Clinical management of idiopathic mastalgia: a systematic review

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ABSTRACT

INTRODUCTION: Idiopathic mastalgia (benign breast pain of unknown origin) is often poorly managed because of its subjective nature and unclear aetiology. Mastalgia is a reason for up to 50% of breast outpatient referrals. Existing systematic reviews discuss dated treatment options that provide limited symptomatic relief.

METHODS: A systematic review was conducted for aetiology and treatment of idiopathic mastalgia in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance. Databases such as PubMed, MEDLINE, Cochrane Database and the Clinical Trial Registry were searched (February 2016).

RESULTS: Reassurance plus bra-fitting advice provides relief for most women. If symptoms persist, addition of topical non-steroidal anti-inflammatory drugs (NSAIDs) provides relief in 70–92% of women. There is some benefit in reducing dietary coffee and fat intake. Medical treatments have serious side-effects (often androgenic or menopausal) and should be considered only in cases resistant to simpler measures. Dopamine agonists are useful, but less effective than endocrine treatments such as Danazol or Tamoxifen. Of the Selective Oestrogen Receptor Modulator drugs, Ormeloxifene appears most effective, but is not licenced in the United Kingdom. Relaxation therapy, acupuncture and kinesiology may be useful but currently lack good evidence of effectiveness.

DISCUSSION: First-line management of breast pain should be explanation, reassurance and a bra-fitting advice. Subsequent drug therapy should be balanced against its side-effects; topical NSAIDs and Ormeloxifene show greatest benefit with least side-effects. Newer agents (Ormeloxifene) currently being used for mastalgia in India could be considered in the developed world.

KEYWORDS: breast pain; bra-fitting; mastalgia

Introduction

Mastalgia is a common presenting complaint in primary care and accounts for ~50% of referrals to breast outpatient clinics.1 In some centres, dedicated mastalgia clinics have been established due to the burden of patients with breast pain.2 Despite its frequency, mastalgia is difficult to manage well because of its subjective nature and unclear aetiology. Many existing treatments have androgenic side-effects, which affects compliance in female patients. In the past decade in the Western world, there has been little progress in developing new treatments for managing mastalgia. Existing systematic reviews fail to acknowledge newer agents being used internationally. This paper explores current and new treatment options available to women presenting to primary care with mastalgia, focusing on relief of pain symptoms and side-effects associated with these therapies.

Aetiology, classification and diagnosis

The aetiology of mastalgia remains unclear, which is a factor contributing to its poor
management. Women often fear their breast pain is a result of underlying malignancy and can experience overwhelming anxiety combined with difficult self-examination due to the natural ‘lumpy’ nature of the breast. Therefore, after excluding underlying breast pathology such as fibrocystic disease, chest wall pain, mastitis, fat necrosis, trauma, referred pain from biliary and cardiac pathology and coincidental cancer, clinicians need a clear evidence-based strategy for managing the symptoms and anxiety related to this condition. Proposed mastalgia aetiologies are as follows:

Hormone dependant

Elevated endogenous oestrogen: High levels of endogenous oestrogen can cause mastalgia. The pathophysiological mechanism remains unclear, but it has been associated with the stimulation of breast epithelium by oestradiol. In a randomised controlled trial (RCT) (n = 195), levels of serum oestradiol in women with untreated cyclical mastalgia were higher than in women with non-cyclical mastalgia. The role of elevated oestrogen in mastalgia is plausible due to its physiological effect on normal breast tissue (stimulates cellular proliferation). However, a smaller study of women with benign breast disease (n = 17) found that oestradiol, progesterone, thyroid hormone and thyrotropin levels were normal.6

Low endogenous progesterone: Low progesterone levels theoretically result in unopposed oestrogen activity stimulating breast tissue. However, RCTs have demonstrated normal serum progesterone levels in untreated mastalgia patients. Maddox et al. also demonstrated that levels of progesterone were normal before and after treatment with medroxyprogesterone acetate in women with mastalgia. Furthermore, replacement progesterone did not provide any more therapeutic benefit than placebo.7

Elevated prolactin: Studies have demonstrated higher levels of prolactin in mastalgia sufferers than oestradiol, progesterone, thyroid hormone and thyrotropin levels, which have often been normal. Hypothalamic-pituitary dysfunction has been theorised as a more likely cause of mastalgia than alteration of female hormones.8,9 The exact mechanism of how a hyperprolactinaemic state causes mastalgia remains unclear. Its role in mastalgia is plausible given the influence of prolactin on breast lobule development in normal physiology and lactation.

Water retention: Preece et al. measured Total Body Water at the beginning and end of the menstrual cycle of 56 women and found no significant difference in water content between mastalgia and control groups. Only a handful of studies have explored water retention as a contributing factor for mastalgia and a clear relationship between the two has not been identified.10

Dietary

Dietary lipids and lipid metabolism: High dietary lipid intake has been associated with mastalgia, with improvement of symptoms when lipid intake is reduced. The mechanisms for this remain unclear, but one controlled trial concluded that serum lipid profiles (in particular high-density lipoprotein (HDL) levels) were abnormally elevated in mastalgia sufferers. Other research has demonstrated improvement in mastalgia symptoms when HDL and low-density lipoprotein (LDL) cholesterol levels normalise. Aberrations in lipid metabolism may be associated with the proposed elevated oestrogen activity in the aetiology of mastalgia, as oestrogen is a steroid-based hormone synthesised from lipids and fatty acids.

Essential fatty acids and vitamins: Essential fatty acids and vitamins inhibit the production of prostaglandins and create anti-inflammatory actions. The rationale for this effect is that there is an inflammatory component to mastalgia and this is why historically Evening Primrose Oil (a natural source of essential fatty acids) has been used for mastalgia. Evening Primrose Oil can be administered as topical oil or in tablet form. It is also suspected that essential fatty acid deficiency can lead to over-sensitivity of the breast tissue making it more receptive to sex hormones, leading to breast pain.

Methylxanthines

Methylxanthines are in everyday foods such as chocolate, tea and coffee. They may cause
mastalgia through enhancing the cyclic adenosine monophosphate (cAMP) pathway. cAMP has a functional role through protein kinase production in stimulating cellular proliferation and is believed to cause fibrocystic changes in the breast and mastalgia. Increased amounts of cAMP exist when methylxanthine intake is high, as methylxanthines inhibit the enzyme that hydrolyses cAMP. It is therefore postulated that by reducing methylxanthine intake, increased enzyme activity results in reduced cAMP activity, thus reducing mastalgia symptoms.18–21

Soya
Soya contains isoflavones that bind to oestrogen receptors and block oestrogen binding and its end effects on breast tissue, thus reducing mastalgia symptoms.22,23

Lifestyle
Smoking: One cohort study (n = 874) showed higher incidence of mastalgia in smokers than non-smokers. This study identified women participants through random selection followed with telephone interviews that questioned women about their smoking habits and mastalgia symptoms.24 The research methodology was poor from patient selection through to the questions asked. The aetiological mechanism of smoking in mastalgia has not been clearly identified in the literature, but smoking interferes with endogenous oestrogen production, with smokers tending to exhibit oestrogen deficiency and earlier onset of menopause. However, this mechanism conflicts with literature that suggests elevated levels of oestrogen cause mastalgia.5,25

Breast size
It has been suggested that the weight of breasts creates weakness and strain on the suspensory ligaments, thus creating discomfort. No research has directly explored the role of breast size and mastalgia; however, a survey examined the role of mastalgia on exercise behaviour in 1397 women who ran the 2012 London Marathon and identified, as secondary outcomes, that one-third of women who did experience breast pain had larger breast size.26

Psychological
Mastalgia has been considered to be part of a psychosomatic disorder, because there is no clear organic cause that has been identified in its aetiology. Consequently, women with mastalgia have been reported as having anxious personalities, resulting in their physical symptoms.27,28 Preece et al. demonstrated that when mastalgia patients completed personality and mental health questionnaires alongside control patients (suffering from varicose veins) and psychiatric patients, the control group scored higher for psychoneurotic tendencies than mastalgia patients.28 A small subset of mastalgia patients who were resistant to mastalgia treatment scored higher for depression and anxiety than patients who responded to treatment. In contrast, Yilmaz et al. demonstrated that depression and anxiety scores were much higher in mastalgia patients (although not within a diagnostic range for psychiatric conditions).29–31

Classification
Although cyclical and non-cyclical mastalgia are clearly defined in the literature, their difference in terms of pathogenesis and response to treatment is not clarified and their clinical management is similar.

Diagnosis
Patients presenting with mastalgia symptoms should provide a thorough history and undergo clinical examination. In current practice, most patients are managed with reassurance and in persistent cases, pain diaries (eg Cardiff Breast Pain Chart) can be used to evaluate response to first-line treatments or assess severity of mastalgia. The UK’s National Institute for Health and Care Excellence (NICE) guidance on the management of mastalgia recommends that referral to secondary care should be considered in cases where mastalgia is “impacting quality of life or sleep and does not respond to first-line treatment after three months”.32 On referral, outpatient clinic patients with a lump or signs and symptoms suggesting neoplasia undergo a triple assessment. Idiopathic mastalgia (benign breast pain of unknown aetiology) is a diagnosis of exclusion. A differential diagnosis of musculoskeletal pain may be considered,
as it can be challenging and sometimes impossible to differentiate between the two diagnoses.

**Methods**

An electronic literature search of PubMed, Medline, the Cochrane database and the Clinical Trials registry was carried out in February 2016 in accordance with the PRISMA guidelines (Fig. 1). Articles were identified using the following search terms: mastalgia (n = 586), mastodynia (n = 225), cyclical breast pain (n = 115) and non-cyclical breast pain (n = 54). Boolean operators were used to refine the search.

**Selection criteria**

Relevant articles were selected from title headings and abstracts, followed by review of full articles. Only manuscripts written in English (between 1975 and 2015) were included, as were studies using comparison groups, editorials, case reports, anecdotal literature and case series with more than 20 subjects (Table 1). Cancer and post-surgery-related breast pain was excluded, as well as breast pain that resulted from side-effects of medications or hormonal therapy. Male breast pain was not considered in this review as male cases are rare when not accompanied with gynaecomastia. We included only articles using established objective pain assessment tools; for example, Visual Analogue Scale (VAS) for pain assessment and Cardiff breast pain chart.

**Results**

A total of 980 articles were identified, 111 were deemed relevant for review and 89 fulfilled the inclusion criteria. For this review, 41 full papers were appraised (Fig. 1) because 48 papers were unavailable from the University of Manchester Library Archives. These papers were still appraised and screened by accessing the electronic abstracts for each paper and ‘low-level’ evidence articles were omitted from the review.

**Natural therapies**

**Reassurance**

A cohort study (n = 121) demonstrated that 70% of women with mastalgia were managed effectively by providing reassurance without needing further intervention. This was the only study (level II evidence) exploring the role of reassurance alone in the management of mastalgia. Short-term follow up was conducted through serial assessment of pain symptoms by using validated pain assessment tools. A comparison of pain symptoms before and after providing reassurance (intervention) was used to draw conclusions regarding the effectiveness of reassurance as a treatment option for mastalgia. The authors concluded that mastalgia in women who exhibit anxious personalities or depression can be effectively managed with reassurance alone and that this is often sufficient to allay their anxieties.33

Summary: Active reassurance is recommended as first-line management.

**Bra support**

Approximately 70–90% of women wear ill-fitting bras.4 In a non-randomised comparative single-centre trial (n = 200) of Danazol versus sports bras, 85% of women experienced relief from mastalgia by wearing a sports bra for 12 weeks compared to 58% in the Danazol group. There were no side-effects from wearing a bra, whereas 42% of women experienced side-effects with
Table 1. Summary of included articles

<table>
<thead>
<tr>
<th>Study/Intervention</th>
<th>Year</th>
<th>Level</th>
<th>Sample Size</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural Therapies &amp; Conservative</strong></td>
<td></td>
<td></td>
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<tr>
<td>Reassurance</td>
<td>1999</td>
<td>II</td>
<td>121</td>
<td>70% improved*</td>
</tr>
<tr>
<td>Brasierie support</td>
<td>1976</td>
<td>II</td>
<td>114</td>
<td>49% improved, 26% complete resolution*</td>
</tr>
<tr>
<td>Brasierie vs. Danazol</td>
<td>2000</td>
<td>II</td>
<td>200</td>
<td>85% benefit</td>
</tr>
<tr>
<td>Brasierie</td>
<td>2014</td>
<td>II</td>
<td>1397</td>
<td>Improves mastalgia symptoms*</td>
</tr>
<tr>
<td>Soya vs. placebo</td>
<td>2002</td>
<td>II</td>
<td>18</td>
<td>44% improved vs. 13% in placebo*</td>
</tr>
<tr>
<td>Soya vs. placebo</td>
<td>2000</td>
<td>II</td>
<td>20</td>
<td>56% experienced benefit*</td>
</tr>
<tr>
<td>Progesterone supplementation</td>
<td>1990</td>
<td>II</td>
<td>26</td>
<td>No benefit*</td>
</tr>
<tr>
<td><strong>Medical Management</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EPO capsules</td>
<td>2010</td>
<td>II</td>
<td>85</td>
<td>No benefit*</td>
</tr>
<tr>
<td>EPO capsules</td>
<td>1999</td>
<td>II</td>
<td>66</td>
<td>97% experienced improvement*</td>
</tr>
<tr>
<td>EPO vs. placebo/vitamin/antioxidant groups</td>
<td>2005</td>
<td>II</td>
<td>555</td>
<td>No benefit*</td>
</tr>
<tr>
<td>EPO versus laser therapy</td>
<td>2007</td>
<td>II</td>
<td>80</td>
<td>63% improvement (EPO) vs. 83% (laser)*</td>
</tr>
<tr>
<td>Topical NSAID versus EPO</td>
<td>2005</td>
<td>II</td>
<td>50</td>
<td>64% had improvement with EPO vs. 92% in NSAID group*</td>
</tr>
<tr>
<td>Topical NSAID (Piroxicam) gel</td>
<td>2005</td>
<td>II</td>
<td>50</td>
<td>92% improvement with Piroxicam topical gel*</td>
</tr>
<tr>
<td>Topical NSAID gel</td>
<td>1998</td>
<td>II</td>
<td>26</td>
<td>77% experienced improvement*</td>
</tr>
<tr>
<td>Topical NSAID vs. placebo</td>
<td>2003</td>
<td>II</td>
<td>108</td>
<td>Improved mastalgia with minimal side-effects*</td>
</tr>
<tr>
<td>Oral NSAID</td>
<td>2008</td>
<td>II</td>
<td>81</td>
<td>No benefit*</td>
</tr>
<tr>
<td>Bromocriptine vs. placebo</td>
<td>1979</td>
<td>II</td>
<td>10</td>
<td>80% experienced relief*</td>
</tr>
<tr>
<td>Bromocriptine vs. placebo</td>
<td>1990</td>
<td>II</td>
<td>272</td>
<td>Symptoms significantly greater with bromocriptine than with placebo (not SS) 29% dropout: nausea &amp; dizziness*</td>
</tr>
<tr>
<td>EPO/Bromocriptine vs. laser</td>
<td>2007</td>
<td>II</td>
<td>80</td>
<td>64% improved vs. 83% (laser)*</td>
</tr>
<tr>
<td>Bromocriptine versus placebo</td>
<td>1975</td>
<td>II</td>
<td>15</td>
<td>Beneficial; nausea &amp; dizziness dose dependant*</td>
</tr>
<tr>
<td>Lisuride Maleate vs. placebo</td>
<td>2001</td>
<td>II</td>
<td>60</td>
<td>Improvement in VAS scores with Lisuride*</td>
</tr>
<tr>
<td>Vitex Agnus-Castus (VAC) versus placebo</td>
<td>1999</td>
<td>II</td>
<td>97</td>
<td>‘Differences of the VAS-values for VACS were significantly greater than those with placebo’*</td>
</tr>
<tr>
<td><strong>Endocrine Treatments</strong></td>
<td></td>
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<tr>
<td>Gestrinone</td>
<td>1992</td>
<td>II</td>
<td>145</td>
<td>80% decrease in pain scores 41% androgenic side-effects*</td>
</tr>
<tr>
<td>Danazol vs. Ormeloxifene</td>
<td>2011</td>
<td>II</td>
<td>81</td>
<td>90% improved (Ormeloxifene); 70% (Danazol)*</td>
</tr>
<tr>
<td>Danazol vs. placebo</td>
<td>1999</td>
<td>II</td>
<td>100</td>
<td>‘Highly effective for the relief of premenstrual mastalgia*</td>
</tr>
<tr>
<td>Zoladex</td>
<td>1990</td>
<td>II</td>
<td>21</td>
<td>Symptom relief in 81% of patients*</td>
</tr>
<tr>
<td>Zoladex vs. sham</td>
<td>2004</td>
<td>II</td>
<td>147</td>
<td>67% (active) vs. 25% (sham) improvement (not SS)*</td>
</tr>
<tr>
<td><strong>SERMs</strong></td>
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<tr>
<td>Tamoxifen vs. Ormeloxifene</td>
<td>2015</td>
<td>II</td>
<td>52</td>
<td>45% improved with Tamoxifen vs. 92% with Ormeloxifene*</td>
</tr>
<tr>
<td>Afimoxifene Gel vs. placebo</td>
<td>2007</td>
<td>II</td>
<td>106</td>
<td>Greater improvement in pain scores in active arm (SS)*</td>
</tr>
<tr>
<td>Tamoxifen vs. placebo</td>
<td>1986</td>
<td>II</td>
<td>60</td>
<td>71% in Tamoxifen group had a successful outcome compared to 11% in placebo group (Menopausal side-effects)*</td>
</tr>
<tr>
<td>Toremifene vs. placebo</td>
<td>2006</td>
<td>II</td>
<td>195</td>
<td>69% improvement with Toremifene vs. 32% with placebo*</td>
</tr>
<tr>
<td>Toremifene vs. placebo</td>
<td>2006</td>
<td>II</td>
<td>62</td>
<td>64% symptom reduction vs. 26% (placebo)*</td>
</tr>
<tr>
<td>Ormeloxifene</td>
<td>2007</td>
<td>II</td>
<td>60</td>
<td>VAS score reduction of 10 to 3 in 90%*</td>
</tr>
<tr>
<td>Ormeloxifene vs. Danazol</td>
<td>2011</td>
<td>II</td>
<td>81</td>
<td>90% women improved vs. 70% (Danazol)*</td>
</tr>
<tr>
<td>Ormeloxifene vs. Tamoxifen</td>
<td>2015</td>
<td>II</td>
<td>52</td>
<td>Similar effectiveness in providing relief*</td>
</tr>
<tr>
<td>Ormeloxifene vs. placebo</td>
<td>2013</td>
<td>II</td>
<td>151</td>
<td>‘Significant reduction in symptoms in the active group compared to the placebo group (minimal side-effects &amp; well tolerated)*</td>
</tr>
</tbody>
</table>

(Continued)
Danazol. The most popular treatment women adopted (without clinical guidance) was to wear a good supporting bra, followed by taking pain medication and finally holding the breast (elevating the breast themselves when experiencing mastalgia). A further prospective cohort study (n = 100) demonstrated the role of a supportive bra in the treatment of mastalgia, with 26% gaining resolution of mastalgia and 49% reporting an improvement.

It may be worthwhile for clinical teams to provide a 'bra fitting' service rather than referring women to retail stores where they may feel uncomfortable and avoid wearing a correctly fitting bra to manage their mastalgia. Bra fitting in many retailer stores is based on a dated measurement model that was originally established for cup sizes up to a D cup and the accuracy of fitting in sizes beyond this remains uncertain. Additionally, size charts and grading methods differ between bra companies, resulting in inconsistencies in bra sizes produced by bra manufacturers. Thus, advocating 'one size' using this dated bra-fitting model is not appropriate (see Table 2 for a 'dated' bra fitting model used by retailers). The 'best fit criteria' introduced in 2012 allows women to appropriately evaluate the fit of their bras themselves. This should be the key focus rather than promoting the traditional under bust and chest circumference measurement method that perpetuates the issue of inappropriate bra fit.

Summary: A supportive bra improves mastalgia symptoms and is recommended as first-line management (level II evidence).

Diet advice

Two of the three studies of methylxanthine identified in this review demonstrated that reduced methylxanthine intake resulted in some symptom improvement, but this improvement was not quantified.

There is little scientific evidence of the role of fat intake in mastalgia. However, we found evidence from two small studies that a reduction in dietary fat by 15% of the total calorie intake provided clinical improvement. There were no side-effects from reducing dietary fat intake.

In a small RCT of soya protein in the treatment of idiopathic cyclical mastalgia, 20 participants were given either soya milk or cow’s milk for 3 months, and 56% of patients experienced some improvement with the soya milk compared to 11% in the cow’s milk group. A small RCT (n = 18) of placebo versus isoflavone tablets showed improvement in 44% of women on isoflavones compared to 14% on placebo. An isoflavone-rich diet requires discipline, as food choices are limited, so compliance may be challenging.

There is insufficient evidence for recommending a reduction in dietary methylxanthine and fat intake or for recommending soya in treating mastalgia. Due to the overall lifestyle benefits of reducing dietary fat intake and in absence of any side-effects, it could be considered as an adjunct to other treatments, in patients whose dietary fat intake is excessive.

Summary: Dietary advice not recommended.
Medical management

The role of Evening Primrose Oil in mastalgia has been extensively reviewed (three RCTs, one prospective study and one non-randomised comparative trial). In these studies, Evening Primrose Oil provided no clinically significant benefit in the treatment of mastalgia versus placebo. Any improvement in mastalgia was attributed to a placebo effect.16,38–41 This evidence outweighed the one cohort study conducted in China that demonstrated improvement in 97% of women taking Evening Primrose Oil for their mastalgia.42 NICE guidelines no longer advocates the use of Evening Primrose Oil in the treatment of mastalgia.32,43

Three RCTs and a prospective study demonstrated improvement in up to 92% of mastalgia cases with the use of topical non-steroidal anti-inflammatory drugs (NSAIDS). Reported side-effects were negligible. An RCT demonstrated no superiority of oral NSAIDS over topical agents in mastalgia treatment.44–45

One RCT studied progesterone supplements in the treatment of mastalgia. Administering 20 mg day\(^{-1}\) of medroxyprogesterone acetate in 26 women with cyclical mastalgia showed no clear benefit.7

Summary: Evening Primrose Oil is not recommended (level II evidence). NSAIDs (where not contraindicated) are recommended as second-line management.44–46 Medroprogesterone is not recommended, as there is insufficient evidence to demonstrate its benefit in the treatment of mastalgia.

Endocrine treatments

Danazol is currently the only drug licensed in the UK for the treatment of mastalgia. RCTs report up to 80% improvement in mastalgia symptoms, with relief of symptoms reported as early as 4 weeks after commencing treatment.47 However, there is a higher relapse rate on treatment cessation than for newer agents such as Ormeloxifene.48 The side-effects of Danazol are androgenic, including menstrual disruption (menorrhagia or scanty menses), acne, hirsutism, vaginal dryness and voice changes (hoarseness). Potential teratogenic effects may limit its use in women of child-bearing age.4

Gestrinone is anti-oestrogenic and anti-progestogenic. An RCT in 1992 reported improved pain scores following 3 months of treatment compared to placebo. However, 41% of participants experienced androgenic side-effects such as greasy skin and hair, hirsutism, acne, inter-menstrual bleeding, reduced libido and reduced breast size.49

Bromocriptine decreases serum prolactin. Three RCTS and one prospective study of Bromocriptine reported improvement in mastalgia in 65% of women.11,50 Side-effects include nausea and dizziness secondary to hypotension in 69% of...
women. Dizziness was sometimes significant, causing trial dropout (11%). Naturally occurring dopamine agonists include Lisuride Maleate and Vitex Agnus-Castus extract. In an RCT \( (n = 60) \), Lisuride Maleate demonstrated 56% mean pain reduction compared to 7% in the placebo group. An RCT of Vitex Agnus-Castus extract versus placebo reported greater improvement (56%) in mastalgia in the treatment group.

Summary: In appropriately screened patients, Danazol can be considered as third-line management of severe, resistant mastalgia. Gestrinone is not recommended. Bromocriptine can be considered as third-line management in appropriate patients with severe, resistant mastalgia. There is insufficient evidence to recommend Lisuride Maleate or Vitex Agnus-Castus.

Selective oestrogen receptor modulators

Tamoxifen is associated with improvement in mastalgia for ~71% of women, but many patients experience side-effects such as hot flushes, loss of libido, nausea and vaginal discharge. Due to its serious menopausal side-effects, some studies have explored the role of Tamoxifen at a lower dose of 10 mg, but these studies lack long-term follow up. A phase II trial was the only study to investigate the role of topical tamoxifen (Afimoxifen gel) and reported significant improvement in the active arm compared to placebo.

There is some variation in efficacy among the different selective oestrogen receptor modulators (SERMs). A study comparing Tamoxifen with Ormeloxifene (primarily used as a contraceptive and for breast pain in India, and is not licensed for mastalgia in the UK) showed contrasting results for mastalgia symptom relief (Tamoxifen 45% vs. Ormeloxifene 92%) at 6 months. Another RCT \( (n = 151) \) demonstrated greater symptomatic relief with Ormeloxifene than with placebo. In RCTs comparing Ormeloxifene to Danazol, Ormeloxifene provided quicker relief, longer efficacy after treatment cessation and fewer side-effects.

Similarly, Toremifene (a SERM licensed in the US for use in metastatic breast cancer) provided improvement in mastalgia symptoms in 64% of cases compared to 26% on placebo \( (n = 62) \), but when compared with Ormeloxifene (89%), its effects were significantly lower \( (n = 195) \). Side-effects with Toremifene included hot flushes, sweating, fatigue, nausea, menstrual disorders, dizziness and chest pain. Tamoxifen and Danazol induce androgenic side-effects that Toremifene and Ormeloxifene are not associated with. Toremifene and Ormeloxifene also have greater central effects, elevating serotonin levels.

Studies exploring the role of Ormeloxifene in mastalgia have been conducted in India, where it is provided as a free contraceptive and is also widely used for the management of menorrhagia, uterine bleeding and benign breast disease. In these studies, it demonstrates a good safety profile with high patient compliance. A further advantage of Ormeloxifene over other SERMs is that unlike Tamoxifen and Danazol, it does not necessitate the use of barrier contraception. Currently, in the UK, Ormeloxifene is not licensed for treating benign breast disease.

Luteinizing hormone-releasing hormone (LHRH) agonists induce medical castration, thus reducing circulating oestradiol and progesterone to almost negligible levels. The main concern with LHRH agonists is their menopausal side-effects, including risk of osteoporosis, and the invasive method of delivery (injected subcutaneously). A cohort study looking at the role of Zoladex treatment in mastalgia demonstrated at 3 months that 15 women were pain free, increasing to 17 women at 6 months. Over half of women who responded to Zoladex had previously trialled Danazol and Tamoxifen, which had failed to provide benefit. Another RCT \( (n = 147) \) demonstrated 67% improvement in patients treated with LHRH agonist versus placebo (25%), but did report menopausal side-effects.

Summary: Tamoxifen can be considered as third-line management in treating severe resistant mastalgia (contraindicated in patients with a history of endometrial cancer and thromboembolic disease). Ormeloxifene and Toremifene may be attractive treatments for severe resistant mastalgia, but with current evidence, cannot be recommended (level II evidence). Where
endocrine therapies have failed, LHRH agonists can be considered as fourth line management for the most resistant and severe cases.

**Surgery and local injections**

We found no research exploring the role of surgery to treat idiopathic mastalgia. Existing case reviews (<20 cases) have shown where surgery was performed for resistant mastalgia surgical complication rates were as high as 50%.63–65

The use of combined local anaesthetic and steroid injections injected into focal areas of breast tenderness has demonstrated improvement in 94% of cases. Many women required further injections to maintain relief. At 6-weeks follow up, 83% of women continued to have resolution of symptoms.65

Summary: Surgery is not recommended as there is insufficient evidence.

**Holistic medicine and psychotherapy**

With many drugs demonstrating significant side-effects, there has been interest in the potential benefit of alternative therapies for mastalgia, such as acupuncture needles inserted into pressure points (HT3 and HT7 – along the inner side of the arm). Although qualitative improvement in symptoms has been documented with acupuncture, much of the evidence is anecdotal and retrospective. A pilot study of 37 patients at the Mayo Clinic trialled four sessions of acupuncture over 2 weeks, delivered by two experienced acupuncturists, and 67% of women experienced significant improvement in symptoms.66–68 Kinesiology involves massage of tender spots on the breast. In one cohort study, improvement in pain was established in 60% of patients; however, 45% did not return for further sessions.68

There is extensive evidence that positive mental attitude, low stress levels, absence of depression and good external social support can improve management of chronic pain. Effective management of co-existing mental health issues may influence patients’ coping strategies and their overall perception of mastalgia. This was demonstrated in an RCT in patients with mastalgia who received psycho-education and subsequently experienced an improvement in the perception of their pain and anxiety versus women receiving no intervention.69 Another RCT evaluated the effect of muscle relaxation techniques in managing mastalgia and reported improvement in 61% of participants.27

Summary: Acupuncture and kinesiology are not recommended, as there is insufficient evidence. There are no recommendations for the use of holistic medicine and psychotherapy. A holistic management approach is needed by patients with mastalgia, but there is insufficient evidence supporting the role of relaxation techniques in the treatment of mastalgia.

**Discussion**

This review reinforces the existing NICE guidance pathway for managing mastalgia32 and it adds to the existing evidence base for a new agent (Ormeloxifene) to be considered for mastalgia treatment beyond India, as this drug appears effective in managing mastalgia symptoms and has a palatable side-effect profile. The review has identified that reassurance and good bra support is invaluable and mastalgia can be managed effectively for many women without further intervention. This can be combined with general lifestyle advice, including smoking cessation. Adjunctive use of topical NSAIDs provides further relief. For severe persistent cases, endocrine agents such as Danazol may be considered as first-line drug treatment after conservative management has failed. Tamoxifen and Bromocriptine appear less effective, but can be considered where Danazol is ineffective or contraindicated. Danazol has serious androgenic side-effects and lacks long-term data on the lower doses administered for the treatment of mastalgia. New agents such as Ormeloxifene have not yet been trialled in western countries.

**Conclusion**

A stepwise approach should be adopted when managing idiopathic mastalgia (Fig. 2). With breast clinic outpatient appointments costing ~£165 per session in the UK’s National Health Service, it is important to manage
mastalgia effectively to avoid unnecessary clinic attendances for patients and ensure cost-effectiveness. Much of the research to date regarding mastalgia has reiterated the same clinical management pathway for the last decade without any obvious amendment to the treatment pathway. This review has identified that there is a need for further research into the use of Ormeloxifene in treating mastalgia, as this may help identify a safer and better-tolerated drug treatment for severe cases of idiopathic mastalgia.

References


COMPETING INTERESTS
None.

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