Breast pain

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ABSTRACT

INTRODUCTION: Breast pain may be cyclical (worse before a period) or non-cyclical, originating from the breast or the chest wall, and occurs at some time in 70% of women. Cyclical breast pain resolves spontaneously in 20% to 30% of women, but tends to recur in 60% of women. Non-cyclical pain responds poorly to treatment but tends to resolve spontaneously in half of women. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for breast pain? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 24 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antibiotics, bromocriptine, combined oral contraceptive pill, danazol, diuretics, evening primrose oil, gestrinone, gonadorelin analogues, hormone replacement therapy (HRT), lisuride, low-fat diet, progestogens, pyridoxine, tamoxifen, tibolone, topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), toremifene, and vitamin E.

QUESTIONS

INTERVENTIONS

TREATMENTS

Covered elsewhere in Clinical Evidence

Premenstrual syndrome

To be covered in future updates

Centchroman

Iodine

Footnote

*Categorisation based on consensus or expert opinion

Key points

- Breast pain (mastalgia) may be cyclical (worse before a period) or non-cyclical, originating from the breast or the chest wall, and occurs at some time in 70% of women.

  Cyclical breast pain resolves spontaneously in 20% to 30% of women, but tends to recur in 60% of women.

  Non-cyclical pain responds poorly to treatment but tends to resolve spontaneously in half of women.

- Diclofenac (a topical NSAID) seems effective at relieving symptoms of cyclical and non-cyclical breast pain but has been associated with adverse effects.

  There is consensus that topical NSAIDs are effective in relieving breast pain and should be considered as a first-line treatment, as the benefits are thought to outweigh the risk of adverse effects.

- We found insufficient evidence to assess the effects of oral NSAIDs on breast pain.

- Danazol, tamoxifen, toremifene, gonadorelin analogues, and gestrinone may reduce breast pain, but all can cause adverse effects.

  Danazol can cause weight gain, deepening of the voice, menorrhagia, and muscle cramps, and has androgenic effects on the fetus.

  Danazol is less effective than tamoxifen at reducing breast pain and has a less favourable adverse-effects profile compared with tamoxifen (10 mg daily).

  Tamoxifen (20 mg daily) and toremifene may increase the risk of venous thromboembolism, and neither drug is licensed for breast pain in the UK or USA.

  Tamoxifen (10 mg daily) under expert supervision, or danazol, may be considered when first-line treatments are ineffective.
- Bromocriptine reduces breast pain compared with placebo, but its licence for this indication has been withdrawn in the USA because of frequent and intolerable adverse effects.
- Hormone replacement therapy (HRT), which is associated with increased risks of breast cancer, venous thromboembolism, and gall bladder disease, may worsen breast pain. RCTs assessing the effects of HRT as a treatment for breast pain are unlikely to be conducted.
- Evening primrose oil has not been shown to improve breast pain, and its licence has been withdrawn for this indication in the UK owing to lack of efficacy.
- There is consensus that pyridoxine, diuretics, progestogens, tibolone, and antibiotics do not have a role in treating mastalgia.

  CAUTION: tibolone has been associated with increased risk of breast cancer recurrence.
- We don't know whether the combined oral contraceptive pill reduces breast pain, as we found no RCTs.
- We don't know whether a low-fat, high-carbohydrate diet, lisuride, or vitamin E reduce breast pain, as we found few studies.

DEFINITION

Breast pain can be differentiated into cyclical mastalgia (worse before a menstrual period) or non-cyclical mastalgia (unrelated to the menstrual cycle). [1] [2] Cyclical pain is often bilateral, usually most severe in the upper outer quadrants of the breast, and may be referred to the medial aspect of the upper arm. [1] [2] [3] Non-cyclical pain may be caused by true breast pain or chest wall pain, located over the costal cartilages. [1] [2] [4] Specific breast pathology and referred pain unrelated to the breasts are not included in this review.

INCIDENCE/ PREVALENCE

Up to 70% of women develop breast pain in their lifetime. [1] [2] Of 1171 US women attending a gynaecology clinic for any reason, 69% suffered regular discomfort, which was judged as severe in 11% of women, and 36% had consulted a doctor about breast pain. [2]

AETIOLOGY/ RISK FACTORS

Breast pain is most common in women aged 30 to 50 years. [1] [2]

PROGNOSIS

Cyclical breast pain resolves spontaneously within 3 months of onset in 20% to 30% of women. [5] The pain tends to relapse and remit, and up to 60% of women develop recurrent symptoms 2 years after treatment. [1] Non-cyclical pain responds poorly to treatment but may resolve spontaneously in about 50% of women. [1]

AIMS OF INTERVENTION

To reduce breast pain and improve quality of life, with minimal adverse effects.

OUTCOMES

Breast pain score based on the number of days of severe (score 2) or moderate (score 1) pain experienced in each menstrual cycle; visual analogue score of breast pain, heaviness, or breast tenderness; questionnaires; **quality of life**; **adverse effects**.

METHODS

Clinical Evidence search and appraisal May 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2010, Embase 1980 to May 2010, and The Cochrane Database of Systematic Reviews Issue 2, 2010 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single-blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included

systematic reviews of RCTs and RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. Overall, the evidence was poor, and some studies with weaker methods were included when higher-quality evidence was not found, as indicated in the text. We have translated non-English language articles where necessary and have included any trials of sufficient quality. Studies were included whatever the definition of breast pain, as indicated in the text. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 33). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for breast pain?

OPTION NSAIDS (TOPICAL)

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Diclofenac seems effective at relieving symptoms of cyclical and non-cyclical breast pain but has been associated with adverse effects.
- There is consensus that topical NSAIDs are effective in relieving breast pain and should be considered as a first-line treatment, as the benefits are thought to outweigh the risk of adverse effects.

Benefits and harms

Topical NSAIDs versus placebo:

We found one RCT. [6]

Breast pain

Topical NSAIDs (diclofenac) compared with placebo Diclofenac seems more effective at reducing breast pain (cyclical and non-cyclical) at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[6] RCT	60 women with cyclical breast pain Subgroup analysis Total population was 108 women with cyclical or non-cyclical breast pain	**Reduction in cyclical pain measured on visual analogue scale (VAS) from 0 = no pain to 10 = intolerable pain , 6 months** 5.87 with topical diclofenac 1.30 with placebo	P = 0.0001	○○○	topical diclofenac
[6] RCT	60 women with cyclical breast pain Subgroup analysis Total population was 108 women with cyclical or non-cyclical breast pain	**Reduction in non-cyclical pain measured on VAS from 0 = no pain to 10 = intolerable pain , 6 months** 6.33 with topical diclofenac 1.12 with placebo 48 women in this analysis	P = 0.0001	○○○	topical diclofenac
[6] RCT	60 women with cyclical breast pain	**Proportion of women with no cyclical pain , 6 months**	P = 0.0001	○○○	topical diclofenac

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Subgroup analysis Total population was 108 women with cyclical or non-cyclical breast pain	14/30 (47%) with topical diclofenac 0/30 (0%) with placebo			
[6] RCT	60 women with cyclical breast pain Subgroup analysis Total population was 108 women with cyclical or non-cyclical breast pain	**Proportion of women with no non-cyclical pain , 6 months** 12/24 (50%) with topical diclofenac 0/24 (0%) with placebo 48 women in this analysis	P = 0.0001	○○○	topical diclofenac

Quality of life

No data from the following reference on this outcome. [6]

Adverse effects

No data from the following reference on this outcome. [6]

Further information on studies

Comment:

Adverse effects
All products containing diclofenac sodium have been associated with the potential for elevation of liver function tests. [7] [8]

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recently conducted a scientific review on photosensitivity reactions associated with medicines containing topical ketoprofen. It concluded (July 2010) that the benefit–risk balance of these medicines continues to be positive. However, doctors should inform patients on appropriate use to prevent occurrence of serious skin photosensitivity reactions. [9]

Clinical guide:
There is consensus that topical NSAIDs are effective and well tolerated in relieving breast pain, and they are easily available without prescription. [6] Physicians should measure transaminases periodically in patients receiving long-term treatment with diclofenac.

OPTION NSAIDS (ORAL) New

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- There is limited evidence that oral NSAIDs may reduce breast pain compared with placebo.

Benefits and harms

Oral NSAIDs versus placebo:

We found one RCT. [10]

Breast pain

Oral NSAIDs compared with placebo Nimesulide may be more effective at reducing spontaneous breast pain at 15 days in women with non-cyclical breast pain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[10] RCT	40 women (aged 14–65 years, mean 40 years) with non-cyclical breast pain	**Disappearance of spontaneous pain , 15 days** 13/20 (65%) with nimesulide 200 mg 4/20 (20%) with placebo Method of randomisation unclear	Significance not assessed		

Quality of life

No data from the following reference on this outcome. [10]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] RCT	40 women (aged 14–65 years, mean 40 years) with non-cyclical breast pain	**Adverse effects , 15 days** with nimesulide 200 mg with placebo The RCT reported that no women in either group experienced adverse reactions			

Further information on studies

Comment: Nimesulide has been associated with a risk of serious damage to the liver and is not authorised in the UK and several European countries. The Committee for Medicinal Products for Human Use (CHMP) has restricted its use to 15 days. [11]

OPTION DANAZOL

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Danazol may reduce breast pain but can cause adverse effects, including weight gain, deepening of the voice, menorrhagia, and muscle cramps, and has androgenic effects on the fetus.

Benefits and harms

Danazol versus placebo:

We found one good-quality outpatient-based RCT in 93 women. [12]

Breast pain

Danazol compared with placebo Danazol reduces cyclical breast pain after 12 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated tamoxifen 10 mg daily	**Proportion of women with >50% pain relief , at the end of 6 months' treatment** 21/32 (66%) with danazol 200 mg daily 11/29 (38%) with placebo	P <0.01	○○○	danazol
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated tamoxifen 10 mg daily	**Proportion of women with >50% pain relief , 12 months after the 6 months of treatment** 12/32 (38%) with danazol 200 mg daily 0/29 (0%) with placebo	P <0.001	○○○	danazol

Quality of life

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated tamoxifen 10 mg daily	**Weight gain** 10/32 (31%) with danazol 200 mg daily 1/29 (3%) with placebo	P value not reported		
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated tamoxifen 10 mg daily	**Deepening of the voice** 4/32 (13%) with danazol 200 mg daily 0/29 (0%) with placebo	P value not reported		
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated tamoxifen 10 mg daily	**Menorrhagia** 4/32 (13%) with danazol 200 mg daily 0/29 (0%) with placebo	P value not reported		
[12] RCT	93 women with severe cyclical mastalgia	**Muscle cramps**	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	The remaining arm evaluated tamox-ifen 10 mg daily	3/32 (9%) with danazol 200 mg daily 0/29 (0%) with placebo			

Further information on studies

Comment: **Clinical guide:**
Although we found no direct evidence, there is consensus that, once a response is achieved, adverse effects can be avoided by reducing the dose of danazol to 100 mg daily and confining treatment to the 2 weeks preceding menstruation. [12] [13] Non-hormonal contraception is essential with danazol because danazol has deleterious androgenic effects in the fetus. [14]

OPTION GESTRINONE

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Gestrinone may reduce breast pain but can cause adverse effects including greasy skin, hirsutism, acne, reduction in breast size, headache, and depression.

Benefits and harms

Gestrinone versus placebo:

We found one double-blind, outpatient-based RCT (145 women). [15]

Breast pain

Gestrinone compared with placebo Gestrinone is more effective at reducing breast pain after 3 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[15] RCT	145 pre-menopausal wom-en with cyclical breast pain	**Reduction in mean breast pain score (visual analogue score where 0 = no pain and 100 = worst pain) , 3 months** 59.5 to 11.7 with gestrinone 2.5 mg twice weekly 58.2 to 36.7 with placebo	P <0.0001	○○○	gestrinone

Quality of life

No data from the following reference on this outcome. [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	145 pre-menopausal women with cyclical breast pain	**At least one adverse effect** 41% with gestrinone 2.5 mg twice weekly 14% with placebo Adverse effects included greasy skin or hair, hirsutism, acne, intermenstrual bleeding, voice change, reduced libido, reduction in breast size, headache, depression, and tiredness (see figures for individual effects below).	Reported as significant P value not reported	○○○	placebo
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Greasy skin or hair** 13/64 (21%) with gestrinone 2.5 mg twice weekly 2/61 (4%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Hirsutism** 10/64 (16%) with gestrinone 2.5 mg twice weekly 3/61 (5%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Acne** 9/64 (15%) with gestrinone 2.5 mg twice weekly 2/61 (4%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Intermenstrual bleeding** 7/64 (11%) with gestrinone 2.5 mg twice weekly 0/61 (0%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Voice change** 5/64 (8%) with gestrinone 2.5 mg twice weekly 1/61 (2%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Reduced libido** 5/64 (8%) with gestrinone 2.5 mg twice weekly 3/61 (5%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Reduction in breast size** 3/64 (5%) with gestrinone 2.5 mg twice weekly 0/61 (0%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Headache** 4/64 (7%) with gestrinone 2.5 mg twice weekly 0/61 (0%) with placebo	P value not reported		
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Depression** 2/64 (4%) with gestrinone 2.5 mg twice weekly 0/61 (0%) with placebo	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[15] RCT	145 pre-menopausal women with cyclical breast pain	**Tiredness** 2/64 (4%) with gestrinone 2.5 mg twice weekly 0/61 (0%) with placebo	P value not reported		

Further information on studies

Comment: Gestrinone is a synthetic steroid, reported to have androgenic, anti-oestrogenic, and anti-progestogenic properties. [16]

Clinical guide:
Gestrinone is not used for breast pain in clinical practice and is not widely available: it was discontinued in the UK in 2009. This medicine may be harmful to an unborn baby and is not recommended during pregnancy. For this reason, the first dose of this medicine should be taken on the first day of the menstrual period, to be certain that pregnancy is not a possibility. [17]

OPTION GONADORELIN ANALOGUES (LUTEINISING HORMONE-RELEASING HORMONE ANALOGUES)

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Gonadorelin analogues may reduce breast pain but can cause adverse effects. Goserelin injection is associated with vaginal dryness, hot flushes, decreased libido, oily skin or hair, decreased breast size, and irritability.
- There is consensus that goserelin injections should be reserved for severe refractory mastalgia and that treatment should be limited to 6 months.

Benefits and harms

Gonadorelin analogues (luteinising hormone-releasing hormone analogues) versus placebo:
We found one RCT (147 women). [18]

Breast pain

Goserelin injection compared with placebo Goserelin injection reduces breast pain (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[18] RCT	147 pre-menopausal women with breast pain	**Mean days with severe breast pain per cycle (pain measured using Cardiff breast pain chart), 6 months** 17.6 to 5.9 (67% reduction from baseline) with goserelin injection 18.4 to 12.0 (35% reduction from baseline) with placebo injection	P = 0.0001	○○○	goserelin injection

Quality of life

No data from the following reference on this outcome. [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	147 pre-menopausal women with breast pain	**Vaginal dryness** 22% with goserelin injection 13% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Hot flushes** 58% with goserelin injection 16% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Decreased libido** 28% with goserelin injection 7% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Oily hair or skin** 18% with goserelin injection 9% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Breast size reduction** 16% with goserelin injection 9% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Irritability** 24% with goserelin injection 17% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Depression** 16% with goserelin injection 18% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Tension** 18% with goserelin injection 20% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Headache** 50% with goserelin injection 52% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Hirsutism** 4% with goserelin injection 0% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Acne** 14% with goserelin injection 11% with placebo injection	Significance not reported		
[18] RCT	147 pre-menopausal women with breast pain	**Ankle oedema** 14% with goserelin injection 22% with placebo injection	Significance not reported		

Further information on studies

Comment: **Clinical guide:**
There is widespread consensus that goserelin injections should be reserved for severe refractory mastalgia and treatment should be limited to 6 months. Add-back tibolone or HRT can be used to relieve many of the adverse effects.

OPTION TAMOXIFEN

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Tamoxifen may reduce breast pain but can cause adverse effects. Adverse effects of tamoxifen (hot flushes and GI disturbances) are more likely with higher doses (20 mg) compared with lower doses (10 mg). Long-term use of tamoxifen has been associated with an increased risk of venous thromboembolism. Tamoxifen is not licensed for the treatment of mastalgia in the UK or USA.

Benefits and harms

Tamoxifen versus placebo:

We found three RCTs. [12] [19] [20]

Breast pain

Tamoxifen compared with placebo Tamoxifen may be more effective than placebo at reducing breast pain (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[19] RCT	60 premenopausal women with cyclical breast pain The RCT was double blind	**Proportion of women with >50% reduction in mean pain score (measured by visual analogue scale) , 3 months** 22/31 (71%) with tamoxifen 20 mg daily 11/29 (38%) with placebo	P <0.03	○○○	tamoxifen
[12] RCT **3-armed trial**	93 women The remaining arm evaluated danazol 200 mg daily	**Proportion of women with >50% reduction in mean pain score , at the end of 6 months' treatment** 23/32 (72%) with tamoxifen 10 mg daily 11/29 (38%) with placebo	P = 0.04 Results were also significant 6 and 12 months after the end of treatment	○○○	tamoxifen
[20] RCT	88 women aged 22 to 44 years	**Proportion of women who achieved complete recovery (outcome not clearly defined) , 8 months** 40/44 (90%) with tamoxifen 0/44 (0%) with placebo	P value not reported		

Quality of life

No data from the following reference on this outcome. [12] [19] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	60 premenopausal women with cyclical breast pain The RCT was double blind	**Hot flushes** 8/31 (26%) with tamoxifen 20 mg daily 3/29 (10%) with placebo	Reported as not significant	⟷	Not significant
[19] RCT	60 premenopausal women with cyclical breast pain The RCT was double blind	**Vaginal discharge** 5/31 (16%) with tamoxifen 20 mg daily 2/29 (7%) with placebo	Reported as not significant	⟷	Not significant
[12] RCT **3-armed trial**	93 women The remaining arm evaluated danazol 200 mg daily	**Hot flushes** 8/32 (25%) with tamoxifen 10 mg daily 3/29 (10%) with placebo	P value not reported		
[12] RCT **3-armed trial**	93 women The remaining arm evaluated danazol 200 mg daily	**Vaginal discharge** 5/32 (16%) with tamoxifen 10 mg daily 2/29 (7%) with placebo	P value not reported		
[20] RCT	88 women aged 22 to 44 years	**Adverse effects** with tamoxifen with placebo The RCT did not report any significant adverse events.			

Tamoxifen versus danazol:

See benefits of danazol versus tamoxifen, p 25 .

Different doses of tamoxifen versus each other:

We found two RCTs. [21] [22]

Breast pain

Different doses of tamoxifen compared with each other Lower-dose tamoxifen (10 mg) is as effective as higher-dose tamoxifen (20 mg) at reducing breast pain at 3 to 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[21] RCT	301 women with cyclical breast pain for >6 months	**Pain relief (reduction of 2 points on pain score) , 3 months** 127/155 (82%) with 10 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months	P value reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		107/142 (75%) with 20 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months			
[22] RCT	60 women with cyclical and non-cyclical mastalgia	**Response rates , 3 months** 12/14 (86%) with 10 mg daily doses of tamoxifen 11/13 (85%) with 20 mg daily doses of tamoxifen	P value not reported but stated as not significant	⟷	Not significant
[22] RCT	60 women with cyclical and non-cyclical mastalgia	**Response rates , 6 months** 14/15 (93%) with 10 mg daily doses of tamoxifen 13/15 (87%) with 20 mg daily doses of tamoxifen	P value not reported but stated as not significant	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [21] [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT	301 women with cyclical breast pain for >6 months	**Adverse effects** 80/155 (52%) with 10 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months 94/142 (66%) with 20 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months Adverse effects were primarily hot flushes and GI disturbances (see figures for individual effects below). Adverse effects occurred more frequently with tamoxifen 20 mg than with tamoxifen 10 mg between days 15 and 25 of the menstrual cycle	P = 0.01	○○○	10 mg daily doses of tamoxifen
[21] RCT	301 women with cyclical breast pain for >6 months	**Hot flushes** 33/155 (21%) with 10 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months 54/142 (38%) with 20 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months	P = 0.015	○○○	10 mg daily doses of tamoxifen
[21] RCT	301 women with cyclical breast pain for >6 months	**GI disturbances** 30/155 (19%) with 10 mg daily doses of tamoxifen from days 15	P = 0.004	○○○	10 mg daily doses of tamoxifen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		to 25 in the menstrual cycle for 3 months 48/142 (34%) with 20 mg daily doses of tamoxifen from days 15 to 25 in the menstrual cycle for 3 months			
[22] RCT	60 women with cyclical and non-cyclical mastalgia	**Adverse effects** with tamoxifen 10 mg daily with tamoxifen 20 mg daily Adverse effects occurred more frequently with tamoxifen 20 mg than with tamoxifen 10 mg between days 15 and 25 of the menstrual cycle			

Further information on studies

Comment:

Clinical guide:
Tamoxifen is not licensed for mastalgia in the UK or USA. There is consensus to limit its use to no more than 6 months at a time under expert supervision, and with appropriate non-hormonal contraception, because of the high incidence of adverse effects. Tamoxifen 10 mg daily is initially prescribed for 3 months and may be continued for additional 3 months only if a response is observed. One meta-analysis of the 4 largest breast cancer prevention trials found that tamoxifen used long term at 20 mg daily was associated with an increased risk of venous thromboembolism (venous thromboembolic event: RR 1.9, 95% CI 1.4 to 2.6; P = 0.0001). [23] See adverse effects of tamoxifen under treatment of non-metastatic breast cancer. There are no long-term data on thromboembolic adverse effects with a dose of 10 mg given from days 10 to 25, which is the standard dose for treatment of mastalgia and lower than the dose used for breast cancer. Tamoxifen is contraindicated in pregnancy because of potential teratogenicity. [24]

OPTION TOREMIFENE

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Toremifene may reduce breast pain but can cause adverse effects; it has been associated with hot flushes, sweats, DVT, and visual disturbances, and is potentially teratogenic. Toremifene is not licensed for breast pain in the UK or USA.

Benefits and harms

Toremifene versus placebo:

We found two RCTs. [25] [26]

Breast pain

Toremifene compared with placebo Toremifene may be more effective than placebo at decreasing breast pain (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[25] RCT	195 women with moderate to severe breast pain The women randomised had reported little or no benefit following a placebo lead-in cycle	**Proportion of women with >50% reduction in pain scores** 72/104 (69%) with toremifene 30 mg daily for 3 menstrual cycles 29/91 (32%) with placebo for 3 menstrual cycles Pain measured on a visual analogue scale (VAS); 0 = no pain and 10 = worst pain The RCT had a high withdrawal rate and unclear follow-up; see further information on studies	P <0.001	○○○	toremifene
[26] RCT **Crossover design**	62 women with cyclical mastalgia during at least 3 previous menstrual cycles	**Pain scores (median score; post-crossover)** 1.8 with oral toremifene 20 mg 3.7 with placebo Pain scores measured on a VAS (during the late luteal phase of each menstrual cycle) where 0 = no pain and 10 = worst pain See further information on studies for details of treatment regimens and crossover 56 women evaluated post crossover	P = 0.004	○○○	toremifene

Quality of life

Toremifene compared with placebo We don't know whether toremifene is more effective than placebo at increasing quality-of-life scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[26] RCT **Crossover design**	62 women with cyclical mastalgia during at least 3 previous menstrual cycles	**Quality-of-life scores** with oral toremifene 20 mg with placebo Absolute numbers not reported Quality-of-life scores were measured on a modified 36-item Finnish Depression Scale (during the late luteal phase of the baseline cycle and the 3rd and 6th treatment cycles) See further information on studies for details of treatment regimens and crossover 56 women evaluated post crossover	P >0.05	⟷	Not significant

No data from the following reference on this outcome. [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] RCT	195 women with moderate to severe breast pain The women randomised had reported little or no benefit following a placebo lead-in cycle	**Adverse effects** 53/104 (51%) with toremifene 30 mg daily for 3 menstrual cycles 39/91 (43%) with placebo for 3 menstrual cycles Women in each group reported menses disturbances, dizziness, vaginal discharge, and nausea The RCT had a high withdrawal rate and unclear follow-up; see further information on studies	P = 0.45	⟷	Not significant
[26] RCT **Crossover design**	62 women with cyclical mastalgia during at least 3 previous menstrual cycles	**Headache** 3/56 (5%) with oral toremifene 20 mg 2/56 (4%) with placebo See further information on studies for details of treatment regimens and crossover 56 women evaluated post crossover	Significance not assessed		
[26] RCT **Crossover design**	62 women with cyclical mastalgia during at least 3 previous menstrual cycles	**Nausea** 2/56 (4%) with oral toremifene 20 mg 1/56 (2%) with placebo See further information on studies for details of treatment regimens and crossover 56 women evaluated post crossover	Significance not assessed		

Further information on studies

[25] The RCT performed an intention-to-treat analysis. However, the withdrawal rate was high (72/195 women), and it is unclear how those women who withdrew were dealt with in the analysis.

[26] Allocated treatments were given from day 15 of the menstrual cycle until menstruation for 3 consecutive cycles, followed by a no-treatment wash-out cycle before crossover to placebo or toremifene for a further 3 months.

Comment:

Adverse effects
Toremifene has been associated with dose-dependent risk of QT prolongation, which carries a risk of serious cardiac arrhythmia. [27]

Clinical guide:
Toremifene, a metabolite of tamoxifen, is not licensed for mastalgia in the UK or USA. Although there is emerging evidence of its efficacy, there is no evidence that it is superior to tamoxifen, a more widely used and better-understood drug. Other adverse effects reported with use of toremifene include hot flushes, sweats, DVT, and occasional visual problems. Toremifene is potentially teratogenic and should not be used in women who may become pregnant.

OPTION ANTIBIOTICS

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Antibiotics have not been shown to have a role in treating mastalgia.

Benefits and harms

Antibiotics:

We found no systematic review or good-quality RCTs.

Further information on studies

Comment: **Clinical guide:**

Some clinicians have considered that the condition of breast pain reflects infection. However, there is no infection associated with true mastalgia and therefore no value in the use of antibiotics (mastitis is not synonymous with true mastalgia). Conversely, infection caused by, for example, periductal mastitis, can cause breast pain and should therefore be ruled out as a cause of breast pain before diagnosing a patient with true mastalgia. Antibiotics are effective in resolving inflammation in, for example, periductal mastitis, but have no role in true mastalgia.

OPTION DIET (LOW-FAT, HIGH-CARBOHYDRATE)

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- We don't know whether a low-fat, high-carbohydrate diet reduces breast pain, as few RCTs have been found.

Benefits and harms

Advice to eat a low-fat, high-carbohydrate diet versus general dietary advice:

We found one small RCT (21 women). [28]

Breast pain

Advice to eat a low-fat, high-carbohydrate diet compared with general dietary advice Advice to follow a low-fat, high-carbohydrate diet may reduce self-reported premenstrual breast swelling and breast tenderness at 6 months, compared with general dietary advice (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[28] RCT	21 women attending a clinic in Canada with severe cyclical mastalgia for at least 5 years	**Self-reported premenstrual breast swelling , 6 months** 5/10 (50%) with low-fat, high carbohydrate diet 9/9 (100%) with general dietary advice One woman in each group withdrew and was excluded from the analysis See further information on studies for details of dietary interventions	P = 0.04	○○○	low-fat, high-carbohydrate diet
[28] RCT	21 women attending a clinic in Canada with severe cyclical	**Self-reported premenstrual breast tenderness , 6 months** 6/10 (60%) with low-fat, high carbohydrate diet	P = 0.0001	○○○	low-fat, high-carbohydrate diet

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	mastalgia for at least 5 years	9/9 (100%) with general dietary advice One woman in each group withdrew and was excluded from the analysis See further information on studies for details of dietary interventions			
[28] RCT	21 women attending a clinic in Canada with severe cyclical mastalgia for at least 5 years	**Improvement in combined outcome of breast swelling, tenderness, and nodularity on physical examination , 6 months** 6/10 (60%) with low-fat, high carbohydrate diet 2/9 (22%) with general dietary advice One woman in each group withdrew and was excluded from the analysis See further information on studies for details of dietary interventions	P = 0.08	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT	21 women attending a clinic in Canada with severe cyclical mastalgia for at least 5 years	**Adverse effects** with low-fat, high carbohydrate diet with general dietary advice The RCT reported no adverse effects See further information on studies for details of dietary interventions			

Further information on studies

[28] Low-fat, high-carbohydrate diet was defined as instruction to reduce fat content of the diet to 15% of total calorie intake while increasing complex carbohydrates to maintain calorie intake. General dietary advice was defined as principles for a healthy diet based on Canada's Food Guide, but no counselling to modify the fat content of the diet.

Comment: Diets can be difficult to sustain in the long term. Caffeine use has been associated with breast pain, but there is little evidence to support caffeine restriction in the management of this problem.

Clinical guide:
Women should be advised to lower the amount of processed fat that they eat and ensure a high-fibre diet, as this reduces oestrogen levels and is good general health advice.

OPTION DIURETICS

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Diuretics have not been shown to have a role in treating mastalgia.

Benefits and harms

Diuretics:
We found no systematic review or RCTs of adequate quality.

Further information on studies

Comment: **Clinical guide:**
Diuretics are not indicated for the treatment of breast pain. It has been reported that there is no correlation between symptoms of breast pain and retention of body water. [29]

OPTION LISURIDE

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- We don't know whether lisuride (a dopamine agonist) reduces breast pain, as few RCTs have been found. Dopamine agonists have been associated with pathological gambling and hypersexuality.

Benefits and harms

Lisuride maleate versus placebo:
We found one RCT (60 women). [30]

Breast pain

Lisuride maleate compared with placebo Lisuride maleate (a dopamine agonist) may reduce breast pain over 2 months, compared with placebo (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[30] RCT	60 women with premenstrual breast pain The RCT was double blind	**Proportion of women with >50% improvement in pain scores measured on a visual analogue scale , 2 months** 17/30 (57%) with lisuride maleate 200 micrograms daily over 2 months 2/30 (7%) with placebo over 2 months There were methodological flaws with this study; see further information on studies	P <0.001	○○○	lisuride maleate

Quality of life

No data from the following reference on this outcome. [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT	60 women with premenstrual breast pain The RCT was double blind	**Nausea , first month** 5/30 (17%) with lisuride maleate 200 micrograms daily over 2 months 3/30 (10%) with placebo over 2 months There were methodological flaws with this study; see further information on studies	Reported as not significant	⟷	Not significant

Further information on studies

[30] In this RCT, allocation was carried out in blocks of 10 consecutive women. Tablet coding for active treatments and placebo differed, potentially confounding any treatment effect. Response to treatment was defined as a reduction greater than 25% from the baseline score during the first month, or greater than 50% during the second month.

Comment:

Adverse effects
Dopamine agonists including lisuride have been associated with pathological gambling, and with increased libido, including hypersexuality. [31]

Clinical guide:
Lisuride is not widely used and has been discontinued in many countries, including the UK and USA. It should be used with caution in view of the safety alerts from the Medicines and Healthcare products Regulatory Agency.

OPTION CONTRACEPTIVE (COMBINED ORAL) New

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- We don't know whether the oral contraceptive pill reduces breast pain, as we found no RCTs.

Benefits and harms

Oral contraceptive pill:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION PROGESTOGENS

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Progestogens have not been shown to have a role in treating mastalgia.

Benefits and harms

Progestogens versus placebo:

We found two RCTs. [32] [33]

Breast pain

Progesterone cream or medroxyprogesterone acetate tablets compared with placebo Progesterone cream or medroxyprogesterone acetate tablets may be no more effective than placebo at reducing breast pain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[32] RCT **Crossover design**	26 women with cyclical breast pain of at least 6 months' duration who had persistent symptoms after a 2-month observation period with no hormonal treatment	**Pain scores** with oral medroxyprogesterone acetate 20 mg tablets with placebo Absolute results reported graphically Pain scores measured by visual analogue scale (VAS) at the end of each phase before and after crossover See further information on studies for details of crossover design	Reported as not significant The overall withdrawal rate was 15%	⟷	Not significant
[33] RCT **Crossover design**	32 women with breast pain of at least 2 months' duration who were able to keep an updated diary with VAS of pain for 1 month	**Pain scores measured by VAS , before crossover** with progesterone 1% cream with placebo cream Absolute results not reported See further information on studies for details of crossover design	Reported as not significant Insufficient details were provided about the analysis 7/32 (22%) women withdrew from the study	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [32] [33]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT **Crossover design**	26 women with cyclical breast pain of at least 6 months' duration who had persistent symptoms after a 2-month observation period with no hormonal treatment	**Adverse effects , 6 months** with medroxyprogesterone acetate with placebo 5 women reported adverse effects while taking medroxyprogesterone acetate, and 5 while taking placebo, and 1 with both. Symptoms were mostly vague premenstrual symptoms. No further details were reported			

No data from the following reference on this outcome. [33]

Further information on studies

[33] In the active-treatment arm, cream containing progesterone 1% was applied daily from the 10th day of the cycle to the beginning of the next cycle, for 3 months. In the placebo arm, placebo cream was applied daily from the 10th day of the cycle to the beginning of the next cycle, for 3 months. The RCT had a small sample size, a significant level of withdrawals, and a selection phase, which may restrict the generalisability of the evidence.

[32] In the active treatment-first arm, oral medroxyprogesterone acetate 20 mg tablets were given from days 10 to 26 of the menstrual cycle for 3 months, and then placebo for 3 months. In the placebo-first arm, placebo was given from days 10 to 26 of the menstrual cycle for 3 months, and then oral medroxyprogesterone acetate 20 mg tablets for 3 months. The RCT had a small sample size, a significant level of withdrawals, and a selection phase, which may restrict the generalisability of the evidence.

Comment: **Clinical guide:**
Despite claims from Europe that progestogens would prevent breast pain, the evidence does not support this, and progestogens are not indicated as treatment for the condition. Studies have failed to detect a significant difference in progestogen levels between women with and without mastalgia. Mastalgia is not associated with significant luteal-phase progestogen insufficiency. [34] [35]

OPTION PYRIDOXINE

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Pyridoxine has not been shown to have a role in treating mastalgia.

Benefits and harms

Pyridoxine:

We found no systematic review or good-quality RCTs.

Further information on studies

Comment: There is no evidence to support the use of pyridoxine for breast pain. One small, double-blind crossover RCT found no significant difference at 2 months between vitamin B6 (pyridoxine) and placebo for cyclical mastalgia (mean pain difference from baseline measured by linear analogue scale [parameters unclear]: –2.6 cm with B6 200 mg/day *v* –2.3 cm with placebo; reported as not significant). [36] We chose not to report the study in detail because of poor methodology and reporting, but we mention it here because of a paucity of data.

Clinical guide:
The hypothesis of vitamin B6 deficiency in mastalgia is speculative and not supported by experimental results. Deficiency of B6 is rare, while excessive ingestion is associated with peripheral neuropathy. [37]

OPTION TIBOLONE

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Tibolone has not been shown to have a role in treating mastalgia.

Benefits and harms

Tibolone:

We found no systematic review or RCTs.

Further information on studies

Comment: We found one non-randomised, placebo-controlled study comparing tibolone versus calcium carbonate "placebo" in 64 women with breast pain secondary to use of HRT, allocated to treatment according to individual women's preferences. [38] It found no significant difference in breast tenderness or breast pain at 12 months (both symptoms measured on a visual analogue scale from 0 = no symptoms to 10 = greatest severity; mean breast tenderness score: from 7.9 at baseline to 4.1 at 12 months with tibolone *v* from 7.4 at baseline to 3.8 at 12 months with calcium carbonate; P value not reported; mean mastalgia score: from 6.1 at baseline to 2.9 at 12 months with tibolone *v* from 5.7 at baseline to 2.7 at 12 months with calcium carbonate; P value not reported). The study found that the risk of vaginal bleeding was similar with tibolone compared with calcium carbonate in the first 2 months (6/31 [19%] with tibolone *v* 4/30 [13%] with placebo; P value not reported). The study reported no other adverse effects. [38] See also comment on HRT, p 27 .

Adverse effects Tibolone has been associated with increased risk of breast cancer recurrence.

Clinical guide:
Tibolone is a synthetic steroid reported to have oestrogenic, progestogenic, and weak androgenic properties, which can be used as a form of HRT. [16] See comment on HRT, p 27 . Breast pain associated with hormone replacement treatment is less common with tibolone compared with oestrogen-only or combined HRT. [39] Tibolone should not be considered an effective treatment of mastalgia. However, postmenopausal patients with breast pain secondary to use of HRT may benefit by swapping to tibolone.

OPTION VITAMIN E

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- We don't know whether vitamin E reduces breast pain, as few RCTs have been found. Vitamin E use has been associated with an increased risk of haemorrhagic stroke.

Benefits and harms

Vitamin E:

We found no systematic review or RCTs of adequate quality.

Further information on studies

Comment: **Clinical guide:**
There is no evidence that vitamin E improves breast pain.

OPTION BROMOCRIPTINE

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Bromocriptine reduces breast pain compared with placebo, but its licence for this indication has been withdrawn in the USA because of frequent and intolerable adverse effects. Bromocriptine is associated with nausea, dizziness, postural hypotension, and constipation.

Benefits and harms

Bromocriptine versus placebo:

We found two RCTs. [40] [41]

Breast pain

Bromocriptine compared with placebo Bromocriptine (a dopamine agonist) may be more effective at reducing breast pain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[40] RCT	272 pre-menopausal women with diffuse fibrocystic disease of the breast Outpatient-based, European RCT	**Symptoms (self-assessed visual analogue scoring of breast pain, tenderness, and heaviness) , 3 and 6 months** with bromocriptine 2.5 mg twice daily with placebo Absolute results reported graphically	Reported as significant Results must be interpreted with care because analysis was not by intention to treat, and overall withdrawal rates were high (49/135 [36%] with bromocriptine *v* 36/137 [26%] with placebo)	◌◌◌	bromocriptine
[41] RCT **Crossover design**	10 women	**Pain after crossover** with bromocriptine with placebo	P <0.02 after crossover Results before crossover were not reported	◌◌◌	bromocriptine

Quality of life

No data from the following reference on this outcome. [40] [41]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[40] RCT	272 pre-menopausal women with diffuse fibrocystic disease of the breast Outpatient-based, European RCT	**Adverse effects** 61/135 (45%) with bromocriptine 2.5 mg twice daily 41/137 (30%) with placebo Adverse reactions included nausea (32% with bromocriptine *v* 13% with placebo), dizziness (12% with bromocriptine *v* 7% with placebo), postural hypotension, and constipation	Reported as significant	○○○	placebo
[40] RCT	272 pre-menopausal women with diffuse fibrocystic disease of the breast Outpatient-based, European RCT	**Withdrawals related to adverse effects** 15/135 (11%) with bromocriptine 2.5 mg twice daily 8/137 (6%) with placebo Overall, withdrawal rates were high (49/135 [36%] with bromocriptine *v* 36/137 [26%] with placebo)			
[41] RCT **Crossover design**	10 women	**Nausea and dizziness** 8/10 (80%) with bromocriptine 0/10 (0%) with placebo			

Further information on studies

Comment: **Adverse effects** Strokes and death have been reported after use of bromocriptine to inhibit lactation, and the FDA has withdrawn its licence for this indication. [42] Dopamine agonists including bromocriptine have been associated with pathological gambling, and with increased libido, including hypersexuality. [31]

Clinical guide:
Bromocriptine is now rarely used, because frequent and intolerable adverse effects at the therapeutic dose outweigh the benefits for this indication.

OPTION DANAZOL VERSUS TAMOXIFEN

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Danazol may be less effective than tamoxifen for reducing pain. Adverse effects are common with both drugs (although less so with tamoxifen 10 mg), and both are contraindicated in women who have had a previous venous thromboembolism.

Benefits and harms

Danazol versus tamoxifen:

We found one good-quality outpatient-based RCT in 93 women. [12]

Breast pain

Danazol compared with tamoxifen Danazol is less likely than tamoxifen to improve pain scores after 6 months' treatment, and 12 months after the end of 6 months' treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Proportion of women with 50% pain relief , at the end of 6 months' treatment** 21/32 (66%) with danazol 200 mg daily over 6 months 23/32 (72%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P <0.001	○○○	tamoxifen
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Proportion of women with 50% pain relief , 12 months after the 6 months of treatment** 12/32 (37%) with danazol 200 mg daily over 6 months 17/32 (53%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P <0.001	○○○	tamoxifen

Quality of life

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Withdrawals from the study due to adverse effects of treatment** with danazol with placebo 4 women taking tamoxifen withdrew, compared with 3 taking danazol. Reported adverse effects included weight gain, voice deepening, menorrhagia, muscle cramps, hot flushes, and vaginal discharge (see figures for individual effects below) 64 women in this analysis			
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Weight gain** 10/32 (31%) with danazol 200 mg daily over 6 months 0/32 (0%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P value not reported		
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia	**Deepening of the voice** 4/32 (13%) with danazol 200 mg daily over 6 months	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated placebo	0/32 (0%) with tamoxifen 10 mg daily over 6 months			
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Menorrhagia** 4/32 (13%) with danazol 200 mg daily over 6 months 2/32 (6%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P value not reported		
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Muscle cramps** 3/32 (9%) with danazol 200 mg daily over 6 months 0/32 (0%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P value not reported		
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Hot flushes** 4/32 (12%) with danazol 200 mg daily over 6 months 8/32 (25%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P value not reported		
[12] RCT **3-armed trial**	93 women with severe cyclical mastalgia The remaining arm evaluated placebo	**Vaginal discharge** 3/32 (9%) with danazol 200 mg daily over 6 months 5/32 (16%) with tamoxifen 10 mg daily over 6 months 64 women in this analysis	P value not reported		

Further information on studies

Comment:

Clinical guide:
Some clinicians now use tamoxifen 10 mg daily rather than danazol, because of the more favourable adverse-effects profile and greater efficacy. Both drugs are contraindicated in women who have had a previous venous thromboembolism. [43] Women with persistent symptoms after first-line treatment are started on tamoxifen 10 mg daily for 3 to 6 months under expert supervision. Women who do not respond to treatment with tamoxifen are started on danazol 200 mg daily (reduced to 100 mg/day after relief of symptoms) or only during the luteal phase of the menstrual cycle.

OPTION HRT (OESTROGEN)

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- HRT may worsen breast pain, and is also associated with increased risks of breast cancer, venous thromboembolism, and gall bladder disease. RCTs assessing the effects of HRT as a treatment for breast pain are unlikely to be conducted.
- HRT is associated with increased risk of breast pain in postmenopausal women, and studies in HRT as a treatment for breast pain are unlikely to be conducted.

Benefits and harms

HRT (oestrogen):

We found no systematic review or RCTs examining effects of HRT for treating breast pain.

Further information on studies

Comment: HRT is associated with an increased risk of breast pain in postmenopausal women, and RCTs on HRT as a treatment for breast pain are unlikely to be conducted. We found one RCT (44 postmenopausal women with or without breast pain), which found that HRT increased the proportion of women who had breast pain at 1 year compared with tibolone (8/15 [53%] with HRT [transdermal oestrogen patches 50 micrograms twice weekly for 3 weeks/month, plus progestogen 5 mg/day for 12 days/month/cycle] *v* 1/17 [6%] with tibolone 2.5 mg/day; P 0.02). [44] See harms of HRT in review on secondary prevention of ischaemic cardiac events.

Clinical guide:
HRT is considered to increase the risk of breast pain. In women with HRT-induced breast pain (oestrogen-only or combined HRT), swapping to tibolone seems to be as effective as swapping to placebo in reducing breast pain, but tibolone relieves hot flushes and other menopausal symptoms, which placebo does not.

OPTION EVENING PRIMROSE OIL

- For GRADE evaluation of interventions for Breast pain, see table, p 33 .
- Evening primrose oil has not been shown to improve breast pain, and has had its licence withdrawn for this indication in the UK owing to lack of efficacy (it is still available to purchase without prescription).

Benefits and harms

Evening primrose oil (EPO) versus placebo:

We found three RCTs comparing EPO versus placebo. [45] [46] [47]

Breast pain

Evening primrose oil compared with placebo Evening primrose oil seems no more effective than placebo at reducing frequency or severity of pain at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[45] RCT **4-armed trial**	555 women The remaining arms evaluated evening primrose oil (EPO) plus placebo antioxidants over 4 menstrual cycles, and placebo EPO plus placebo antioxidants over 4 menstrual cycles	**Mean breast pain score (recorded on a diary card and a linear analogue chart) , at end of 4th blinded cycle** 15.2 with EPO plus antioxidants over 4 menstrual cycles 14.9 with placebo EPO plus antioxidants over 4 menstrual cycles After 4 menstrual cycles all women received open-label EPO, but randomisation to antioxidants or placebo antioxidants continued for a further 8 cycles	P = 0.3	⟷	Not significant
[46] RCT	120 women with a minimum of 5 days of pain each month	**Decrease in % of days with pain from baseline (scores recorded on a diary card, from**	P = 0.73	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	Factorial design The remaining arms evaluated placebo EPO plus fish oil, and EPO plus fish oil	**0 = no pain to 3 = severe) , 6 months** 12% with EPO plus placebo fish oil 14% with placebo EPO plus placebo fish oil			
[46] RCT **4-armed trial**	120 women with at least 5 days of pain each month Factorial design The remaining arms evaluated placebo EPO plus fish oil, and EPO plus fish oil	**Mean decrease in pain score from baseline (scores recorded on a diary card, from 0 = no pain to 3 = severe) , 6 months** 0.06 with EPO plus placebo fish oil 0.08 with placebo EPO plus placebo fish oil	P = 0.83	⟷	Not significant
[47] RCT	72 women	**Women's recorded scores for pain, tenderness, and lumpiness** with EPO for 6 months with placebo for 3 months followed by EPO for 3 months The RCT reported that women's recorded scores for pain, tenderness, and lumpiness improved in cyclical but not non-cyclical breast pain	The RCT had poor methodological quality; see further information on studies		

Quality of life

No data from the following reference on this outcome. [45] [46] [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT **4-armed trial**	555 women The remaining arms evaluated EPO plus placebo antioxidants over 4 menstrual cycles, and placebo EPO plus placebo antioxidants over 4 menstrual cycles	**GI adverse effects** 36/140 (26%) with EPO plus antioxidants over 4 menstrual cycles 27/137 (20%) with placebo EPO plus antioxidants over 4 menstrual cycles After 4 menstrual cycles all women received open-label EPO, but randomisation to antioxidants or placebo antioxidants continued for a further 8 cycles 277 women in this analysis	P >0.05	⟷	Not significant
[45] RCT **4-armed trial**	555 women The remaining arms evaluated EPO plus placebo	**Respiratory adverse effects** 27/140 (19%) with EPO plus antioxidants over 4 menstrual cycles	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	antioxidants over 4 menstrual cycles, and placebo EPO plus placebo antioxidants over 4 menstrual cycles	22/137 (16%) with placebo EPO plus antioxidants over 4 menstrual cycles After 4 menstrual cycles all women received open-label EPO, but randomisation to antioxidants or placebo antioxidants continued for a further 8 cycles 277 women in this analysis			
[45] RCT **4-armed trial**	555 women The remaining arms evaluated EPO plus placebo antioxidants over 4 menstrual cycles, and placebo EPO plus placebo antioxidants over 4 menstrual cycles	**Reproductive system adverse effects** 19/140 (14%) with EPO plus antioxidants over 4 menstrual cycles 11/137 (8%) with placebo EPO plus antioxidants over 4 menstrual cycles After 4 menstrual cycles all women received open-label EPO, but randomisation to antioxidants or placebo antioxidants continued for a further 8 cycles 277 women in this analysis	P >0.05	⟷	Not significant
[45] RCT **4-armed trial**	555 women The remaining arms evaluated EPO plus placebo antioxidants over 4 menstrual cycles, and placebo EPO plus placebo antioxidants over 4 menstrual cycles	**General disorders** 25/140 (17.9%) with EPO plus antioxidants over 4 menstrual cycles 25/137 (18.2%) with placebo EPO plus antioxidants over 4 menstrual cycles After 4 menstrual cycles all women received open-label EPO, but randomisation to antioxidants or placebo antioxidants continued for a further 8 cycles 277 women in this analysis	P >0.05	⟷	Not significant
[46] RCT **4-armed trial**	120 women with at least 5 days of pain each month Factorial design The remaining arms evaluated placebo EPO plus fish oil, and EPO plus fish oil	**All adverse effects** 14/30 (47%) with EPO plus placebo fish oil 13/30 (43%) with placebo EPO plus placebo fish oil 60 women in this analysis	P value not reported		
[46] RCT **4-armed trial**	120 women with at least 5 days of pain each month Factorial design The remaining arms evaluated placebo EPO plus fish oil, and EPO plus fish oil	**Gastric or abdominal adverse effects** 8/30 (27%) with EPO plus placebo fish oil 12/30 (40%) with placebo EPO plus placebo fish oil 60 women in this analysis	P value not reported		
[47] RCT	72 women	**Adverse effects** with EPO with placebo The RCT found that adverse effects causing treatment discontinuation were similar with EPO and	The RCT had poor methodological quality; see further information on studies		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		placebo (3%), and were largely caused by abdominal bloating			

Further information on studies

[47] The methodology of this RCT included post hoc revision of the inclusion criteria, subgroup analysis, exclusion of withdrawals, and the use of baseline comparisons (with the best response seen in women who were symptomatically worse at baseline), which all cast doubt on the validity of its conclusions.

Comment: We found one survey of randomised and open studies; however, data were reported as overall summary figures, which makes specific data extraction impossible. [5] The survey found that adverse effects causing treatment discontinuation were similar with evening primrose oil and placebo (3%), and were largely caused by abdominal bloating. [5]

Clinical guide:
In the UK, the Committee for Safety of Medicines has withdrawn the prescription licence from evening primrose oil because of lack of efficacy, but it is still available to purchase without prescription. Evening primrose oil can be considered to be an expensive placebo treatment.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Oral NSAIDs Categorised as Unknown effectiveness as we found insufficient RCT evidence to assess their effects.

Contraceptive (combined oral) New option. Categorised as Unknown effectiveness as we found no RCT evidence to assess its effects.

Toremifene New evidence added. Categorisation unchanged (Trade-off between benefits and harms).

Antibiotics Evidence reassessed. Recategorised from Unknown effectiveness to Unlikely to be beneficial, by consensus.

Diuretics Evidence reassessed. Categorisation changed from Unknown effectiveness to Unlikely to be beneficial, by consensus.

HRT (oestrogen) Evidence reassessed. Categorisation changed from Unlikely to be beneficial to Unlikely to be beneficial, by consensus.

Progestogens Evidence reassessed. Categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

Pyridoxine Evidence reassessed. Recategorised from Unknown evidence to Unlikely to be beneficial, by consensus.

Tibolone Evidence reassessed. Categorisation changed from Unknown effectiveness to Unlikely to be beneficial, by consensus.

Topical NSAIDs Evidence reassessed. Categorisation changed from Likely to be beneficial to Trade-off between benefits and harms.

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Disclaimer

GRADE **Evaluation of interventions for Breast pain.**

Important outcomes					, Breast pain, Quality of life				
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for breast pain?									
1 (108) [6]	Breast pain	Topical NSAIDs versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [10]	Breast pain	Oral NSAIDs versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no significance assessment of between-group difference, and unclear method of randomisation
1 (93) [12]	Breast pain	Danazol versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (145) [15]	Breast pain	Gestrinone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (147) [18]	Breast pain	Gonadorelin analogues (luteinising hormone-releasing hormone analogues) versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (241) [12] [19] [20]	Breast pain	Tamoxifen versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about definition of outcomes
2 (361) [21] [22]	Breast pain	Different doses of tamoxifen versus each other	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (257) [25] [26]	Breast pain	Toremifene versus placebo	4	–2	0	0	0	Low	Quality points deducted for lack of pre-crossover results in 1 RCT and for unclear follow-up methods in 1 RCT
1 (62) [26]	Quality of life	Toremifene versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and lack of pre-crossover results
1 (21) [28]	Breast pain	Advice to eat a low-fat, high-carbohydrate diet versus general dietary advice	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results for different outcomes
1 (60) [30]	Breast pain	Lisuride maleate versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data and for randomisation and blinding flaws
2 (58) [32] [33]	Breast pain	Progestogens versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
2 (282) [40] [41]	Breast pain	Bromocriptine versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for poor follow-up, no ITT analysis, and incomplete reporting of results. Directness point deducted for narrow inclusion criteria
1 (93) [12]	Breast pain	Danazol versus tamoxifen	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (747) [45] [46] [47]	Breast pain	Evening primrose oil (EPO) versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor methodology in one RCT

Important outcomes			, Breast pain, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									