Management of Breast Pain

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Abbreviations

CM	Cyclic mastalgia
EP	Extramammary pain
NCM	Noncyclic mastalgia

Introduction

Breast pain, or mastalgia, is one of the most common breast disorders affecting women worldwide. Although some studies have suggested that up to 70 % of women in Western societies experience breast pain in their lifetime, few experience symptoms severe enough to seek care for evaluation and treatment [1, 2]. Additionally, the prevalence is greatly influenced by the overall population being studied and the definitions used by the investigators. Although a common condition, the etiology of mastalgia remains quite enigmatic, also occurring in men but much more limited in terms of incidence as compared to females [3–5].

In a retrospective cohort study involving 2,400 women aged 40–69 who were enrolled in a health maintenance organization, breast pain was the most common breast symptom prompting evaluation, accounting for almost half (47 %) of all breast-related visits [6]. A second study of 1,171 women who answered a questionnaire on breast pain found that 69 % of women experienced premenstrual breast pain, noting that it impacted sexual activity (48 %), physical activity (37 %), social activity (12 %), and work or school activity (8 %) [7].

Pain of extramammary origin may often be perceived as breast pain. The differential diagnosis for pain perceived as emanating from the breasts is broad and should be considered in any patient presenting with the chief complaint of mastalgia (Table 4.1). The definition of breast pain is further classified as cyclic (breast pain that occurs in relationship to the menstrual cycle) and noncyclic (breast pain not associated with the menstrual cycle) [3]. Herein, we will review the etiology, diagnosis, management, and prevention of cyclic and noncyclic breast pain.

Cyclic Mastalgia

Clinical Features

Cyclic mastalgia is defined as breast pain of moderate-to-severe intensity, lasting ≥7 days and, because it demonstrates a relationship to

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Table 4.1 Differential diagnosis of mastalgia

Location	Differential diagnosis
Breast-related	Mastalgia
	Cyclic mastalgia
	Noncyclic mastalgia
	Mastitis
	Breast trauma
	Thrombophlebitis/Mondor's disease
	Cysts
	Benign breast tumors
	Breast cancer
Musculoskeletal	Chest wall pain (intercostal muscle strain/tear)
	Tietze syndrome/costochondritis
	Chest wall trauma/rib fracture or contusion
	Fibromyalgia
	Cervical radiculopathy
	Shoulder pain
	Herpes zoster
Miscellaneous causes	Coronary artery disease/angina
	Pericarditis
	Pulmonary embolus
	Pleurisy
	Gastroesophageal reflux/esophageal spasm
	Peptic ulcer disease
	Cholelithiasis/cholecystitis
	Sickle cell anemia
	Psychological
	Pregnancy
	Medication (see Table 4.2)

Adapted from Smith et al. [3]

the menstrual cycle, occurring in premenopausal women [7]. Typically, it follows a course of relapse and remission, often confused with premenstrual breast pain. However, premenstrual breast tenderness is a normal physiologic response that occurs about 2–3 days before the onset of menstrual flow. In this context, breast symptoms are mild to moderate, most often bilateral, associated with swelling and tenderness, and self-limited [7].

Symptoms of cyclic mastalgia are usually most significant during the luteal phase of the menstrual cycle and may involve one or both breasts. The pain often resolves with the onset of the menstrual cycle, but a low level of pain may persist throughout the month with luteal phase intensification [3]. Most patients report a dull or aching sensation in the breasts, rarely reporting a sharp or stabbing nature to the pain. Women with cyclic mastalgia frequently experience the onset of symptoms in the third or fourth decade of life with almost half demonstrating resolution with the cessation of menses (menopause) [8].

Etiology

A number of theories of causality for cyclic mastalgia have been proposed, but no specific etiology has been determined. In spite of the association with menstrual cyclicity, cyclic mastalgia has not been shown to correlate with specific changes in hormonal levels (i.e., estrogen, progesterone, prolactin) in studies comparing women with and without symptoms [9]. Although an intriguing hypothesis, fluid retention has not been shown to cause cyclic mastalgia. In a study by Preece et al., total body water was measured early and late in the menstrual cycle for women with breast pain and in asymptomatic women, with no apparent correlation identified [10]. Histopathological changes of fibrocystic breast disease can be found in women with and without cyclic mastalgia. Additionally, no nutritional, inflammatory, or psychiatric associations have been substantiated based upon the current literature [3].

Noncyclic Mastalgia

Clinical Features

Noncyclic mastalgia has no clear association with a woman's menstrual cycle and can be intermittent or constant. Pain associated with noncyclic mastalgia may often localize to a specific quadrant of one breast, but it may also be diffuse and similar to that of cyclic mastalgia [11]. In contrast to cyclic mastalgia, noncyclic mastalgia is often a condition of the postmenopausal years, most commonly occurring in the

fourth or fifth decade. Although less common than cyclic mastalgia, it still accounts for 31 % of women presenting with breast pain to some mastalgia clinics [8]. It can occur before, at, or after menopause and for some women may be even more problematic than cyclic mastalgia as the inciting event or cause for resolution can remain a mystery.

Etiology

The majority of noncyclic breast pain is of idiopathic origin, while a minority of patients can attribute their symptoms to anatomical changes resulting from pregnancy, mastitis, or trauma. Noncyclic breast pain is less likely due to thrombophlebitis, macrocysts, benign tumors, cancer, or medications. A number of medications however have been shown to have an association with breast pain. Awareness of this association allows for appropriate patient counseling prior to the institution of therapy (Table 4.2).

Recently, duct ectasia has been proposed as a cause for noncyclic mastalgia. An ultrasound study comparing maximum mean width of milk ducts in asymptomatic women and women with cyclic and noncyclic mastalgia found a significant increase in maximum mean width of milk ducts in women with both types of pain. Pain intensity correlated with ductal width [12]. It is also suggested that the dilatation of the ducts with stagnant secretions leads to periductal inflammation (periductal mastitis which may be subclinical). The pain is often described as a throbbing sensation, and nipple retraction and purulent nipple discharge may also occur. A short course of antibiotics may be considered as the first line of treatment, and if no improvement occurs, surgical management should be considered [13].

Table 4.2 Medications associated with breast pain in women

Categories	Medications
Hormonal medications	Estrogens
	Progestogens
	Combination medication
	Oral contraceptives
	Menopausal hormone therapy
	Diethylstilbestrol
	Clomiphene
	Cyproterone
Antidepressant, antipsychotic, and anxiolytic medications	Sertraline (and other serotonin reuptake inhibitors)
	Venlafaxine
	Mirtazapine
	Chlordiazepoxide
	Amitriptyline[a]
	Doxepin[a]
	Haloperidol (and other antipsychotic agents)
Antihypertensive and cardiac medications	Spironolactone[a]
	Methyldopa
	Minoxidil
	Digoxin[a]
	Reserpine[a]
Antimicrobial agents	Ketoconazole[a]
	Metronidazole[a]
Miscellaneous agents	Cimetidine[a]
	Cyclosporine
	Domperidone
	Penicillamine
	Methadone[a]
	Carboprost, dinoprostone (and other prostaglandins)
	Estramustine

Adapted from Smith et al. [3]
Information obtained from MEDLINE, MICROMEDEX, and discussion with breast specialists and pharmacists
[a]Medications causing galactorrhea and gynecomastia and believed to be associated with breast pain. Other medications (not listed) also may be associated with breast pain and should be considered according to clinical circumstances

Clinical Impact

Cyclic and noncyclic mastalgias significantly impact quality of life for many women. A study by Davies et al. demonstrated a negative impact on sexual relations in 28 % of women with cyclic mastalgia and 20 % with noncyclic mastalgia, for women reporting moderate-to-severe pain [8]. Clinical complaints of mastalgia often lead to further evaluation. In a health maintenance organization cohort study evaluating the outcome of breast symptom episodes, further evaluation

was recommended for 391 (73 %) episodes, which included a surgical consultation (38 %), return for repeat examination (23 %), and diagnostic studies including mammography (30 %), fine-needle aspiration (8 %), biopsy (4 %), and ultrasonography (1 %) [6]. Significant resources are utilized in the ensuing workup leading to an increase in health-care costs.

Interestingly, in a study of 1,200 female veterans, those with frequent mastalgia (defined as ≥ weekly) compared to women without mastalgia were more likely to experience the following: panic disorder (odds ratio [OR] 7.1, 95 % CI 3.9–12.8), posttraumatic stress disorder (OR 5.2, 95 % CI 3.2–8.4), chronic pelvic pain (OR 5.4, 95 % CI 2.7–10.5), major depression (OR 4.2, 95 % CI 2.6–6.9), fibromyalgia (OR 3.9, 95 % CI 2.1–7.4), domestic violence (OR 3.1, 95 % CI 1.9–5.0), irritable bowel syndrome (OR 2.8, 95 % CI 1.6–4.8), eating disorder (OR 2.6, 95 % CI 1.5–4.7), or alcohol misuse (OR 1.8, 95 % CI 1.1–2.8) [14]. This study highlights the need to consider comorbidities in patients presenting with a chief complaint of mastalgia.

Women with cyclic and noncyclic mastalgia often express concerns about the association of pain with breast cancer. However, pain as a presenting symptom, or the only symptom, of breast cancer is a relatively rare occurrence, reported as a presenting symptom in only 5–18 % of breast cancers [2]. Studies of the association of mastalgia and breast cancer have shown conflicting results. A potential association between breast pain and cyclic mastalgia has been identified in premenopausal women with early-stage breast cancer and breast pain. In a cohort study of 247 French women with benign breast disease (and free of any hormonal treatment), the OR for breast cancer was 1.35 (95 % CI 1.01–1.83) for women with any cyclic pain compared to 3.32 for women with symptoms rated as severe when compared to controls. With a mean follow-up of 16 ± 5 years, a total of 22 breast cancers were found. Utilizing the Cox model, the corresponding relative risk for 37 months of cyclical mastalgia was 5.31 % (95 % CI 1.92–14.72) [15]. Results in these studies may have been influenced by bias in reporting, as women with breast cancer may have a higher rate of reporting symptoms. A larger study of 5,463 women seen in a breast care center demonstrated that breast pain was associated with a decreased risk of breast cancer [16]. Clearly, further study is needed to clarify this possible association.

Clinical Evaluation

An approach to evaluating the patient presenting with breast pain entails a thorough history and physical examination. Identifying the onset, quality, and duration of pain, as well as aggravating and alleviating factors or association with a mass or inflammation, can aid in differentiating the etiology of breast pain. Assessing pain severity using a standardized pain scale, such as the Likert scale of 1–10, and documenting the change in severity over time will guide treatment recommendations with both non-pharmacologic and pharmacologic treatment options (Table 4.3).

Although known risk factors for breast cancer include reproductive history, family history, personal breast cancer, or a prior precancerous breast lesion, the presence or absence of these factors should not detract from a thorough evaluation of breast pain in order to exclude malignancy or other benign etiologies. Various medications including hormonal preparations and antidepressants and antihypertensive medications have been associated with breast pain (Table 4.2). Discontinuation, taking a drug holiday, or switching to a different dose or formulation may be indicated in the management of breast pain.

Physical Examination

The diagnostic clinical breast examination entails inspection and palpation performed in the seated or supine position, sometimes both. It is helpful to visualize both breasts at the same time to allow for comparison of size and symmetry and to assess for presence of erythema, skin dimpling (peau d'orange), nipple changes (inversion or discharge), and distortion of the breast architecture.

Table 4.3 Historical factors to elicit in the clinical evaluation of breast pain

History	Differentiating features	Cyclic mastalgia (CM) versus noncyclic mastalgia (NCM) or extramammary pain (EP)
Location	Unilateral and localized	NCM
	Bilateral and generalized	CM
Duration	Acute (<month), subacute (1–6 months), or chronic (<6 months)	CM or NCM or EP
Severity	Likert pain scale 1–10	
Quality of pain	Burning or aching sensation	NCM
	Dull or heavy sensation	CM
Exacerbating or alleviating factors	Relationship to physical activity or activities of daily living (sleep)	NCM or CM
	Initiation of new medication	NCM
	Caffeinated beverage use	NCM
Associated factors	Palpable breast mass, erythema, nipple discharge, or skin changes	NCM
	Chest wall pain	EP
Reproductive factors	Relationship to menstrual cycle	CM
	Pregnancy	NCM
Medications	See Table 4.2	

Palpation of the entire breast including the nipple areolar complex and regional lymph nodes should be performed on all patients. Tenderness may localize to discrete areas in the breast and may be generalized or of extramammary etiology. Having the patient bend over or lie on their side to allow the breast tissue to fall away from the pectoralis muscle and chest wall can help differentiate pain emanating from the breast versus the chest wall [9]. The finding of a discrete mass or localized area of pain should be further evaluated with diagnostic imaging including ultrasound and mammogram.

Diagnostic Evaluation

The diagnostic workup of breast pain can be challenging, with the determination of the ideal imaging study often dependent upon the clinical findings and patient age. In a patient younger than 30, the sensitivity of diagnostic mammography is markedly decreased due to the overall increased density of the young breast. Therefore, if no mass is palpated in association with localized breast pain, we proceed first with a targeted ultrasound as the preferred initial modality for imaging the breast tissue. Mammography may be added depending on the clinical context and perceived individual risk. Patients older than 30 should undergo diagnostic mammography in addition to a focused ultrasound. Diffuse pain without a palpable mass is further categorized into cyclic versus noncyclic etiologies, with patients older than 30 with noncyclic pain undergoing diagnostic mammography first. A reasonable treatment algorithm provides a typical approach to the patient with breast pain (Fig. 4.1).

Irrespective of age, if a palpable mass is clearly found on clinical examination, this will require both a diagnostic mammogram and ultrasound. If clinical suspicion is high for malignancy and diagnostic imaging is negative, referral to a surgeon for consideration of biopsy of the palpable finding is recommended. Masses that are palpable but located deep within the breast tissue are very challenging and may require an open biopsy rather than biopsy in an outpatient setting. If clinical suspicion is low for malignancy and diagnostic imaging is negative, short-term follow-up with reexamination and consideration of additional imaging if the area of concern has changed is recommended. Depending on available resources, MRI may be utilized; however, the utility of diagnostic MRI in this setting is not yet fully defined and may offer a low yield of a cancer diagnosis [17]. In situations where the mass is visible on MRI, consideration could be given to an MRI-guided biopsy.

Smith et al. reported that the yield of either mammography or ultrasound in the context of a

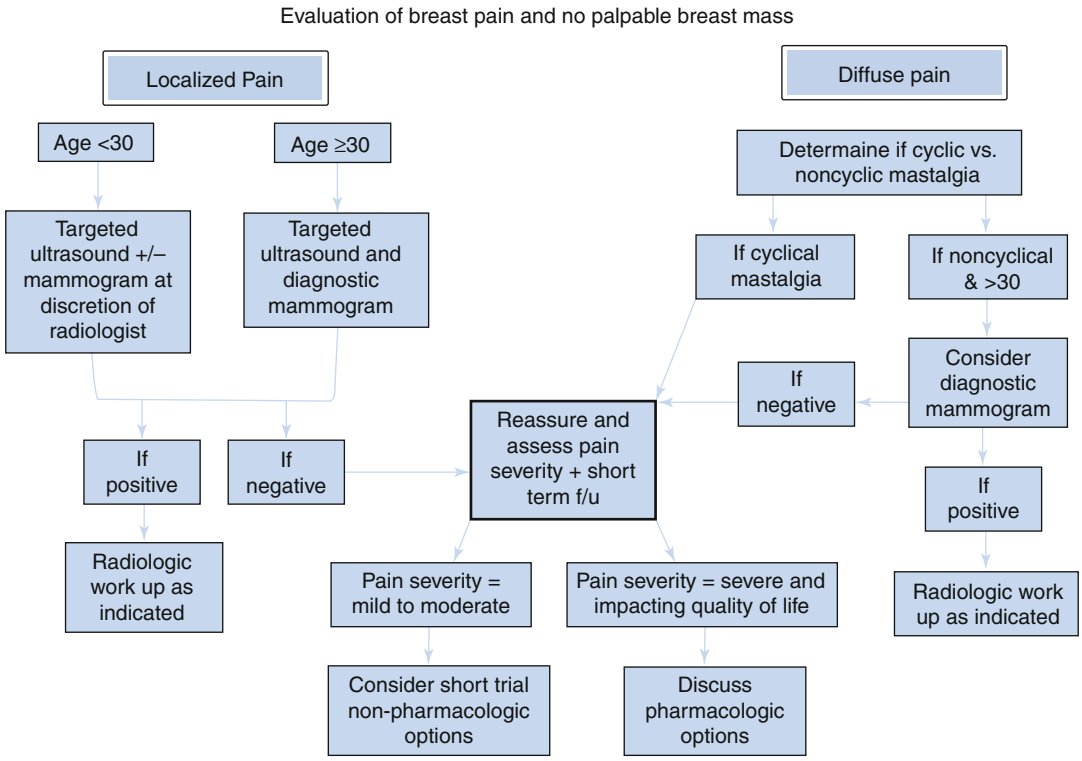

Fig. 4.1 Algorithm: evaluation of breast pain and no palpable breast mass

presenting symptom of breast pain was low for detecting a breast malignancy [3]. Ultrasound is most often ordered as a first-line imaging study primarily to exclude a focal or discrete mass. A study of 110 directed ultrasonographic exams performed for focal breast pain showed no breast cancer, with a benign finding identified at the site of the pain in 18/110 (%) patients [18]. There are no specific laboratory hormonal tests to assist in the evaluation of breast pain other than a pregnancy test if clinically indicated in a woman of reproductive age.

For those patients who are found to have either cyclic or noncyclic mastalgia with negative imaging studies, a short trial of non-pharmacologic therapies may be the logical first step for mild-to-moderate pain. For patients with pain that is clearly impacting their daily quality of life, consideration can be given to pursuing pharmacologic measures as a first-line intervention.

Management Options

The treatment of breast pain requires an individualized approach with careful consideration and understanding of the patient's concerns and its impact upon their quality of life. Often, reassurance that no serious problem underlies the pain is the only intervention required. A minority of women, once reassured, will still require treatment in order to decrease or alleviate symptoms related to the anxiety and uncertainty associated with this often new symptom [19, 20]. Assessing the efficacy of treatment strategies is often clinically challenging as the symptoms may wax and wane, often self-limited. Further complicating the evaluation of therapeutic response is the robust placebo response reported in a number of studies, ranging from 10 to 40 % [21, 22]. Encouraging the use of a symptom diary utilizing a pain scale aids in the choice of therapeutic modalities and the evaluation of efficacy.

Non-pharmacologic Therapies

A number of non-pharmacologic options should first be considered as the initial treatment for both the prevention and treatment of breast pain. These include physical measures, relaxation training, dietary changes, and nutritional supplements. Although evidence-based research on the therapeutic value of these measures is limited, a trial of 3–6 months can certainly be considered, followed by reassessment. It is both reasonable and appropriate to counsel patients presenting with breast pain of mild-to-moderate intensity to try these non-pharmacologic approaches, particularly if the symptoms are interfering with their quality of life.

Physical Measures

Approximately 70 % of women wear a brassiere that does not provide adequate support, is improperly fitted, or has underwiring [23]. For both cyclic and noncyclic breast pain, wearing a well-fitted bra during the day and a soft supporting bra while sleeping can result in an improvement of breast pain. A prospective study comparing danazol to wearing a sports brassiere demonstrated an 85 % relief of symptoms among patients instructed to wear sports brassieres compared to only 58 % relief of symptoms in the group who received danazol [24]. A well-fitted brassiere worn during exercise provides support to Cooper's ligaments which can be impacted by the amplitude of movement especially with activities that involve breast motion (running, aerobics, and walking) [25].

Relaxation Training

There is good evidence regarding the impact of psychological factors and stress as contributors to breast pain, and so, it is important to obtain this as part of the history when evaluating a patient with breast pain. A small study of premenopausal women reporting severe cyclic mastalgia demonstrated higher levels of anxiety and depression compared with women with no symptoms [26]. A psychological assessment may be important to screen for depression, with an appropriate psychological referral considered for further psychiatric consultation and possible intervention. In the circumstance where patients report a high level of stress but are not clinically depressed, implementation of relaxation training into a patient's daily lifestyle may be able to avert psychological distress and possibly prevent breast pain. A study evaluating the use of an audiocassette that discusses progressive muscular relaxation over a 4-week period demonstrated that 61 % of women reported relief of breast pain compared to those who did not use the audiocassette [27].

Dietary Changes

Historically, women have often been counseled to avoid caffeine-containing foods such as coffee, tea, and chocolate as a strategy to decrease or prevent breast pain. However, the data on methylxanthine avoidance (specifically caffeine) has been conflicting.

There have been several trials showing that a caffeine-free diet did not impact symptoms of breast pain [28, 29]. It is postulated that breast pain may be influenced through the effects of caffeine on endogenous hormone levels. Caffeine intake has been found to be associated with altered hormone levels such as elevated plasma estrone, decreased testosterone, and increased sex hormone-binding globulin [30]. A randomized trial assessing caffeine intake and the relationship to fibrocystic changes and nodularity has shown improvement in breast nodularity, but not necessarily a decrease in breast discomfort [31]. For women who do consume moderate-to-heavy caffeine, it is reasonable to discuss reduction of caffeine intake as a preventive intervention.

Nutritional Supplements

The evidence evaluating herbal therapies such as vitamin E and evening primrose oil for management of moderate-to-severe breast pain has

been equivocal. The mechanism of action for vitamin E is primarily through an antioxidant effect and inhibition of the hormonal influence on breast receptors [32, 33]. Evening primrose oil, a nutritional supplement that contains gamma linolenic acid, is speculated to reduce breast sensitivity in women who have a dietary deficiency of gamma linolenic acid [34]. A meta-analysis comparing several pharmacologic therapies versus evening oil of primrose was conducted. In this study, the authors included three randomized placebo-controlled trials of evening primrose oil with the outcomes presented as a mean pain score. The results demonstrated that evening primrose oil compared to placebo showed no benefit in improving the pain score [35].

A small pilot study in premenopausal women was conducted to compare vitamin E alone, evening primrose oil alone versus combining vitamin E with evening primrose oil, and a placebo group for cyclic mastalgia over a 6-month period. The dose of the vitamin E was 400 IU three times per day and evening primrose oil 3,000 IU three times per day. This study demonstrated a trend to improvement in breast pain in all three arms when compared to placebo [36]. A randomized placebo-controlled study of vitamin E 200 IU twice a day versus placebo for cyclic mastalgia demonstrated improvement after two months of treatment, with no additional benefit after 4 months of usage among premenstrual women [32].

Dietary flaxseed is another supplement that has been examined in a randomized placebo-controlled fashion for its effect on cyclic mastalgia. Flaxseed muffins containing 25 g daily consumed for up to four menstrual cycles compared to placebo resulted in a significantly greater degree in breast pain improvement compared to the placebo group and was associated with minimal side-effects [37].

In general, women presenting with mild-to-moderate pain are often more inclined and receptive to a short trial of an herbal supplement before pursuing pharmacologic therapy. The herbal preparations are often better tolerated and considered to be a safe alternative to pharmacologic therapies. Following a short therapeutic trial, follow-up visit and reassessment are prudent, and if no improvement is reported, then the supplement should be discontinued.

Pharmacologic Therapies

In patients who fail to respond to non-pharmacologic measures, consideration should be given to a trial of pharmacologic interventions. First-line interventions for the treatment of breast pain that is related to medication use should include dose and delivery modifications. Postmenopausal hormone therapy has been shown to be associated with breast pain, and the reduction of the estrogen dose may provide a decrease in symptoms [38, 39].

Oral contraceptives may also be associated with breast pain although pain may resolve after completion of a few cycles [2]. If pain persists, a trial of another agent with a lower dose of estrogen may alleviate symptoms. Conversely, oral contraceptives may be used to alleviate symptoms that are related to the cyclicity of the menstrual cycle. Studies evaluating the risk of breast pain in oral contraceptives that contain very low doses of estrogen (ethinyl estradiol 20 mcg) have shown no increased risk when compared with placebo [40]. In women with persistent pain despite a trial of low-dose estrogen preparations, a trial of progestin-only pills or long-acting parenteral progestins may provide relief while still providing adequate contraceptive effect [41].

Danazol

Danazol is the only US Food and Drug Administration-approved medication available for the treatment of breast pain or mastalgia. In numerous clinical trials, 59–92 % of women

treated with danazol reported relief of breast pain [42–55]. Unfortunately, side effects limit the use of danazol, and although dose-related, they are significant enough to cause discontinuation in as many as 15 % of patients. Possible side effects include acne, voice changes, male pattern hair loss, weight gain, mood disturbances, and menstrual irregularity [22]. Luteal phase-only administration of danazol has been shown to provide symptom relief without an increase in side effects when compared to placebo [53, 54].

Dopamine Agonists

Dopamine agonists have shown promising results for the treatment of breast pain with several studies documenting a significant decrease in breast pain in treated patients [56, 57]. The mechanism underlying the efficacy may relate to the impact of dopamine agonists on prolactin secretion. A number of studies have documented the presence of thyrotropin-induced increases in prolactin occurring in women with mastalgia [58, 59]. Bromocriptine has shown efficacy ranging from 47 to 88 % of women studied, but its use is also limited by its side effect profile (GI upset, headache, fatigue). Interestingly, clinical improvement of mastalgia may persist despite discontinuation of bromocriptine [60].

Selective Estrogen Receptor Modulators

The selective estrogen receptor modulators (SERMS) are used in the treatment and prevention of breast cancer. Tamoxifen has been studied in cyclic and noncyclic mastalgia and has demonstrated efficacy in pain reduction with studies revealing a decrease in pain in cyclic mastalgia ranging from 71 to 96 % of women treated and in 56 % of those treated who had noncyclic mastalgia. A number of controlled trials have been conducted assessing the efficacy of treatment with tamoxifen [61–67].

When considering the use of tamoxifen for mastalgia, the risk of side effects must be factored into the decision. Although effective, the risk of significant adverse side effects often outweighs the benefits especially in mild-to-moderate pain. We recommend that tamoxifen be reserved for the treatment of symptoms that are moderate to severe in intensity and have failed more conservative measures. The dose of the tamoxifen used for management of breast pain ranges from 10 to 20 mg per day. Raloxifene, another SERM, has not been specifically studied for efficacy in the treatment of mastalgia (Table 4.4 [61–67]).

Gonadotropin-Releasing Hormone Agonists

The administration of gonadotropin-releasing hormone agonists results in the suppression of pituitary ovarian hormone production. In estrogen-deficient states, women experience improvement in breast pain but experience significant symptoms resulting from the lack of estrogen. Although promising for treatment efficacy, these agents can only be used short term and must be further evaluated to assess their role in the ongoing treatment of mastalgia [3, 68].

Simple analgesics such as nonsteroidal anti-inflammatories or acetaminophen often provide adequate therapy for the treatment of mild-to-moderate breast discomfort and can be recommended for use during periods of pain intensification. They should be considered as first-line therapy and may be used in addition to other agents.

Finally, there is no role for surgical management as a preventive therapy of cyclic or noncyclic mastalgia. For a majority of women, the reassurance that the breast pain is not due to malignancy is often the most effective therapy and uniformly well received [3].

Table 4.4 Clinical trials of tamoxifen for treatment of mastalgia

	No. (%) of subjects responding to intervention					
	Tamoxifen					
Study	10 mg	20 mg	Danazol	Bromocriptine	Placebo	Comments
Fentiman et al. [61]	NE	22/31 (71)	NE	NE	11/29 (38)	Randomized double-blind trial of daily tamoxifen or placebo in 60 subjects with cyclic or noncyclic pain; response (≥50 % decrease in mean pain score) at 3 months. Significant difference between groups ($P<0.025$); 6 in each group stopped study due to adverse effects
Powles et al. [62]	NE	22/25 (88)	20/25 (80)	NE	NE	Randomized trial of tamoxifen 20 mg/d and danazol 100 mg twice daily; agents were of equal efficacy ($P>0.10$), but fewer adverse effects were noted with tamoxifen ($P<0.01$)
Messinis and Lolis [63]	16/18 (89)	NE	NE	NE	6/16 (38)	Randomized trial of tamoxifen or placebo administered from days 5 to 24 for 6 consecutive menstrual cycles; significant difference between groups ($P<0.0001$)
Fentiman, et al. [64]	26/29 (90)	24/28 (86)	NE	NE	NE	Randomized double-blind trial of 10 or 20 mg of tamoxifen daily for 3 or 6 months. Each dosage and duration equally effective[a]; fewer adverse effects in 10 mg compared with 20-mg group (21 % vs 64 %; $P<0.0001$)
GEBM [65]	127/155 (82)	107/142 (75)	NE	NE	NE	Randomized trial of 10 or 20 mg of tamoxifen from days 15 to 25 of menstrual cycle; doses equally effective ($P=$NS) with fewer adverse effects[b] in 10-mg group ($P<0.05$)
Sandrucci et al. [66]	18/20 (90)	NE	NE	16/18 (89)	NE	Randomized, blind trial of tamoxifen 10 mg from days 15 to 25 of menstrual cycle or bromocriptine 7.5 mg/d; agents equally effective ($P=$NS); adverse effects reported as mild and similar
Kontostolis et al. [67]	23/32 (72)	NE	21/32 (66)	NE	11/29 (38)	Randomized trial of tamoxifen 10 mg from days 5 to 24 of menstrual cycle, danazol 100 mg twice daily, or placebo for 6 months. Tamoxifen was more effective than danazol ($P<0.001$), but both were more effective than placebo ($P<0.035$, $P<0.011$, respectively)

Adapted from Smith et al. [3]
GEMB Grupo de Estudio de Mastopatias Benignas, *NE* not evaluated in the study
[a]Relapse occurred in 48 and 39 % of subjects in 10- and 20-mg group at 3 months median time after treatment
[b]Hot flashes, gastrointestinal discomfort, vaginal discharge, ankle edema, and menorrhagia

Conclusion

Breast pain is a very common complaint in women, affecting up to 70 % of women in Western societies during their lifetime. Although frequently concerning and anxiety-producing, it is rarely associated with breast cancer. Simple reassurance is often the only therapy required to alleviate concern and to mitigate pain intensity. If education and reassurance fail to achieve adequate symptom relief, a number of non-pharmacologic and pharmacologic measures have demonstrated efficacy. Selection of a specific agent must be guided by patient expectation, side effect

profile, and severity of symptoms. Ongoing follow-up is necessary as mastalgia often resolves allowing for discontinuation of therapy. Spontaneous remission can occur and therapeutic interventions can lead to long-lasting resolution of symptoms. Further study is needed to assess newer agents for efficacy.

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