b; Pearlstein 2005a, Miner 2002a,b; Steiner 2005 a,b; Cohen 2004a,b	Assesses the extent to which their symptoms affect work, social life/leisure activities and family life/home responsibilities (scale 0 = not at all impaired to 10 = cannot function)
Penn Daily Symptom Rating Form (DSR)	Arrendondo-Soberon 1997, Freeman (2004), Freeman 1999	Depression, feeling hopeless or guilty, anxiety/tension, mood swings, irritability/anger, decreased interest, concentration difficulties, fatigue, food cravings/increased appetite, insomnia or hypersomnia, feeling out of control/overwhelmed, poor coordination, headache, aches, swelling/bloating/weight gain, cramps and breast tenderness. Rated on a five point scale from 0-4 (no disruption to severe disruption). Scores were calculated by adding the ratings of cycle days 5 through 10 for post menstrual scores and by adding the scores for the 6 days before menses for the premenstrual scores
Subject Global Ratings of Functioning	Freeman (2004)	Depression, feeling hopeless or guilty, anxiety/tension, mood swings, irritability/anger, decreased interest, concentration difficulties, fatigue, food cravings/increased appetite, insomnia or hypersomnia, feeling out of control/overwhelmed, poor

Table 1. Outcome measures utilised by included studies (*Continued*)

		coordination, headache, aches, swelling/ bloating/weight gain, cramps and breast tenderness. Rated on a five point scale from 0-4 (no disruption to severe disruption). Scores were calculated by adding the ratings of cycle days 5 through 10 for post menstrual scores and by adding the scores for the 6 days before menses for the premenstrual scores
Prospective Record of the Impact and Severity of Menstrual Symptomatology Calendar	Steiner 1995a,b; 2001	No details in paper.
Hamilton Rating Scale for Depression (HAM-D) (HRSD)	Crnobaric 1998, Yonkers 1997, Halbreich 1997, Freeman, 1999, Halbreich 2002, Pearlstein 1997, Yonkers 2006	No details in paper.
Daily Record of Severity of Problems (DRSP)	Miner 2002a,b; Cohen 2002 a,b; Yonkers 1997; Halbreich 2002, Yonkers 2006	Scale consisting 21 numbered items grouped into 11 categories (depressed/ hopeless/worthless; tension; mood swings/ feelings hurt; irritability; less interest in activities; difficulty concentrating; lethargy; increased appetite/cravings; sleeping more/ insomnia; overwhelmed/out of control; breast tenderness/bloating/headache/joint or muscle pain.). It has three additional questions measuring impairment of social functioning (at work/school/home; hobbies or social activities; relationships). Severity of each symptom is rated on a scale from 1 (not at all) to 6 (extreme). Mean score was calculated as average scores for the five most symptomatic days from six days before through to the first days of menses. Yonkers used an updated version using 24 items
Daily Assessment Form (DAF)	Stone 1991	33-item checklist used to assess each of the 10 symptom categories found in the DSM-III-R criteria. Symptoms are rated with a 6-point rating scale ranging from 1 (none) to 6 (extreme)
Global Assessment Scale (GAS)	Stone 1991, Pearlstein 1997	Self assessed scale with 18 summary scale scores reflecting composite ratings from 4-14 items scored from 1(no premenstrual change) to 6 (extreme change)

Table 1. Outcome measures utilised by included studies (*Continued*)

Premenstrual Assessment Form (PAF)	Menkes 1993	Includes irritability, low energy, mood swings, mastalgia, depression, bloating, impulsivity, abdominal pain, anxiety, food cravings. Scale of no change or worse to remitted
Daily Ratings Form (DRF)	Menkes 1993	Includes irritability, low energy, mood swings, mastalgia, depression, bloating, impulsivity, abdominal pain, anxiety, food cravings. Scale of no change or worse to remitted
Daily Ratings Form (DRF)	Su 1997	21-item 6-point scale; including sadness, anxiety, irritability, mood swings, breast pain, bloating, fatigue, food cravings, impaired social and work functioning, impulsivity and global impairment, sleep and sexual interest
Modified Daily Ratings Form (DRF)	Halbeich 1997	No details in paper.
Beck Depression Inventory	Su 1997; Jermain 1999, Wood 1992	22-item patient rated scale assessing depression. Rated on a 4-point severity scale
Stait Trait Anxiety Inventory State Form	Su 1997, Wood 1992	No details in papers.
Physical symptom checklist	Su 1997	Designed to detect the side effects of fluoxetine.
Profile of Mood State	Wood 1992	No details in paper.
Global Ratings of Functioning and Improvement	Freeman 1999	5-point rating scale using descriptors for each point ranging from 0 (none) to 4 (complete). Functioning rated for work, family life, and social activity with 0 (no disruption) to 4 (severe disruption)
Prospective Record of the Impact and Severity of Menstrual Symptomology calnder	Steiner 1995a,b	No details in paper but completed daily.
Menstrual Distress Questionnaire	Veeninga 1990	No details in paper.
Symptom Checklist-90	Veeninga 1990	No details in paper.
Global assessment of improvement	Eriksson 1995	No details in paper.

Table 1. Outcome measures utilised by included studies (*Continued*)

Quality of Life Scale (QOLS)	Freeman 1999	Self reported measure of various aspects of daily living plus a global assessment of QOL over the past week. The 14 QOLS items are the summary scales of the Quality of Life Enjoyment and Satisfaction Questionnaire

APPENDICES

Appendix 1. Medline search strategy

1 Premenstrual Syndrome/
2 premenstrua$.tw.
3 pre-menstrua$.tw.
4 late luteal.tw.
5 luteal phase.tw.
6 (luteal adj5 symptom$).tw.
7 (PMS or PMD or PMDD or LLPDD).tw.
8 or/1-7
9 exp serotonin uptake inhibitors/ or amoxapine/ or citalopram/ or clomipramine/ or fenfluramine/ or fluoxetine/ or fluvoxamine/ or norfenfluramine/ or paroxetine/ or sertraline/ or trazodone/ or zimeldine/
10 (serotonin adj5 inhibitor$).tw.
11 (amoxapine or citalopram or clomipramine or fenfluramine or fluoxetine or fluvoxamine or norfenfluramine or paroxetine or sertraline or trazodone or zimeldine).tw.
12 SSRI.tw.
13 (5-hydroxytryptamine adj5 inhibitor$).tw.
14 (5-ht adj5 inhibitor$).tw.
15 or/9-14
16 8 and 15
17 randomised controlled trial.pt.
18 controlled clinical trial.pt.
19 Randomized Controlled Trials/
20 Random allocation/
21 Double-blind method/
22 Single-blind method/
23 or/17-22
24 clinical trial.pt.
25 exp clinical trials/
26 (clin$ adj25 trial$).ti,ab,sh.
27 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
28 Placebos/
29 placebo$.ti,ab,sh.
30 random$.ti,ab,sh.
31 Research design/
32 or/24-31

33 animal/ not (human/ and animal/)
34 23 or 32
35 34 not 33
36 16 and 35
37 (2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$).ed.
38 36 and 37

WHAT'S NEW

Last assessed as up-to-date: 28 April 2008.

Date	Event	Description
11 February 2009	New citation required but conclusions have not changed	Review updated May 2008

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 4, 2002

Date	Event	Description
4 May 2008	New search has been performed	New studies identified and major update completed
31 March 2008	Amended	Converted to new review format.
28 February 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julie Brown took the lead in writing the updated review, performed searches, selected included and excluded trials, performed data extraction and quality assessment of trials and assisted in statistical analysis and interpretation of the data.

Shaughn O'Brien conceptualised the original review. He commented on drafts of the protocol and the original and updated review, and provided clinical interpretation of the data. He also assisted in providing comments on draft versions of the update.

Jane Marjoribanks assisted in data extraction in the update.

Katrina Wyatt took the lead in writing the original protocol and review, performed initial searches for trials, was involved in selection of included trials, performed data extraction and quality assessment of trials and assisted in statistical analysis and interpretation of the data in the original review.

Paul Dimmock assisted in writing the original protocol and review, contacted authors for additional information, was involved in selection of included trials, performed data extraction and quality assessment of trials and conducted the statistical analysis and interpretation of the data.

DECLARATIONS OF INTEREST

Julie Brown and Jane Majoribanks have no conflict of interest.

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KM Wyatt and PW Dimmock have no conflict of interest.

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Adolescent; Premenstrual Syndrome [*drug therapy; psychology]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [*therapeutic use]

MeSH check words

Adult; Female; Humans; Middle Aged; Young Adult