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Mastalgia is a common breast symptom that may affect up to 70 % of women in their lifetime [1]. It is most common in women aged 30–50 years. Breast pain may be bilateral, unilateral, or in part of one breast. While most patients experience mastalgia of mild or moderate severity and accept this as a part of the normal changes that occur in relation to the menstrual cycle, a proportion (10–20 %) experience severe pain that causes distress, affects their daily lives, and leads them to seek treatment [2]. The severity of pain associated with cyclical mastalgia can be substantial, similar in magnitude to chronic cancer pain and slightly less than that associated with rheumatoid arthritis [3].

In a study of 1171 premenopausal women attending a gynecology clinic, 69 % reported regular premenstrual discomfort, 11 % had moderate-to-severe cyclic mastalgia, and 36 % had consulted a doctor about the symptoms. Breast pain interfered with usual sexual activities (48 %), physical activities (37 %), social activities (12 %), and school activities (8 %) [4].

4.1 Etiology

The etiology of cyclical mastalgia has not been established. Some evidence has implicated elevated estrogen levels, low progesterone levels, or an abnormal estrogen/progesterone ratio [5]. The cyclical nature of pain, swelling, tenderness, and nodularity together with postmenopausal cessation suggests a relationship between the symptoms and estrogen effects [6, 7]. However, measurement of estrogen,

progesterone, and prolactin levels has not shown consistent abnormalities. There is no correlation of water retention, psychological factors, or caffeine intake with mastalgia. The role of iodine deficiency, alterations in levels of fatty acid in the breast, and fat intake in the diet remains unclear.

4.2 Classification

Mastalgia can be separated into four main groups, cyclical mastalgia, non-cyclical mastalgia, chest wall pain, and non-chest wall pain [8] (Table 4.1). History will often reveal the temporal association of cyclical mastalgia with the menstrual cycle, but the best way to assess whether pain is cyclical is to ask the patient to complete a breast pain chart (Fig. 4.1). This is especially useful in patients who have had a hysterectomy. A pain chart quantifies patient's symptoms and has the added advantage of assessing effectiveness of therapy. Two-thirds of women have cyclical pain, and the remaining third have non-cyclical pain.

4.3 Cyclical Mastalgia

Cyclical breast pain usually occurs during the late luteal phase of the menstrual cycle and resolves at the onset of menses (Table 4.1). Patients with cyclical pain are by definition premenopausal and most often in their thirties. Many women normally experience premenstrual discomfort, fullness, tenderness, or heaviness of the breast 3–7 days before each period in relation to the menstrual cycle. Tender lumpiness in breasts and increased breast size at this time, which regresses postmenstrually, are equally normal. Patients with cyclical mastalgia typically suffer increasing severity of pain from mid-cycle onward, with the pain improving at menstruation. The pain is usually bilateral, described as heaviness with the breast being tender to touch, and it commonly affects the upper outer quadrant of the

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Table 4.1 Classification of mastalgia

Breast pain	Cause
Cyclical pain	Hormonal stimulation of normal breast lobules before menses
Non-cyclical pain	Stretching of Cooper's ligaments Pressure from brassiere Fat necrosis from trauma Hidradenitis suppurativa Focal mastitis Periductal mastitis Cyst Mondor's disease (sclerosing periphlebitis of breast veins)
Non-breast pain	
Chest wall pain	Tietze's syndrome (costochondritis) Localized lateral chest wall pain Diffuse lateral chest wall pain Radicular pain from cervical arthritis
Non-chest wall pain	Gallbladder disease Ischemic heart disease

Source From The New England Journal of Medicine, Santen RJ, Mansel R, Benign breast disorders, Vol. 353, pp. 275–85 [8] © 2005 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

This chart is intended to help you and your doctor/nurse to see when your breast pain occurs. Record the amount of breast pain you experience each day by shading in each box as illustrated.



For example: if you get severe breast pain on the fifth day of the month then shade in completely the square under 5. Please note the day your period starts each month with the letter P.

MONTH	DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Fig. 4.1 Cardiff breast pain chart

breast. The pain may radiate to the axilla and down the medial aspect of the upper arm. The pain varies in severity from cycle to cycle but can persist for many years. Cyclical mastalgia is relieved by menopause. Physical activity can increase the pain; this is particularly relevant for women whose occupations include lifting and prolonged use of the arms. The impact of mastalgia on quality of life is often underestimated. Cyclical mastalgia is distinct from premenstrual syndrome (PMS), which is characterized by physical, psychological, and emotional symptoms associated with the menstrual cycle. The two may occur together or independently. Although mastalgia is a well-documented symptom in PMS, PMS is not necessarily present in women with cyclical mastalgia [9].

4.4 Non-cyclical Mastalgia

Non-cyclical breast pain is unrelated to the menstrual cycle and occurs in both pre- and postmenopausal women. Patients are usually in their forties. Pain may be continuous

but is usually described as having a random time pattern. The pain is often localized and described as “burning” or “drawing.” The pain may be due to a tender cyst, periductal mastitis, stretching of Cooper's ligaments, trauma (including breast biopsy or surgery), sclerosing adenosis, Mondor's disease, and cancer [8]. The majority of patients, however, are found to have no cause to explain their mastalgia despite thorough investigations.

4.5 Chest Wall Pain

Musculoskeletal pain is almost always unilateral, brought on by activity, and can be reproduced by pressure on specific area of the chest wall. Women known to have spondylosis or osteoarthritis are more likely to have musculoskeletal pain rather than true breast pain. Pain arising from the chest wall may be mistakenly attributed to the breast. Pain that is limited to a particular area and characterized as burning or knifelike in nature may arise from the chest wall. Several distinct types of pain can be distinguished, including

localized or diffuse lateral chest wall pain, radicular pain from cervical arthritis, and pain from Tietze's syndrome (costochondritis). In Tietze's syndrome, the pain is often felt in the medial quadrants of the breast overlying the costal cartilages, which are the source of the pain. It has a chronic time course, and on examination, one or several costal cartilages are tender and feel enlarged.

4.6 Non-chest Wall Pain

This group consists of patients who have pain due to a non-breast cause, such as gallstones and angina.

4.7 Mastalgia and Breast Cancer

Cancer is an uncommon cause of breast pain. Breast pain associated with cancer is non-cyclical, unilateral, and well localized. Breast cancer is found in 2–7 % of patients presenting with pain as the primary symptom [10–14]. It is not clear whether breast pain increases the risk of subsequent breast cancer. Two case-control studies and one cohort study [15–17] have shown a significant increase in breast cancer risk in women with cyclical mastalgia. Plu-Bureau et al. [17] studied 210 premenopausal women diagnosed to have breast cancer who were matched with 210 controls from the same geographic area on age, education level, and age at first full-term pregnancy. The previous history of cyclical mastalgia was found to be associated with an increased risk of breast cancer (relative risk adjusted for family history of breast cancer, prior benign breast disease, age at menarche, oral contraceptive use >2.12). Similar findings were reported by the authors in a cohort study of 247 premenopausal women diagnosed to have benign breast disease [15]. They showed that the breast cancer risk increased with increasing duration of cyclical mastalgia. Goodwin et al. [16] studied 192 premenopausal women with a node-negative breast cancer and 192 age-matched premenopausal controls. Breast tenderness scores were significantly higher premenstrually in patients with breast cancer. The odds ratio of breast cancer for severe tenderness was 3.32. However, it is documented that women presenting to physicians with symptoms have higher mammographic and biopsy interventions, which may lead to a diagnosis bias in these studies.

In contrast, Khan et al. [18] found that women who experienced breast pain were less likely to have breast cancer. They analyzed data of 5463 women attending a breast care center in New York. Eight hundred and sixty-one of thousand five hundred and thirty-two women who

reported breast pain at their initial visit were diagnosed with breast cancer. Odds ratio after adjustment for age and additional risk factors was 0.63.

Further evidence is needed to define the association between mastalgia and breast cancer. Clinical examination of the breasts and assessment of the patient's individual risk of breast cancer should be the main determinants of offering diagnostic breast imaging to patients with mastalgia.

4.8 Psychosocial Factors

Traditional surgical view that pain in the breast is largely an expression of psychoneurosis was challenged by Preece et al. [19] who found that women with mastalgia had similar anxiety, and depression and phobia to women with varicose veins. The psychological morbidity in varicose vein and mastalgia patients was significantly lower than that of psychiatric patients, except for few patients with breast pain who failed to respond to treatment.

Other studies have found that women with mastalgia have increased anxiety and depression compared with asymptomatic women [20]. It is not clear whether psychological distress contributes to or is a consequence of mastalgia. The emotional symptoms are significantly higher in women with severe mastalgia. The anxiety and depression in women with severe mastalgia are comparable with those of women with newly diagnosed breast cancer on the morning of their surgery [21]. Those who respond to treatment have a significant improvement in psychosocial function, but patients refractory to treatment continue to have high levels of distress [21].

More recently, Colegrave et al. [22] found that women with breast pain had increased anxiety, depression, somatization, and history of emotional abuse compared to women with breast lumps alone, suggesting psychosocial factors contribute to mastalgia. Relaxation therapy by listening to relaxation audio tape can improve symptoms of mastalgia [23].

4.9 Clinical Assessment and Investigations

A careful history is necessary to exclude non-breast conditions. Clinical examination must be performed to exclude a mass lesion in the breast and define breast tenderness and chest wall tenderness. Breast lump should be evaluated by "triple assessment," which includes palpation, imaging, and percutaneous core needle biopsy or fine-needle aspiration cytology. Chest wall should be examined by lifting the breast with one hand while palpating the underlying muscles

and ribs with the other hand (Fig. 4.2). Lateral and medial chest wall tenderness can be elicited by rolling the patient to her side, allowing the breast to fall away from the chest wall (Fig. 4.2). If no mass is identified, further investigation is not indicated and the patient should be reassured that there is no sinister cause for her symptoms. The impact of the pain on the patient's quality of life should then be determined. Severe mastalgia tends to interfere with work, hugging children, and sexual relationships. If treatment is being considered, patients should be asked to complete a pain chart (Fig. 4.1) for at least 2 months to allow identification of the pattern of pain and to assess the number of days of pain in each menstrual cycle.

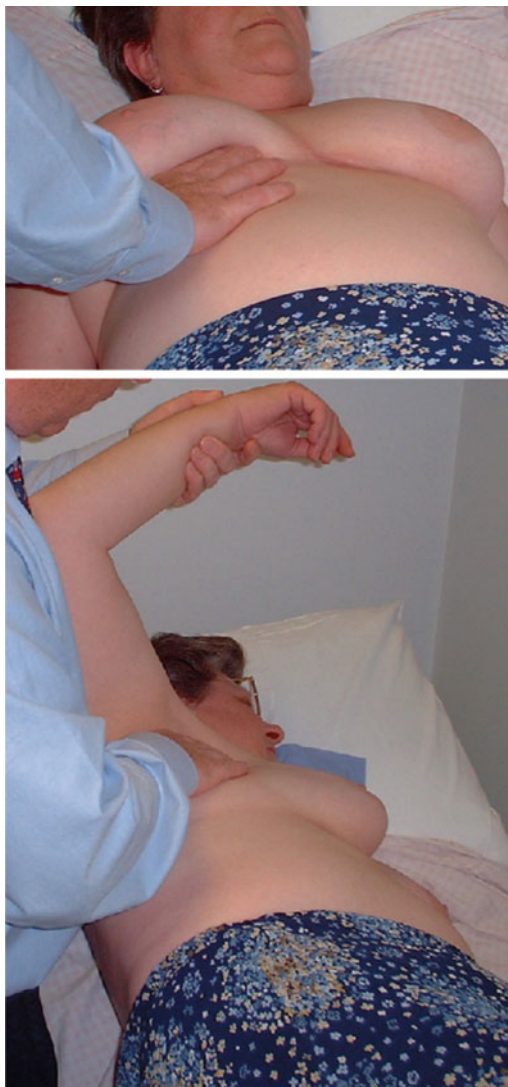


Fig. 4.2 Examination techniques to elicit chest wall tenderness

4.10 Treatment

4.10.1 Cyclical Mastalgia

The primary indication for treatment is pain, which interferes with everyday activities. Many women who present to hospital do so because they are worried that mastalgia may indicate breast cancer. Reassurance that cancer is not responsible for their symptoms is the only treatment necessary in up to 85 % of women with cyclical mastalgia [24]. The key to effective management of patients with mastalgia is a “listening physician” who can express empathy and understanding for the impact that breast pain has on women's lifestyle. Some women can improve their pain with simple measures such as wearing a well-fitting bra to support the pendulous breasts. Antibiotics are ineffective for mastalgia and should be used only when a specific diagnosis of periductal mastitis or lactational infection has been made. Diuretics, vitamin E, vitamin B6, caffeine reduction, and progestogens (oral or topical) have not been shown to be of value in cyclical mastalgia [25–31]. Women who start oral contraceptive or hormone replacement therapy may report breast pain, which usually settles with continued therapy. Some patients who are taking an oral contraceptive find that their breast pain improves after stopping the pill and changing to mechanical contraception, but no individual oral contraceptive has been shown to specifically cause mastalgia. The use of oral contraceptives and hormone replacement therapy has not been systematically studied, but for persistent symptoms, the use of alternative preparations, preparations that contain low-dose estrogen or stopping medication, may produce relief.

Evening primrose oil has been used, at oral doses of 1–3 g daily; however, two recent randomized trials have found that its efficacy does not differ from that of placebo [31, 32]. Evening primrose oil's prescription license in the UK was revoked in October 2002 due to lack of efficacy over placebo. One small randomized trial found improvement in premenstrual breast swelling and tenderness with low-fat (15 % of total calories) and high-carbohydrate diet [33]. This diet may be difficult to sustain, and further research is needed before low-fat diet can be recommended to reduce breast pain. There has been a growing interest in phytoestrogens, herbal agents, and nutritional supplements for the treatment of breast pain. Isoflavones were found to be effective in cyclical mastalgia in a small randomized trial [34]. *Agnes castus* was well tolerated and was effective in controlling the symptoms of cyclical mastalgia in a placebo-controlled, randomized trial of 97 women suffering from cyclical mastalgia [35]. These studies need to be repeated in larger numbers to clarify the therapeutic value of these alternative approaches in breast pain.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are well tolerated and effective in treating breast pain and should be considered for pain control in those who prefer topical therapy. In a randomized controlled trial, diclofenac gel was found to be superior to placebo in premenopausal women with cyclical or non-cyclical mastalgia [36].

The efficacy of bromocriptine (dopamine agonist) has been confirmed in randomized trials and in a recent meta-analysis [37], but it is not used these days because of frequent and intolerable side effects (nausea, dizziness, headache, and postural hypotension).

Goserelin (Zoladex[®]), a potent synthetic analog of luteinizing hormone-releasing hormone (LHRH), induces reversible ovarian suppression with castrate levels of ovarian hormones being attained within 72 h [38–40]. In a randomized controlled trial, we found that goserelin injection was superior to sham injection in treating severe mastalgia [41]. However, side effects (vaginal dryness, hot flushes, decreased libido, oily skin or hair, and decrease in breast size) are common, and thus, goserelin should be kept in reserve for patients who are refractory to other forms of treatment. Goserelin can be used to induce a rapid relief of symptoms in patients with severe mastalgia, and the response can be maintained with alternative therapies.

Danazol is a synthetic androgen that has antigonadotrophic effects on the pituitary. It prevents luteinizing hormone surge and inhibits ovarian steroid formation. Danazol relieves breast pain and tenderness, and the response is usually seen within 3 months [42, 43]. However, side effects occur in 30 % of patients and result in discontinuation of treatment in a significant number of patients [44]. Danazol has superior efficacy compared with bromocriptine [45]. The side effects of danazol treatment (weight gain, deepening of the voice, menstrual irregularity or amenorrhea, hot flashes, depression, headaches, and muscle cramps) can be limited by reducing the dose once the response has been achieved. The response can be maintained with doses as low as 100 mg daily, given on days 14–28 of the menstrual cycle [42].

Tamoxifen has proven to be effective in the treatment of both cyclical and non-cyclical mastalgia in randomized controlled trials [46, 47]. Tamoxifen 10 mg daily has equal efficacy but fewer adverse effects compared with 20 mg daily [48]. Its use is limited to no more than 6 months under specialist supervision as tamoxifen is not licensed for mastalgia in the USA or the UK. Common side effects with 10-mg daily regimen are menstrual irregularities, hot flashes, weight gain, vaginal dryness, and bloating. The incidence of thromboembolic events, endometrial cancer, and cataracts with short-term treatment for mastalgia is unknown. Tamoxifen is cheaper and has higher response rates and less side effects compared with danazol [49].

4-hydroxytamoxifen (4-OHT) is a potent antiestrogenic metabolite of tamoxifen with much higher affinity for estrogen receptors than tamoxifen. A percutaneous gel formulation of 4-hydroxytamoxifen (Afimoxifene[®]) has been found to be superior to placebo in the treatment of cyclical mastalgia in a phase II randomized trial [50]. Topical application avoids high systemic exposure to 4-OHT compared with oral tamoxifen, thus potentially reducing the risk of systemic side effects. Further studies are needed before Afimoxifene[®] can be recommended for mastalgia.

There is insufficient evidence on the role of surgery in the treatment of mastalgia, and surgical intervention should be approached with great caution. Retrospective data from Cardiff found that mastectomy in contrast to localized excision needs to be performed for symptom relief [51]. Surgery should be reserved for a minority of women who suffer from intractable symptoms and in whom non-breast causes of pain have been excluded. A multidisciplinary team approach involving the surgeon, psychologist, and breast care nurse is required when offering surgery to these women. The women should be counseled to inform them of the potential complications and the risk of persistence of symptoms.

4.10.2 Non-cyclical Mastalgia

When pain is truly arising from the breast, the approach outlined for cyclical pain is used. Musculoskeletal pain often responds to oral or topical NSAIDs. Patients with persistent localized chest wall symptoms can be effectively treated by injection of a combination of local anesthetic and steroid into the tender site. Injection of local anesthetic confirms the correct identification of the painful area by producing complete disappearance of the pain.

4.11 Management Algorithm

The protocol followed in Cardiff Breast Unit is outlined in Fig. 4.3. Most patients can be reassured and discharged from the clinic if breast examination is normal. Imaging (mammogram/ultrasonography) is only done based on the patient's breast cancer risk and examination findings. Patients requesting treatment are given lifestyle advice (e.g., wear well-fitted bra) and asked to record their pain in the Cardiff Breast Pain Chart and return to the clinic in 3 months. First-line treatment includes the use of topical or oral mild analgesic agents such as paracetamol and NSAIDs. Patients with persistent symptoms after 3 months of treatment are started on tamoxifen, at a dose of 10 mg daily for three to 6 months. Treatment failures are started on danazol, at a dose of 200 mg daily (reduced to 100 mg a day after

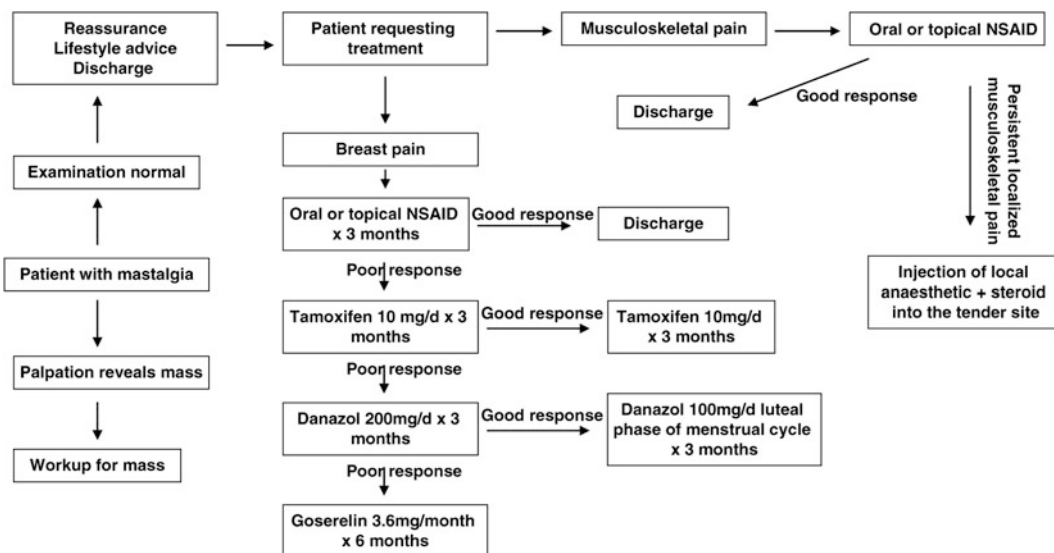


Fig. 4.3 Algorithm for the management of mastalgia

relief of symptoms) or only during the luteal phase of the menstrual cycle. Non-responders with severe pain are started on goserelin depot injection, 3.6 mg/month for 6 months. If the outlined treatment plan is followed, about 70–80 % of patients should experience substantial relief of symptoms. Non-hormonal contraception is essential with tamoxifen and danazol because both have deleterious effects on the fetus.

References

- Ader DN, South-Paul J, Adera T, Deuster PA. Cyclical mastalgia: prevalence and associated health and behavioral factors. *J Psychosom Obstet Gynaecol.* 2001;22:71–6.
- Cyclical breast pain—what works and what doesn't. *Drug Ther Bull.* 1992;30:1–3.
- Khan SA, Apkarian AV. The characteristics of cyclical and non-cyclical mastalgia: a prospective study using a modified McGill Pain Questionnaire. *Breast Cancer Res Treat.* 2002;75:147–57.
- Ader DN, Shriver CD. Cyclical mastalgia: prevalence and impact in an outpatient breast clinic sample. *J Am Coll Surg.* 1997;185:466–70.
- Rose DP, Boyar AP, Cohen C, Strong LE. Effect of a low-fat diet on hormone levels in women with cystic breast disease. I. Serum steroids and gonadotropins. *J Natl Cancer Inst.* 1987;78:623–6.
- Wang DY, Fentiman IS. Epidemiology and endocrinology of benign breast disease. *Breast Cancer Res Treat.* 1985;6:5–36.
- Wisbey JR, Kumar S, Mansel RE, Preece PE, Pye JK, Hughes LE. Natural history of breast pain. *Lancet.* 1983;2:672–4.
- Santen RJ, Mansel R. Benign breast disorders. *N Engl J Med.* 2005;353:275–85.
- Ader DN, Shriver CD, Browne MW. Cyclical mastalgia: premenstrual syndrome or recurrent pain disorder? *J Psychosom Obstet Gynaecol.* 1999;20:198–202.
- Barton MB, Elmore JG, Fletcher SW. Breast symptoms among women enrolled in a health maintenance organization: frequency, evaluation, and outcome. *Ann Intern Med.* 1999;130:651–7.
- Lumachi F, Ermani M, Brandes AA, Boccagni P, Polistina F, Basso SM, Favia G, D'Amico DF. Breast complaints and risk of breast cancer. Population-based study of 2,879 self-selected women and long-term follow-up. *Biomed Pharmacother.* 2002;56:88–92.
- Fariselli G, Lepera P, Viganotti G, Martelli G, Bandieramonte G, Di Pietro S. Localized mastalgia as presenting symptom in breast cancer. *Eur J Surg Oncol.* 1988;14:213–5.
- Smallwood JA, Kye DA, Taylor I. Mastalgia; is this commonly associated with operable breast cancer? *Ann R Coll Surg Engl.* 1986;68:262–3.
- Preece PE, Baum M, Mansel RE, Webster DJ, Fortt RW, Gravelle IH, Hughes LE. Importance of mastalgia in operable breast cancer. *Br Med J (Clin Res Ed).* 1982;284:1299–300.
- Plu-Bureau G, Le MG, Sitruk-Ware R, Thalabard JC. Cyclical mastalgia and breast cancer risk: results of a French cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006;15:1229–31.
- Goodwin PJ, DeBoer G, Clark RM, Catton P, Redwood S, Hood N, Boyd NF. Cyclical mastopathy and premenopausal breast cancer risk. Results of a case-control study. *Breast Cancer Res Treat.* 1995;33:63–73.
- Plu-Bureau TJC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P. Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. *Br J Cancer.* 1992;65:945–9.
- Khan SA, Apkarian AV. Mastalgia and breast cancer: a protective association? *Cancer Detect Prev.* 2002;26:192–6.
- Preece PE, Mansel RE, Hughes LE. Mastalgia: psychoneurosis or organic disease? *Br Med J.* 1978;1:29–30.
- Jenkins PL, Jamil N, Gateley C, Mansel RE. Psychiatric illness in patients with severe treatment-resistant mastalgia. *Gen Hosp Psychiatry.* 1993;15:55–7.
- Ramirez AJ, Jarrett SR, Hamed H, Smith P, Fentiman IS. Psychosocial adjustment of women with mastalgia. *Breast.* 1995;4:48–51.
- Colegrave S, Holcombe C, Salmon P. Psychological characteristics of women presenting with breast pain. *J Psychosom Res.* 2001;50:303–7.
- Fox H, Walker LG, Heys SD, Ah-See AK, Eremin O. Are patients with mastalgia anxious, or does relaxation therapy help? *Breast.* 2009;6:138–42.

24. Barros AC, Mottola J, Ruiz CA, Borges MN, Pinotti JA. Reassurance in the treatment of mastalgia. *Breast J*. 1999;5:162–5.
25. Smallwood J, Ah-Kye D, Taylor I. Vitamin B6 in the treatment of pre-menstrual mastalgia. *Br J Clin Pract*. 1986;40:532–3.
26. Ernster VL, Goodson WH III, Hunt TK, Petrakis NL, Sickles EA, Miike R. Vitamin E and benign breast “disease”: a double-blind, randomized clinical trial. *Surgery*. 1985;97:490–4.
27. Parazzini F, La Vecchia C, Riundi R, Pampallona S, Regallo M, Scanni A. Methylxanthine, alcohol-free diet and fibrocystic breast disease: a factorial clinical trial. *Surgery*. 1986;99:576–81.
28. Allen SS, Froberg DG. The effect of decreased caffeine consumption on benign proliferative breast disease: a randomized clinical trial. *Surgery*. 1987;101:720–30.
29. McFadyen IJ, Raab GM, Macintyre CC, Forrest AP. Progesterone cream for cyclic breast pain. *BMJ*. 1989;298:931.
30. Maddox PR, Harrison BJ, Horobin JM, Walker K, Mansel RE, Preece PE, Nicholson RI. A randomised controlled trial of medroxyprogesterone acetate in mastalgia. *Ann R Coll Surg Engl*. 1990;72:71–6.
31. Goyal A, Mansel RE. A randomized multicenter study of gamolenic acid (Efamast) with and without antioxidant vitamins and minerals in the management of mastalgia. *Breast J*. 2005;11:41–7.
32. Blommers J, de Lange-De Klerk ES, Kuik DJ, Bezemer PD, Meijer S. Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. *Am J Obstet Gynecol*. 2002;187:1389–94.
33. Boyd NF, McGuire V, Shannon P, Cousins M, Kriukov V, Mahoney L, Fish E, Lickley L, Lockwood G, Trichler D. Effect of a low-fat, high-carbohydrate diet on symptoms of cyclical mastopathy. *Lancet*. 1988;2:128–32.
34. Ingram DM, Hickling C, West L, Mahe LJ, Dunbar PM. A double-blind, randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. *Breast*. 2002;11:170–4.
35. Halaska M, Beles P, Gorkow C, Sieder C. Treatment of cyclical mastalgia with a solution containing a Vitex agnus castus extract: results of a placebo-controlled double-blind study. *Breast*. 1999;8:175–81.
36. Colak T, Ipek T, Kanik A, Ogetman Z, Aydin S. Efficacy of topical nonsteroidal anti-inflammatory drugs in mastalgia treatment. *J Am Coll Surg*. 2003;196:525–30.
37. Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of mastalgia: a meta-analysis of randomised trials. *Breast*. 2007;16:503–12.
38. Thomas EJ, Jenkins J, Lenton EA, Cooke ID. Endocrine effects of goserelin, a new depot luteinising hormone releasing hormone agonist. *Br Med J (Clin Res Ed)*. 1986;293:1407–8.
39. Shaw RW. An open randomized, comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. Zoladex endometriosis study team. *Fertil Steril*. 1992;58:265–72.
40. Fraser HM, Sandow J. Suppression of follicular maturation by infusion of a luteinizing hormone-releasing hormone agonist starting during the late luteal phase in the stump-tailed macaque monkey. *J Clin Endocrinol Metab*. 1985;60:579–84.
41. Mansel RE, Goyal A, Preece P, Leinster S, Maddox PR, Gateley C, Kubista E, von Fournier D. European randomized, multicenter study of goserelin (Zoladex) in the management of mastalgia. *Am J Obstet Gynecol*. 2004;191:1942–9.
42. O’Brien PM, Abukhalil IE. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol*. 1999;180:18–23.
43. Mansel RE, Wisbey JR, Hughes LE. Controlled trial of the antigonadotropin danazol in painful nodular benign breast disease. *Lancet*. 1982;1:928–30.
44. Gateley CA, Miers M, Mansel RE, Hughes LE. Drug treatments for mastalgia: 17 years experience in the Cardiff mastalgia clinic. *J R Soc Med*. 1992;85:12–5.
45. Hinton CP, Bishop HM, Holliday HW, Doyle PJ, Blamey RW. A double-blind controlled trial of danazol and bromocriptine in the management of severe cyclical breast pain. *Br J Clin Pract*. 1986;40:326–30.
46. Fentiman IS, Caleffi M, Brame K, Chaudary MA, Hayward JL. Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet*. 1986;1:287–8.
47. Messinis IE, Lolis D. Treatment of premenstrual mastalgia with tamoxifen. *Acta Obstet Gynecol Scand*. 1988;67:307–9.
48. Fentiman IS, Caleffi M, Hamed H, Chaudary MA. Dosage and duration of tamoxifen treatment for mastalgia: a controlled trial. *Br J Surg*. 1988;75:845–6.
49. Kontostolis E, Stefanidis K, Navrozoglou I, Lolis D. Comparison of tamoxifen with danazol for treatment of cyclical mastalgia. *Gynecol Endocrinol*. 1997;11:393–7.
50. Mansel R, Goyal A, Nestour EL, Masini-Eteve V, O’Connell K. A phase II trial of Afimoxifene (4-hydroxytamoxifen gel) for cyclical mastalgia in premenopausal women. *Breast Cancer Res Treat*. 2007;106:389–97.
51. Davies EL, Cochrane RA, Stansfield K, Sweetland HM, Mansel RE. Is there a role for surgery in the treatment of mastalgia? *Breast*. 1999;8:285–8.