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 February 2014 (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 11 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: bra wearing, combined oral contraceptive pill, danazol, gonadorelin analogues, progestogens, tamoxifen, and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs).

QUESTIONS

INTERVENTIONS

TREATMENTS

Covered elsewhere in Clinical Evidence

Premenstrual syndrome

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 up to 60% of women.

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

  An accurate diagnosis of true breast pain should be made and other non-breast pathology should be excluded. Other differential diagnoses include pain arising from the chest wall.

- Overall, the trials we found were small and of limited quality. There is a need for large, good-quality trials in this area.

- We found limited evidence that topical diclofenac may be effective at relieving symptoms of cyclical and non-cyclical breast pain but has been associated with adverse effects.

  There is consensus that topical non-steroidal anti-inflammatory drugs (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.

- We don't know whether topical NSAIDs are more effective than oral NSAIDs at reducing breast pain.

- Danazol, tamoxifen, and gonadorelin analogues (goserelin) may reduce breast pain, but all can cause adverse effects. These agents would usually only be prescribed by a specialist.

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

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There is consensus to limit the use of tamoxifen 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 including teratogenicity and venous thromboembolism.

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.

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

Tamoxifen (10 mg daily) under expert supervision, or danazol, may be considered when first-line treatments are ineffective.

Tamoxifen (20 mg daily) may increase the risk of venous thromboembolism.

- There is consensus that progestogens do not have a role in treating mastalgia.
- We don't know whether the combined oral contraceptive pill or wearing a bra reduce breast pain, as we found no RCTs.

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 February 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2014, Embase 1980 to February 2014, and The Cochrane Database of Systematic Reviews 2014, issue 1 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. An information specialist identified titles and abstracts in an initial search, which an evidence scanner then assessed against predefined criteria. An evidence analyst then assessed full texts for potentially relevant studies against predefined criteria. An expert contributor was consulted on studies selected for inclusion. An evidence analyst then extracted all data relevant to the review. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English 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. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs, where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we used 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. 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 20). 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

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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 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (TOPICAL)

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- We found limited evidence that topical diclofenac may be more effective than placebo 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 don't know whether topical NSAIDs are more effective than oral NSAIDs at reducing breast pain.

Benefits and harms

Topical NSAIDs versus placebo:

We found one RCT. [6]

Breast pain

Topical NSAIDs compared with placebo Topical diclofenac may be more effective than placebo at reducing breast pain (cyclical and non-cyclical) at 6 months (low-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 Subgroup analysis Total population was 108 women with cyclical or non-cyclical breast pain	**Proportion of women with no cyclical pain , 6 months** 14/30 (47%) with topical di-clofenac 0/30 (0%) 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	**Proportion of women with no non-cyclical pain , 6 months** 12/24 (50%) with topical di-clofenac 0/24 (0%) with placebo 48 women in this analysis	P = 0.0001	○○○	topical diclofenac

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	non-cyclical breast pain				

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]

Topical NSAIDs versus oral NSAIDs:
We found one RCT. [7]

Breast pain

Topical NSAIDs compared with oral NSAIDs We don't know whether topical diclofenac is more effective than oral diclofenac at reducing breast pain (cyclical and non-cyclical) in women with mastalgia at 7 days, 30 days, and 90 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[7] RCT	100 women with mastalgia	**Mean Cardiff Breast pain Score (CBS score 1–4), where CBS 1 is 'an excellent response leaving no pain' and CBS 4 is 'no response' , 7 days** 1.92 with topical diclofenac 2.16 with oral diclofenac	P = 0.56	⟷	Not significant
[7] RCT	100 women with mastalgia	**Response rate (percentage of women with no pain or some residual pain which is considered 'bearable') , 7 days** 39/50 (78%) with topical diclofenac 31/50 (62%) with oral diclofenac	Significance not assessed		
[7] RCT	100 women with mastalgia	**Response rate (percentage of women with no pain or some residual pain which is considered 'bearable') , 30 days** 36/40 (90%) with topical diclofenac 32/36 (88.9%) with oral diclofenac	Significance not assessed		
[7] RCT	100 women with mastalgia	**Response rate (percentage of women with no pain or some residual pain which is considered 'bearable') , 90 days**	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		19/20 (95%) with topical diclofenac 18/18 (100%) with oral diclofenac			

Quality of life

No data from the following reference on this outcome. [7]

Adverse effects

No data from the following reference on this outcome. [7]

Further information on studies

[7] Of the 100 women with mastalgia, nine had cyclical mastalgia and 91 had non-cyclical mastalgia. Baseline Cardiff Breast pain Score (CBS) was not reported.

Comment:

Adverse effects
All products containing diclofenac sodium have been associated with the potential for elevation of liver function tests. [8] [9]

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) 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. [10]

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)

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- We don't know whether oral NSAIDs are more effective than placebo at reducing breast pain as we found insufficient evidence.
- We don't know whether topical NSAIDs are more effective than oral NSAIDs at reducing breast pain.

Benefits and harms

Oral NSAIDs versus placebo:
We found one RCT. [11]

Breast pain

Oral NSAIDs compared with placebo We don't know whether nimesulide is more effective than placebo at reducing spontaneous breast pain at 15 days in women with non-cyclical breast pain (very low-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[11] 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 4/20 (20%) with placebo Method of randomisation unclear Nimesulide has been associated with serious adverse effects (see Comment)	Significance not assessed		

Quality of life

No data from the following reference on this outcome. [11]

Adverse effects

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

Oral NSAIDs versus topical NSAIDs:
See option on Topical NSAIDs, p 3 .

Comment: Nimesulide has been associated with a risk of serious damage to the liver and is not authorised for use in several countries including the UK and US. The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of nimesulide use systemically continue to outweigh its risks, but that its use should be restricted to the treatment of acute pain and primary dysmenorrhoea. [12]

Clinical guide:
There is consensus that oral NSAIDs are effective in relieving breast pain. However, physicians should note that oral NSAIDs are more likely to lead to side effects than topical NSAIDs.

OPTION DANAZOL

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- 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. This agent would usually only be prescribed by a specialist.

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Benefits and harms

Danazol versus placebo:

We found one outpatient-based RCT in 93 women. [13]

Breast pain

Danazol compared with placebo Danazol may be more effective than placebo at reducing pain in women with severe cyclical mastalgia at 6 months, and 12 months after the end of 6 months' treatment (low-quality evidence).

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

Quality of life

No data from the following reference on this outcome. [13]

Adverse effects

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

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[13] RCT **3-armed trial**	93 women with severe cyclical mastalgia	**Muscle cramps** 3/32 (9%) with danazol 0/29 (0%) with placebo The remaining arm evaluated tamoxifen	P value not reported		

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

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 and confining treatment to the 2 weeks preceding menstruation. [13] [14] Non-hormonal contraception is essential with danazol because danazol has deleterious androgenic effects on the fetus. [15]

OPTION GONADORELIN ANALOGUES (GOSERELIN; LUTEINISING HORMONE-RELEASING HORMONE ANALOGUES)

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- Goserelin injection may reduce breast pain but it 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. This agent would usually only be prescribed by a specialist.

Benefits and harms

Gonadorelin analogues (goserelin; luteinising hormone-releasing hormone analogues) versus placebo:
We found one RCT (147 women). [16]

Breast pain

Gonadorelin analogues compared with placebo Goserelin injection seems to be more effective than placebo at reducing mean days with severe breast pain in premenopausal women with breast pain (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[16] RCT	147 premenopausal women with breast pain	**Mean days with severe breast pain per cycle (pain measured using the 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. [16]

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Adverse effects

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

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Comment: Goserelin injection is associated with vaginal dryness, hot flushes, decreased libido, oily skin or hair, and irritability.

Clinical guide:
There is widespread consensus that goserelin injections should be reserved for severe refractory mastalgia and that treatment should be limited to 6 months.

OPTION TAMOXIFEN

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- Tamoxifen may reduce breast pain but it 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 US. This agent would usually only be prescribed by a specialist.

Benefits and harms

Tamoxifen versus placebo:

We found three RCTs. [13] [17] [18]

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					
[17] RCT	60 pre-menopausal 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
[13] RCT **3-armed trial**	93 women	**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 The remaining arm evaluated danazol	P = 0.04 Results were also significant 6 and 12 months after the end of treatment	○○○	tamoxifen
[18] 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. [13] [17] [18]

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Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	60 pre-menopausal 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
[17] RCT	60 pre-menopausal 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
[13] RCT **3-armed trial**	93 women	**Hot flushes** 8/32 (25%) with tamoxifen 10 mg daily 3/29 (10%) with placebo The remaining arm evaluated danazol	P value not reported		
[13] RCT **3-armed trial**	93 women	**Vaginal discharge** 5/32 (16%) with tamoxifen 10 mg daily 2/29 (7%) with placebo The remaining arm evaluated danazol	P value not reported		
[18] 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 15 .

Different doses of tamoxifen versus each other:

We found two RCTs. [19] [20]

Breast pain

Different doses of tamoxifen compared with each other Lower-dose tamoxifen (10 mg) seems to be 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					
[19] RCT	301 women with cyclical breast pain for >6 months	**Pain relief (reduction of 2 points on pain score) , 3 months**	P value reported as not significant	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		127/155 (82%) with 10 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months 107/142 (75%) with 20 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months			
[20] 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
[20] 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. [19] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	301 women with cyclical breast pain for >6 months	**Adverse effects** 80/155 (52%) with 10 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months 94/142 (66%) with 20 mg daily doses of tamoxifen from days 15–25 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 15–25 of the menstrual cycle	P = 0.01	○○○	10 mg daily doses of tamoxifen
[19] RCT	301 women with cyclical breast pain for >6 months	**Hot flushes** 33/155 (21%) with 10 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months 54/142 (38%) with 20 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months	P = 0.015	○○○	10 mg daily doses of tamoxifen

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] RCT	301 women with cyclical breast pain for >6 months	**GI disturbances** 30/155 (19%) with 10 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months 48/142 (34%) with 20 mg daily doses of tamoxifen from days 15–25 in the menstrual cycle for 3 months	P = 0.004	○○○	10 mg daily doses of tamoxifen
[20] 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 15–25 of the menstrual cycle			

Comment: **Clinical guide:**
Tamoxifen is not licensed for mastalgia in the UK or US. 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 four 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). [21] 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. [22]

OPTION CONTRACEPTIVE (COMBINED ORAL)

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- 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.

Comment: **Clinical guide:**
Women who start oral contraceptives may report breast pain, which usually settles with continued therapy. The use of oral contraceptives in this setting has not been systematically studied. However, for persistent symptoms, either use of alternative preparations that contain low-dose oestrogen or stopping medication may provide relief.

OPTION PROGESTOGENS

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .

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- We don’t know whether oral medroxyprogesterone acetate and progesterone cream and placebo differ in effectiveness as we found insufficient evidence from two small RCTs.
- There is consensus that progestogens do not have a role in treating mastalgia.

Benefits and harms

Progestogens versus placebo:

We found two RCTs. [23] [24]

Breast pain

Progestogens compared with placebo We don't know whether progesterone cream or medroxyprogesterone acetate tablets and placebo differ in effectiveness (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[23] 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 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
[24] 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. [23] [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] 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			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Symptoms were mostly vague premenstrual symptoms; no further details were reported			

No data from the following reference on this outcome. [24]

Further information on studies

[24] 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.

[23] In the active treatment-first arm, oral medroxyprogesterone acetate 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 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. [25] [26]

OPTION DANAZOL VERSUS TAMOXIFEN

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- 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 outpatient-based RCT in 93 women. [13]

Breast pain

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Breast pain					
[13] RCT **3-armed trial**	93 women with severe cyclical mastalgia	**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 The remaining arm evaluated placebo	P <0.001	○○○	tamoxifen

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		64 women in this analysis			
[13] RCT **3-armed trial**	93 women with severe cyclical mastalgia	**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 The remaining arm evaluated placebo 64 women in this analysis	P <0.001	○○○	tamoxifen

Quality of life

No data from the following reference on this outcome. [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT **3-armed trial**	93 women with severe cyclical mastalgia	**Withdrawals from the study due to adverse effects of treatment** with danazol with tamoxifen The remaining arm evaluated 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			
[13] RCT **3-armed trial**	93 women with severe cyclical mastalgia	**Weight gain** 10/32 (31%) with danazol 200 mg daily over 6 months 0/32 (0%) with tamoxifen 10 mg daily over 6 months The remaining arm evaluated placebo 64 women in this analysis	P value not reported		
[13] 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 0/32 (0%) with tamoxifen 10 mg daily over 6 months	P value not reported		

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

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. [27] 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 BRA-WEARING New

- For GRADE evaluation of interventions for Breast pain, see table, p 20 .
- We don't know whether bra-wearing reduces breast pain, as we found no RCTs.

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Benefits and harms

Bra-wearing:

We found no systematic review or RCTs.

Comment: Women are advised to wear a well-supporting bra to improve their breast pain. While breast support is effective in reducing the amplitude of breast displacement during walking and running, there is no research studying its effect on breast pain.

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

Bra-wearing New option. Categorised as unknown effectiveness, as we found no RCT evidence to assess its effects.

Oral NSAIDs One RCT added. [7] Categorisation unchanged (unknown effectiveness).

Topical NSAIDs One RCT added. [7] Categorisation unchanged (trade-off between benefits and harms).

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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 (60) [6]	Breast pain	Topical NSAIDs versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and sub-group analysis
1 (100) [7]	Breast pain	Topical NSAIDs versus oral NSAIDs	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (40) [11]	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 (61) [13]	Breast pain	Danazol versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for restricted population
1 (147) [16]	Breast pain	Gonadorelin analogues (goserelin; luteinising hormone-releasing hormone analogues) versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (241) [13] [17] [18]	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) [19] [20]	Breast pain	Different doses of tamoxifen versus each other	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (58) [23] [24]	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
1 (64) [13]	Breast pain	Danazol versus tamoxifen	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for restricted population

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.

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