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A Study of the Effect of Selective Estrogen Receptor Modulators on Pubertal Gynecomastia and Mastalgia: A Systematic Review

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Abstract

Objectives: Gynecomastia and mastalgia are the most typical clinical breast conditions. This systematic review aims to assess the effect of selective estrogen receptor modulators (SERMs) on pubertal gynecomastia and mastalgia.

Methods: In this review study, online English databases such as PubMed, Scopus, Web of Science, and Cochrane Library were systematically searched without a time limit until January 10, 2025.

Results: Tamoxifen and centchroman are both more effective than placebo in relieving breast pain. Centchroman can reduce the severity of mastalgia by 92-100%. Pain score significantly reduced in the centchroman group compared to the placebo group ($P < 0.0001$). Centchroman and tamoxifen similarly affected pain relief ($P < 0.005$). Tamoxifen was more effective than danzol in relieving breast pain ($P < 0.001$). The effects of tamoxifen were not dose dependent, as 10 mg and 20 mg did not follow a trend, but 10 mg produced significantly fewer side effects. There are inconsistent results when comparing the efficacy of danazol and centchroman at 12 weeks. However, tamoxifen outperformed danazol long-term AT 24 weeks. Four case series were included in the systematic review. Tamoxifen and raloxifene may be effective for the treatment of pubertal gynecomastia. In the first, reduction in breast nodule diameter was 86% in the tamoxifen group and 91%in the raloxifene group. However, a more significant improvement was observed in the tamoxifen group than in the raloxifene group ($P = 0.03$). In the second study, both groups had a statistically significant breast size reduction (tamoxifen group, $P = 0.013$; no treatment group, $P = 0.038$). In the third and fourth studies, the treatment success rate with tamoxifen was calculated to be 86 to 94%.

Conclusions: Mild cyclic mastalgia can be treated by making appropriate lifestyle changes. Moderate to severe mastalgia usually requires medical treatment. Ormeloxifene, tamoxifen, and danazol were all effective in relieving breast pain. Tamoxifen and raloxifene may be effective for the treatment of pubertal gynecomastia.

Keywords: Selective estrogen receptor modulators, Mastalgia, Systematic review, Gynecomastia

Introduction

Gynecomastia and mastalgia are the most typical clinical breast conditions in males (1) and women, respectively (2). These diseases are usually associated with pain, anxiety, psychosocial discomfort, and fear of malignancy (1). The prevalence of gynecomastia (3,4) and mastalgia (5) is reported to be nearly 30%-70%. These diseases are more common during the third and fourth decades of life (6-8), affecting the quality of life (9,10). Most cases of gynecomastia (11) and mastalgia (12) appear to have an unknown etiology. However, it is likely that the hormonal changes that produce hormonal disturbances leading to gynecomastia (13) and mastalgia. Hormonal changes in mastalgia include elevated estrogen, decreased progesterone, elevated ratio of estrogen to progesterone, increased prolactin, diminished FSH and LH secretion, low androgen levels, decreased ratio of unsaturated to saturated fatty acid, and heightened receptor sensitivity. Psychological and nutritional causes, water retention in the body, weight gain, and breast weight are other causes of cyclic mastitis (14). True gynecomastia is a common feature often related to estrogen excess and/or androgen deficiency as a consequence of different endocrine disorders (15).

Various drugs have been used to treat gynecomastia and mastalgia, including oral analgesics, danazol, and selective estrogen receptor modulator (SERM) (16,17). Though many pharmacological treatments have been used in the past, adverse effects have overwhelmed the benefits(18). Some studies showed that tamoxifen is used more than danazol for mastalgia due to its improved therapeutic effects and fewer side effects (19,20).

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Drugs with SERM activity are a more acceptable treatment in a wide spectrum of benign breast disease than the other alternatives due to fewer side effects and good response (18). A growing body of studies has examined the impact of SERMs such as centchroman and tamoxifen on gynecomastia (20,21) and mastalgia (22). Centchroman and tamoxifen have estrogen antagonist activity in the breast (23-25). One possible mechanism of mediation with SERM activity on mastalgia and gynecomastia may be related to their links with hormonal mechanisms. Therefore, this systematic review aims to evaluate the effect of SERMs on pubertal gynecomastia and mastalgia.

Methods

To conduct this review, English online databases such as PubMed, Scopus, Web of Science, and Cochrane Library were systematically searched without a time limit until January 10, 2025. The following keywords were used to find articles about the effects of SERM treatment on mastalgia and gynecomastia: "mastodynia" OR "mastalgia" OR "breast pain" OR "benign breast disorders" OR "gynecomastia" OR "gynecomasty" OR "gynaecomast" AND "tamoxifen" OR "nolvadex" OR "soltamox" OR "evista" OR "raloxifene" OR "fareston" OR "toremifene nolvadex" OR "selective estrogen receptor modulators" OR "SERM" OR "centchroman". The keywords were searched individually and in combination. The bibliography of the articles included in the review was also carefully investigated in order to conduct a complete search. The search results obtained from these five databases were merged, and duplicates (with the same title, year of publication, and authors) were excluded.

Inclusion and Exclusion Criteria

The criteria for including studies in this systematic review were as follows: studies using oral SERM for treating patients with pubertal gynecomastia or mastalgia. Because of the limited number of relevant studies, we included all types of studies as well as reports of case series. Non-English articles were also removed from the study. Summary of conference proceedings, review papers, editorial notes, letters, case reports, and animal studies were also excluded. In cases where several reports from a single study have been published, only one report that contained thorough information was considered, and the rest were excluded. These cases were identified by controlling for the resemblance of the authors' team, the center, the study period, and the statistical results.

Selection of Related Studies

Two independent researchers selected the relevant studies in two stages. The paper titles were first read in the screening stage to decide their inclusion. In case of ambiguity, the abstracts were also examined. The titles and abstracts of the articles were also checked against the inclusion and exclusion criteria. In this case, decision-making was conditional on reading the full text of articles, and they were moved to the second stage. In this stage, the full text of articles was reviewed, and papers that met the inclusion and exclusion criteria were incorporated into a systematic review. Also, all included articles, review papers, and references of articles were meticulously reviewed to ensure the inclusiveness of the search. The study selection process is shown in Figure 1.

Data Extraction

The research team designed the data extraction table, and two researchers reviewed each article. The following data were extracted and reported in a table: author, year of publication, disease types, type of study, number of patients, type of interventions, results, age, and duration (Table 1).

Assessing the Quality of Studies

Two independent investigators implemented quality scales, with disagreements resolved through further discussion. All studies, regardless of quality, were included in the review. The quality of studies was reviewed using the modified Jadad scale (44). In this scale, three criteria of randomization, blinding, and reporting of deleted or missing items are scored for each article. The total score of this scale is between 3 and 5. The quality of each article was evaluated independently by two researchers. Any disagreement regarding the quality of articles was initially resolved by discussion, and in case of disagreement, a third party was consulted (Table 2). The quality of the case series and case reports was measured by the 8-point scale, based on the domains of selection, ascertainment, causality, and reporting outlined by Murad and colleagues (45). The total scale was reported in the current review. Results were also examined regardless of study quality score.

Results

The systematic review included 20 studies. Four case series assessed the effects of SERM on pubertal gynecomastia, and 16 studies assessed the effects of SERM on mastalgia.

SERM on Mastalgia

Several studies evaluated the effect of centchroman on mastalgia. Mohakul et al conducted a clinical trial with a single arm. Patients received 60 mg of centchroman daily, twice a week, for three months after ruling out the risk of breast cancer. 57% experienced no pain at the end of the first month. By the end of the second month, 82% of patients reported no pain, and the majority (92.8%) reported full recovery by the end of the third month ($P < 0.0001$). Meanwhile, 4.8% continued with mild pain, and in 2.4% of patients, no change in pain intensity was observed (38). In Rajswaroob and colleagues' research, 51 patients with mastalgia/fibromatosis received 30 mg centchroman daily for three months. Comparison of

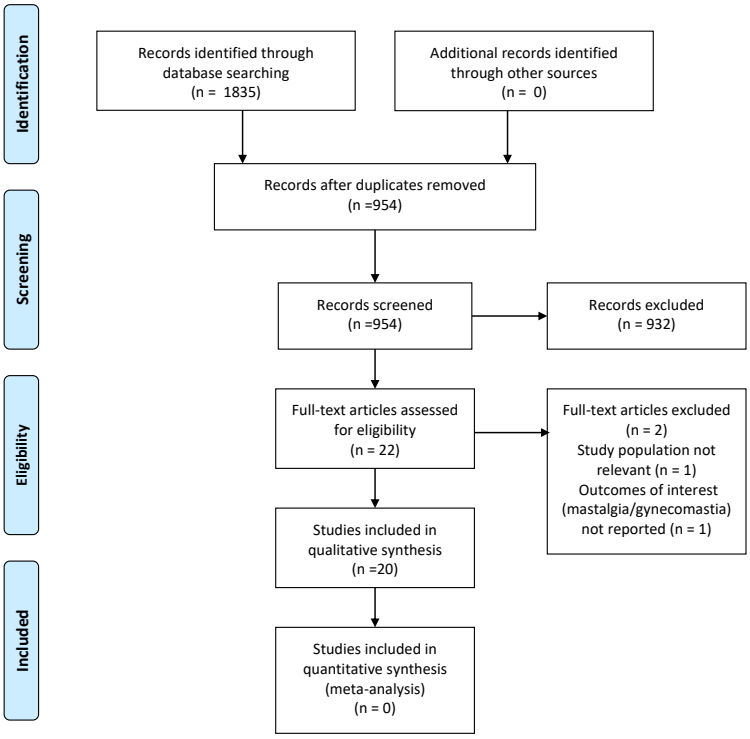

Figure 1. PRISMA Flow Diagram of the Study Selection.

mean scores before and after intervention manifested the effectiveness of centchroman ($P=0.001$) (33). In the study of Bansal et al, patients with mastalgia and fibrocystic (without cancer) received 30 mg of centchroman daily for 3 months. The mean pain intensity reflected a significant decreasing trend ($P<0.001$) from 5.8 to 0.86 (30). In Shrivastava and colleagues' research, patients with mastalgia received 30 mg of centchroman daily for 3 months. In this study, which lasted 24 weeks, the mean pain level declined from 4.72 to 0.51 ($P<0.05$). At week 24, 70% and 24% of patients reported a score of 0 and 2 out of 10, respectively. A total of 151 patients were randomly divided into centchroman and placebo using blocks of size 4 (10). In the study of Kumar et al, in 2013, patients were divided into two groups: 30 mg of centchroman and placebo twice a week for three months. The mean pain level dropped from 5.71 to 0.98 in the centchroman group and from 5.46 to 4.70 in the placebo group. Pain score significantly reduced in the centchroman group compared to the placebo group ($P<0.0001$). The therapeutic effects of tamoxifen lasted up to 6 full months ($P<0.001$) (32).

Three studies compared the effects of danazol and centchroman. In the study of Kumar and Hasan, in 2017, patients were divided into danazol (100 mg) and centchroman (30 mg) for 12 weeks. At 1 and 4 weeks, danazol (n = 30) was more effective in relieving mastalgia than centchroman (n = 34). While at 12 weeks, centchroman (86%) was more effective ($P<0.005$) in relieving mastalgia than danazol (71%) (31). In Neogi and colleagues' study, patients older than 25 with at least 3 months of mastalgia were included. Centchroman (20 mg) was more effective ($P<0.001$) than danazol (200mg) at 24 weeks (26). In Khanna and colleagues' study, 120 patients were divided into three groups: danazol (50 mg), centchroman (30 mg), and placebo bid for 3 and 6 months. Centchroman was as effective as danazol in relieving pain at 12 weeks ($P=0.6$), but centchroman was more effective than danazol ($P=0.027$) at 24 weeks (37).

Several studies assessed the effect of tamoxifen on mastalgia. Semiglazov et al, 82% of patients in the tamoxifen group (10 mg) and 75% in the tamoxifen group (20 mg) reported two degrees of pain relief. Both doses reduced breast pain. However, the two groups had no significant difference (39). In Messinis and Lolis' study, 36 patients were divided into three groups and received daily tamoxifen (10 mg) and placebo for 6 months. Tamoxifen is more effective ($P<0.001$) than placebo in relieving breast pain. Twelve months after the end of tamoxifen treatment, 53% women receiving tamoxifen were still asymptomatic, compared to none of the patients treated with placebo ($P<0.001$). These results suggest that tamoxifen could be highly effective for managing severe recurrent mastalgia (36).

Two studies compared the effects of danazol and tamoxifen. In Kontostolis et al, patients were divided into three groups and received daily danazol (100 mg), tamoxifen (10 mg), and placebo for 6 months. 72% of subjects received tamoxifen, 65% received danazol, and 38% received a placebo. Three months after treatment, 53% of women receiving tamoxifen were still asymptomatic compared to 37% of patients treated with

Table 1. Characteristics of Studies Included in the Systematic Review

Authors/ Country/ Years	Type of Study	Disease Types	Age (y)	Number of Subjects	Type of Intervention	Control Group	Duration	Results
Shrivastava et al, 2017 (10)	Clinical trial	Mastalgia	50-20	63	Centchroman 30 mg daily for up to 3 months	-	3 months	10 and 20 mg doses of tamoxifen were compared. Patients received tamoxifen between 15 and 25 days of the menstrual cycle. 85% of patients in the tamoxifen group (10 mg) and 75% in the tamoxifen group (20 mg) reported two degrees of pain relief. There was no statistically significant difference between the two groups.
Neogi et al, 2019 (26)	Clinical trial	Mastalgia	More than 25 years	78 patients	Centchroman 30 mg daily Danazol 200 mg daily Tamoxifen 20 mg daily	Placebo	One week 4, 12, and 24 weeks follow-up	Tamoxifen and centchroman were more effective than danazol in relieving pain after 24 weeks ($P < 0.001$), while centchroman and tamoxifen had comparable results ($P > 0.05$).
Khadka et al , 2019 (27)	Clinical trial	Mastalgia	20-49	106 patients	Centchroman 30 mg, Tamoxifen 10 mg daily	Placebo	3-month therapy and a 6-month follow-up	Centchroman was not inferior to tamoxifen in terms of relieving breast pain (P=0.33)
Jain et al, 2015 (28)	Clinical trial	Mastalgia	Aged >18 years	60 patients	Centchroman was administered 30 mg daily, and group B received tamoxifen at 10 mg daily.	Tamoxifen	12 weeks 4-, 8-, 12, and 24-week follow-up	The mean pain scores did not reflect a significant difference between the meloxicam and tamoxifen groups (4.15 ± 2.78 and 3.04 ± 3.01; $P = 0.18$)
Dhar et al, 2018 (29)	Clinical trial	Mastalgia	Reproductive age	84	Centchroman 30 mg daily	Tamoxifen 10mg daily	3 months	Pain intensity dropped significantly in the centchroman group compared to the tamoxifen group ($P = 0.001$)
Bansal et al, 2015 (30)	Clinical trial	Mastalgia	20 –50 years	203 patients	Oral centchroman 30 mg	One arm	3 months 1, 2, 3, and 6 months.	The mean pain intensity decreased from 5.8 to 0.86 ($P < 0.001$).
Kumar and Hasan, 2017 (31)	Prospective study	Mastalgia	12-44 years	64 patients	Centchroman 30 mg daily	Danazol 100 mg daily	3 Months	Centchroman (86%) was more effective in relieving mastalgia than danazol (71%).
Kumar et al, 2013 (32)	Clinical trial	Mastalgia	12-44 years	151 patients	Centchroman 30 mg daily	Placebo	3 Months	The mean pain level dropped from 5.71 to 0.98 in the ormeloxifene group and from 5.46 to 4.70 in the placebo group ($P < 0.001$).
Rajswaroob, et al, 2016 (33)	Clinical trial	Mastalgia	26-35 years	51 patients	Centchroman 30 mg daily	One arm	3 months and followed up weekly for 6 months	Comparison of mean scores before and after intervention showed the effectiveness of centchroman ($P = 0.001$)
Sinha et al, 2024 (34)	Clinical trial	Mastalgia	36.5 ± 9.	51 patients	Tamoxifen 10 mg	Centchroman 30mg daily	3 Months	Compared with tamoxifen, centchroman appeared superior in relieving pain in the first month ($P = 0.04$). However, no significant difference in pain score was reported in the third or sixth month.
Kontostolis, et al, 2009 (35)	Clinical trial	Mastalgia	-	93 patients	Tamoxifen 10 mg daily, danazol 100 mg twice daily	Placebo	6 months	Comparison of mean scores between the three groups revealed that tamoxifen was more effective than danazol and placebo ($P <0.001$).

Table 1. Continued

Authors/ Country/ Years	Type of Study	Disease Types	Age (y)	Number of Subjects	Type of Intervention	Control Group	Duration	Results
Messinis and Lolis 1988 (36)	Clinical trial	Mastalgia	25-38	36 patients	Tamoxifen (10 mg daily)	Placebo	6 months	Comparison of the mean score between the two groups showed that tamoxifen was more effective than placebo ($P < 0.001$).
Khanna et al, 2019 (37)	Clinical trial	Mastalgia	20-50	120 patients	Centchroman 30 mg Danazol 50 mg bid for 3	Evening Primrose Oil 1000 mg bid	3 months	Evening promiscuity was more effective than centchroman at three-month (P = 0.02) and 6-month ($P < 0.001$) follow-up.
Mohakul et al, 2017 (38)	Clinical trial	Mastalgia	21 to 55	84 patients	Centchroman 60 mg twice weekly on day 1 and day 4 of the week	One arm	3 months end of the first, second, and third months of the treatment follow-up	57% had no pain at the end of the first month. 82% had no pain at the end of the second month, and 92.8% had no pain at the end of the third month. Also, 4.8% continued to have mild pain. In 2.4%, no change in intensity was observed.
Semiglazov, 1997 (39)	Clinical trial	Mastalgia	15 to 25	301	Tamoxifen 10 mg daily	Tamoxifen 20 mg daily	30 months	Pain intensity was significantly reduced, but the side effects of 10 mg tamoxifen were lower.
Dhar et al, 2023 (40)	Clinical trial	Mastalgia		93 patients	Centchroman 30 mg twice (group 1); 30 mg thrice a week (group 2)	Tamoxifen 10 mg daily,	3 months with a follow-up of 3 more months	Centchroman, 30 mg twice or thrice a week, was as effective as a daily dose of tamoxifen 10 mg in relieving pain.
Lawrence et al, 2004 (41)	Retrospective case series	Pubertal gynecomastia	14.6 years	38 patients	Tamoxifen 10 to 20 mg orally twice a day; Raloxifene 60 mg orally once daily	No treatment	3–9 months	Reduction in breast nodule diameter was 86% in the tamoxifen group and 91%in the raloxifene group
Derman et al, 2004 (42)	Case series	Pubertal gynecomastia	10–15	22	10 or 20 mg bid for	No treatment	4–40 months	Reduction was 100% in the tamoxifen group compared to 75% in the Control group.
Sabanci et al, 2022 (43)	Retrospective, case series	Pubertal gynecomastia	14.12	83 male adolescents	Tamoxifen	One arm	1–8 months	The gynecomastia disc diameter was significantly reduced in patients with an initial disc diameter ≥3 cm.
Alagaratnam 1987 (21)	Retrospective, case series	Pubertal gynecomastia		12 patients	Tamoxifen	One arm	1–4 months (2.4)	Complete regression was observed in 86% of patients, and recurrence was a 14 % rate.

Table 2. Assessment of the Quality of Studies Using the Jadad Scale

Author	Randomization			Blinding			Sample
	Mention Randomization	Method: Appropriate	Method: Inappropriate	Mention Blinding	Method: Appropriate	Method: Inappropriate	Account of All Patients
Dhar et al, 2018 (46)	+	?	?	-	-	-	+
Khadka et al, 2019 (27)	+	?	?	-	-	-	+
Jain et al, 2015 (28)	+	+	-	?	?	?	+
Bansal et al, 2015 (30)	-	-	-	-	-	-	+
Kumar et al, 2013 (32)	+	+	-	+	+	-	+
Kumar and Hasan, 2017 (31)	+	?	?	?	?	?	+
Kontostolis et al, 2009 (35)	+	+	-	?	?	?	+
Messinis and Lolis, 1988 (36)	-	-	-	-	-	-	+
Neogi et al, 2019 (26)	-	-	-	-	-	-	+
Khanna et al, 2019 (37)	+	+	-	?	?	?	+
Sinha et al, 2024 (34)	+	+	-	+	+	-	+
Dhar et al, 2023 (40)							
Semiglazov et al, 1997 (39)				One arm			
Mohakul et al, 2017 (38)				One arm			
Rajswaroob, et al, 2016 (33)				One arm			
Shrivastava et al, 2017 (10)				One arm			

+ → The item was met.
– → The item was not met.
? → Unclear, not reported, or insufficient information to judge.

danazol ($P<0.001$). The results indicate tamoxifen is a highly effective and cost-effective drug for managing severe cyclic mastalgia (35). In Neogi and colleagues' study, tamoxifen (20 mg) was more effective than danazol ($P<0.001$) at 24 weeks (26).

Several studies compared tamoxifen and centchroman. In Khadka and colleagues' study, 106 women with mastalgia were randomly assigned to three groups: tamoxifen (10 mg), centchroman (30mg), and placebo for 3 months. 96.2% of patients in the centchroman group and 92.5% in the tamoxifen group responded to treatment after 3 months. Centchroman was not inferior to tamoxifen in relieving breast pain ($P=0.33$) (27). In Jain et al study, women with mastalgia were randomly divided into two groups: group A received 30 mg of centchroman daily, and group B received 10 mg of tamoxifen daily for 12 weeks. The women were followed up for another 12 weeks without receiving any relief medication during this period. The share of women who reported pain relief at 4, 8, 12, and 24 weeks was identical in the two groups. The mean pain score did not differ significantly between centchroman and B groups ($P=0.18$). After discontinuing treatment at 12 weeks, a partial recurrence was observed after 24 weeks (28). In Neogi and colleagues' study, patients older than 25 with at least 3 months of mastalgia were included. 78 patients were divided into four groups: centchroman (30 mg/daily), danazol (200 mg/daily), tamoxifen (20 mg/daily) and placebo. Centchroman and tamoxifen had a similar effect on pain relief ($P<0.005$) at 4 and 12 weeks (26). In the study by Sinha et al, 51 women with mastalgia were randomly assigned to two groups for 3 months. In comparison with tamoxifen(10 mg), centchroman (30 mg) appeared to be superior in relieving pain in the first month ($P=0.04$). However, no significant difference in pain score was reported in the third or sixth month. The recurrence rate at the sixth month was also not different ($P=0.41$) (34). In Dhar and colleagues' study in 2023, women with mastalgia were randomly assigned to three groups: tamoxifen 10 mg daily (group 1), centchroman 30 mg twice a day (group 2), and centchroman 30 mg three times a week (group 3) for 3 months with a follow-up of 3 more months. Centchroman in dosages of 30 mg twice or thrice a week was as effective as a daily dose of 10 mg of tamoxifen in relieving pain (40). In a study by Dhar et al in 2018, patients with mastalgia and adenoma fibers were randomly divided into tamoxifen 10mg and centchroman 30 mg. Patients received interventions for 3 months and were followed up for 6 months. 66% of patients treated with centchroman and 43% treated with tamoxifen reported pain severity <2. Pain intensity dropped significantly in the centchroman group compared to the tamoxifen group ($P=0.001$) (29).

SERM on Pubertal Gynecomastia

In Lawrence and colleagues' study, with a study quality score of 6, patients (n=38) with persistent pubertal gynecomastia received an estrogen receptor modifier (tamoxifen or raloxifene) for 3- to 9-month. The mean reduction in breast nodule diameter was 2.1 cm (95% CI 1.7, 2.7) with tamoxifen, while it was 2.5 cm (95% CI 1.7, 3.3) with raloxifene. Reduction in breast nodule diameter was 86% in the tamoxifen group and 91% in the raloxifene group. However, a more significant improvement was observed in the tamoxifen group than in the raloxifene group ($P=0.03$). No side effects were seen in any patients (41). In the Derman et al study with a study quality score 5, there was a statistically significant breast size reduction in both groups (tamoxifen group, $P=0.013$) and (no treatment group, $P=0.038$). Reduction was 100% in the tamoxifen group compared to 75% in the control group. However, a significant decrease was observed only in serum SHBG level in the no treatment group ($P=0.012$) but not in the first group ($P=0.169$) (42). In the Sabancı et al study, with a study quality score of 6, the mean treatment duration with tamoxifen was 4.1 ± 2.01 (1–8) months. The gynecomastia disc diameter was significantly reduced in patients with an initial disc diameter ≥3 cm. The reduction of the disc started significantly after the fourth month of tamoxifen treatment, and the reduction continued significantly to the sixth month ($P<0.01$). Treatment success was 94% (43). In Alagaratnam, with a study quality score of 5, patients (n=14) of puberty gynecomastia treated with tamoxifen over a mean period of 2.4 months. Complete regression was observed in 86% of patients, and recurrence was a 14 % rate. No side effects were reported during the use of tamoxifen (21).

Discussion

According to the current systematic review, moderate to severe mastalgia usually requires medical treatment. Centchroman and tamoxifen are effective in relieving breast pain, and tamoxifen and raloxifene may be effective for the treatment of pubertal gynecomastia. Several studies have compared the effects of intervention before and after the intervention. According to their results, centchroman can reduce the severity of mastalgia by 92-100% (30,33,38,46,47).

Ting et al recorded complete resolution of gynecomastia in 78.2% of the tamoxifen group (20 mg/d) and 40% in the danazol group (400 mg/d) (20). Consistent with our systematic review, Lapid et al (48) conducted a systematic review to compare the effect of tamoxifen in improving idiopathic pubertal gynecomastia. They concluded that tamoxifen had a significant benefit for treating pubertal gynecomastia. The etiology of mastalgia is not precisely known, but hormonal, metabolic, and psychological factors, among other things, are assumed to be involved. Inadequate corpus luteum function, decreased progesterone production, or greater estrogen production compared to progesterone may also be involved. Other hormonal stimuli, such as overproduction of aldosterone by retention fluids or elevated serum prolactin during the

luteal phase, have been implicated in the pathophysiology of premenstrual syndrome. The hormone manipulations that suppress LH hormone and ovulation are effective in treating periodic mastalgia (35).

Mild cyclic mastalgia can be treated by adopting appropriate lifestyle measures. Moderate to severe mastalgia usually requires medical treatment.

All studies except one (29) showed identical efficacy of tamoxifen and centchroman. Reasons for these discrepancies are unclear but could be related to differences in inclusion criteria, statistical method, and length of follow-up. There are inconsistent results when comparing the efficacy of danazol and centchroman at 12 weeks. However, tamoxifen outperforms danazol long-term at 24 weeks. That could be explored in pharmacological or patient factors. Danazole use is known to be associated with significant side-effects, including amenorrhea, weight gain, acne, etc, forcing clinicians to try other medications. Centchroman is well tolerated by patients. Moreover, practically, there was no undesirable side effect (49,50).

Ghassab-Abdollahi et al (22) did a systematic review about the effects of raloxifene on mastalgia by searching Cochrane, Medline (PubMed), Embase, ProQuest, and ClinicalTrials.gov libraries. Thirteen articles were included in this review study. Their results suggested inadequate evidence to evaluate the effects of raloxifene on mastalgia. They suggested well-designed experimental studies in the future to compare the effects of a placebo or other RCT drugs on mastalgia. There are divergent findings about the efficacy of tamoxifen and centchroman. However, side effects in patients receiving meloxifen, especially the development of ovarian cysts, are of great concern (28). The lower cost of tamoxifen compared to other drugs is due to the greater effectiveness of centchroman (27). The results of various studies on tamoxifen intake have demonstrated that patients in whom tamoxifen is effective experience a reduction in pain and tenderness over one month. Nikbakhsh and colleagues' paper on the effect of tamoxifen in the treatment of tenderness caused by gynecomastia concluded that treatment with tamoxifen was associated with decreased breast tenderness and reduced breast size (51). The results of various studies have shown that among drugs used for the treatment of mastalgia, tamoxifen is more popular than danazol and bromocriptine due to its greater therapeutic effects and fewer side effects (19).

The main etiology of mastalgia is unknown. Cyclic mastalgia appears around 30, while non-cyclic mastalgia usually manifests at 41. The fact that cyclic mastalgia improves with hormonal changes such as menopause, pregnancy, and lactation may explain the hormonal cause of mastalgia (52). A study by Groen et al suggested that patients with cyclic and non-cyclic mastalgia with persistent pain or inadequate pain relief should be treated with SERMs such as tamoxifen and centchroman (for non-cyclical pain) (53).

Singh et al in a comparative study of the effect of oral and topical tamoxifen in mastalgia treatment, stated that topical tamoxifen is associated with fewer side effects and recurrences in reducing breast pain and breast nodularity (54).

The authors also compared these two drugs, centchroman and tamoxifen, in terms of cost-effectiveness. Mastalgia relief cost 393 nepalese rupees in the centchroman group and 311.5 in the tamoxifen group. In general, they concluded that tamoxifen is more cost-effective than centchroman. Tamoxifen should be considered the drug of first choice because of its high efficacy, high tolerance with minimal side effects, and low cost (27). These findings support the cost-effectiveness of implementing tamoxifen in clinical practice for mastalgia.

Limitations and Suggestions for Future Studies

The first limitation of the review is that we have not conducted a meta-analysis with these data due to heterogeneity, paucity, and inadequate reporting of data (some studies did not report mean and standard deviation, some reported mean without standard deviation, and some reported improvement as a percentage) and outcome measures. Therefore, a narrative synthesis was chosen over a quantitative approach. The second limitation is that some non-English papers may have been excluded since the search was conducted in English. The third limitation is that data on pubertal gynecomastia is limited to four case series, a weak evidence base for a systematic review. The fourth limitation is that some studies included in this systematic review were of low methodological quality. The main drawbacks were the lack of adequate reporting of random allocation sequences or blinding and the lack of intention for treatment analysis. Moreover, some studies were not conducted as clinical trials, which posed the risk of bias in results. Future studies should be designed and reported based on CONSORT protocols. Data must be fully reported as means and standard deviations before and after the intervention. Other limitations were the small number of studies and their low sample size, which reflects the need for further studies with a larger sample size. Besides, in some published studies, no placebo had been used.

Conclusions

Mild cyclic mastalgia can be treated by making appropriate lifestyle changes. Moderate to severe mastalgia usually requires medical treatment. Centchroman, tamoxifen, and danazol were all effective in relieving breast pain. The effects of tamoxifen are also not dose-dependent. Tamoxifen and centchroman may effectively treat pubertal gynecomastia based on weak evidence (case series). The findings of these studies should be interpreted with caution due to their heterogeneity, small number of studies, and sample size.

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Conflict of Interests

None to declare.

Ethical Issues

Not applicable.

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