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# An observational study comparing ormeloxifene with evening primrose oil for benign breast diseases

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## ABSTRACT

**Background:** Fibroadenosis, popularly termed aberrations of normal development and involution (ANDI), is by far the most common female breast presentation to a surgeon. ANDI accounts for the most common breast lumps in women <30 years of age. Mastalgia, a significant spectrum of ANDI, is usually classified as (1) cyclical mastalgia (more common) and (2) non-cyclical mastalgia. Breast nodularity, the other spectrum of ANDI may either present as a predominant feature or coexist with mastalgia. **Aims and Objectives:** The aims of this study were to comparatively study ormeloxifene and evening primrose oil with respect to regression of fibroadenosis and mastalgia and evaluate their side effects. **Materials and Methods:** This prospective study was conducted in the Department of General Surgery of Calcutta National Medical College and Hospital, Kolkata from February 15th, 2021 to February 14th, 2022, after obtaining prior Institutional Ethical Committee Clearance. Two hundred and eighty patients were equally divided into two groups of 140 in each and screened for inclusion in this study. **Results:** At the start of treatment, Group A (Ormeloxifene) presented with a mean visual analog scale (VAS) score value of 5.71, while patients of Group B presented with a similar mean VAS score value of 5. Group B recorded a VAS score of 4.50 at the end of the 6th month, while Group A recorded a significant downhill slope of negligible mean VAS score value of 0.80 at the of the 6th month. In breast nodularity gradings too, Group A showed significant down staging of grades returning, 95% confidence interval at the end of 6th month as 1.144, while 2.280 was recorded for Group B. **Conclusion:** Benign breast disease is a common presenting problem in females of reproductive age. Ormeloxifene can be a better alternative to evening primrose oil in both cyclical and non-cyclical types of mastalgia. Larger trials are however required, to finally conclude on.

**Key words:** Fibroadenosis; Fibrocystic breast disease; Mastodynia

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## INTRODUCTION

Fibroadenosis, popularly termed aberrations of normal development and involution (ANDI), is by far the most common female breast presentation to a surgeon. ANDI accounts for the most common breast lumps in women <30 years of age and rates as the most common solid tumor of female breast of all ages.[1] Hormonal therapy of ANDI with tamoxifen and danazol is the common treatment modality, though both claim to reduce volume of fibroadenomas/fibroadenotic nodularities by a meager 20%.

Mastalgia (Greek: Masto-breast and algia-pain), a significant spectrum of ANDI, is usually classified as (1) cyclical mastalgia (more common) and (2) non-cyclical mastalgia.[2] Breast nodularity, the other spectrum of ANDI may either present as a predominant feature or coexist with mastalgia. This non-carcinogenic breast lump is frequently found connected with female hormonal changes of menstrual

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cycle.[3] Courtillot et al., in 2005, found (postmortem) that half of all women suffer from some form of fibrocystic breast disease and one-fifth of them present with fibroadenomas during their life-time.[4]

The popular drugs used till date for ANDI do not comply with the norms of cost-effectiveness. Few literature is available till date comparing ormeloxifene with evening primrose oil. Our present study has been conducted as a non-randomized prospective observational study comparing ormeloxifene with evening primrose oil for regression of fibroadenosis and mastalgia.

### Aims and objectives

The aims of this study were to comparatively study ormeloxifene and evening primrose oil with respect to regression of fibroadenosis and mastalgia and evaluate their side effects.

## MATERIALS AND METHODS

This prospective study was conducted in the Department of General Surgery of Calcutta National Medical College and Hospital, Kolkata from February 15, 2021, to February 14, 2022, after obtaining prior Institutional Ethical Committee Clearance. Two hundred and eighty patients were equally divided into two groups of 140 in each and screened for inclusion in this study. All the patients presented with mastalgia as well as breast nodularities. High-resolution ultrasonography of both breasts and axillae coupled with ultrasound-guided fine-needle aspiration cytology (FNAC) was used as a diagnostic tool. Further, ultrasound examination of the abdomen was mandatorily done for all to rule out ovarian and cervicouterine pathologies. Patients (280), who fulfilled the inclusion criteria were divided as Group A (140), who received Ormeloxifene 30 mg every alternate day for a period of 3 months and Group B (140), who received evening primrose oil 1000 mg, twice daily for a period of 3 months. All patients were taught before the start of the study as to how to mark the mastalgia visual analog scale (VAS) chart. The breast ultrasound examination was repeated on 1$^{st}$, 2$^{nd}$, 3$^{rd}$, and at the end of 6$^{th}$ month. All the findings of both the groups were recorded following clinical breast examination at start of study, end of 1$^{st}$, 2$^{nd}$, 3$^{rd}$, and 6$^{th}$ month. Results of VAS score and ultrasound nodularity grading were compared using Odds Ratio and Confidence Interval (CI) (95%).

### Inclusion criteria

All patients with mastalgia and breast nodularity in the age group of 20–50 years, presenting to the surgery outdoors were included the study.

### Exclusion criteria

The following criteria were excluded from the study:

- Pregnant, lactating, and pregnancy planning women in the study age group
- Breast malignancy or familial history thereof
- Patients with polycystic ovarian disease or cervicouterine diseases
- Those who did not agree with the treatment regime.

## RESULTS

This study included 280 patients having both mastalgia and breast nodularity. One hundred patients of both Group A and Group B were between 20 and 35 years of age and 40 patients of each group ranged between 35 and 50 years of age.

Ultrasonography of both breasts was done for all 280 patients coupled with FNAC, to confirm the diagnosis and record the changes of breast nodularity following the treatment protocols for both Group A and Group B (Table 1).

Similarly, the visual analog scale scores, for mastalgia pain, were recorded from the individual VAS charts of both groups to arrive at a mean VAS score.

(Figure 1), displaying the response to the treatment meted out for both groups depicted in (Figure 2) as, at the beginning (A), end of 1$^{st}$ month (B), 2$^{nd}$ month (C), 3$^{rd}$ month (D), and 6$^{th}$ month (E).

As regards side effects, 30 patients of Group A, (21.42%) complained of scanty flow and delayed menstrual cycles, which got rectified spontaneously on cessation of therapy. No other significant side effects were reported. Patients of Group B did not report any significant side effects.

At the start of treatment Group A (Ormeloxifene) presented with a mean VAS score value of 5.71, while patients of Group B presented with a similar mean VAS score value of 5.6. After onset of therapy, at the end of 1$^{st}$ month, Group A showed significant reduction of mastalgia recording a mean VAS score of 4.00, while Group B recorded 4.90. Gradual reduction was seen in Group B, which recorded a VAS score mean value of 4.50 at the end of the 6$^{th}$ month. Group A, recorded a significant downhill slope recording a negligible mean VAS score value of 0.80 at the of the 6$^{th}$ month (Figure 1).

The breast nodularity gradings were recorded using ultrasound examinations of both breasts, at initial and subsequent 1$^{st}$, 2$^{nd}$, 3$^{rd}$, and 6$^{th}$ month end visits (Figure 2a-e). Group A showed significant downstaging

**Table 1: Frequency (probability) of breast nodularity grades in patients receiving ormeloxifene and EPR oil at initial and subsequent visits**

| Ormeloxifene | Grades of nodularity | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 6 |
| Start | 10 (0.071) | 50 (0.357) | 40 (0.286) | 30 (0.214) | 10 (0.071) |
| 1 months | 30 (0.214) | 60 (0.429) | 25 (0.179) | 20 (0.143) | 5 (0.035) |
| 2 months | 50 (0.357) | 50 (0.357) | 20 (0.143) | 15 (0.107) | 5 (0.035) |
| 3 months | 70 (0.500) | 50 (0.357) | 15 (0.107) | 5 (0.035) | 0 (0.000) |
| 6 months | 90 (0.643) | 38 (0.271) | 10 (0.071) | 2 (0.014) | 0 (0.000) |
| **EPR oil** | **Grades of nodularity** | | | | |
| | 1 | 2 | 3 | 4 | 6 |
| Start | 10 (0.071) | 60 (0.429) | 40 (0.286) | 20 (0.143) | 10 (0.071) |
| 1 months | 20 (0.143) | 70 (0.500) | 30 (0.214) | 15 (0.107) | 5 (0.035) |
| 2 months | 25 (0.179) | 70 (0.500) | 35 (0.250) | 8 (0.057) | 2 (0.014) |
| 3 months | 29 (0.207) | 69 (0.493) | 35 (0.250) | 6 (0.043) | 1 (0.007) |
| 6 months | 31 (0.221) | 69 (0.493) | 34 (0.243) | 5 (0.035) | 1 (0.007) |

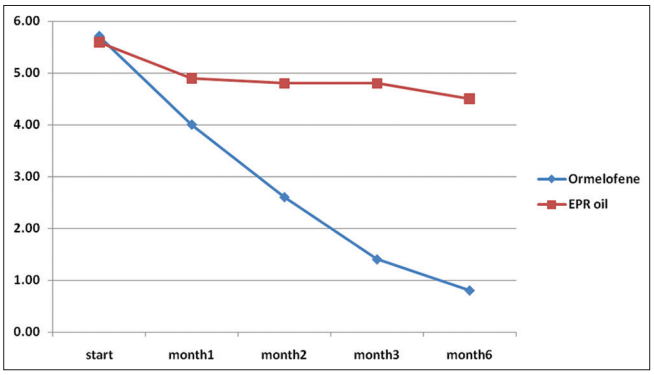


**Figure 1:** Mean visual analog scale VAS score between Group A (Ormeloxifene) and Group B (Evening Primrose oil)

of grades. At the initial visit, ten patients had grade 1 nodularity, 50 patients had grade 2, 40 patients had grade 3, 30 patients had grade 4, and 10 patients showed grade 5 nodularity. At the end of 6th month 90 of the patients had downgraded to grade 1, 38 patients recorded grade 2, ten patients recorded grade 3, only two patients had grade 4 nodularity, and none reported with grade 5 nodularity (Table 1). All the patients of Group A recorded significant improvement with nodularity downgrading. Group B patients, who received evening primrose oil at start, had ten patients in grade 1, 60 patients in grade 2, 40 patients in grade 3, 20 patients in grade 4, and ten patients in grade 5. At the end of 6th month, only 31 patients recorded grade 1 nodularity, 69 patients were in grade 2, 34 patients in grade 3, five patients in grade 4, and one patient in grade 5 (Table 1). The 95% CI at the end of 6th month was 1.144 for Group A and 2.280 for Group B, returning an Odds Ratio of 1.712, with a statistically significant P<0.0001 (Table 2).

**Table 2: Odds ratio, confidence interval (95%), and significance of nodularity in each successive visit**

| Visit | Estimate odds ratio (OR) | 95% CI | P-value |
|---|---|---|---|
| Start | 0.140 | −0.326, 0.606 | 0.556 |
| 1 months | 0.474 | 0.031, 0.917 | 0.036 |
| 2 months | 1.385 | 0.904, 1.866 | <0.0001 |
| 3 months | 1.607 | 1.110, 2.114 | <0.0001 |
| 6 months | 1.712 | 1.144, 2.280 | <0.0001 |

## DISCUSSION

Our study aimed to observe the effects of both ormeloxifene and evening primrose oil on the frequently attending surgery outdoor female patients troubled with fibroadenosis, which is an observational type of study. The dosage schedule followed in this study is the most widely accepted drug regimen. Kaur et al., in 2012, published a study, where 76% of patients attending surgery outpatients services for breast conditions (benign), turned out to have ANDI.[5] Way back in 2004, Smith et al., documented while evaluating patients of mastalgia that the risk of cancer with mastalgia as a solitary symptom was extremely low and on proper clinical evaluation were found to favorably respond to reassurance and pharmacological measures.[6] In the present study, we similarly had not observed any single patient that presented with the symptoms of mastalgia develop into malignancy. Kataria et al., in 2013, did a systematic review of understanding and management of mastalgia concluding antiestrogen therapy (centchroman), as being more effective when compared with evening primrose oil.[7] Similarly, Nigam et al., in a prospective comparative study of 90 consecutive patients of mastalgia, found ormeloxifene to be more effective than evening primrose oil in the treatment of mastalgia in the long term.[8] Uma et al., in 2004, noted in a small number of patients labeled as refractory mastalgia, where >94% turned out to respond with dietary modifications coupled with reassurance.[9] In a large (n=1000) observational study in Pondicherry, India, Janaki et al., in 2016, showed that self-breast examination to be poorly understood and clinical breast examination is

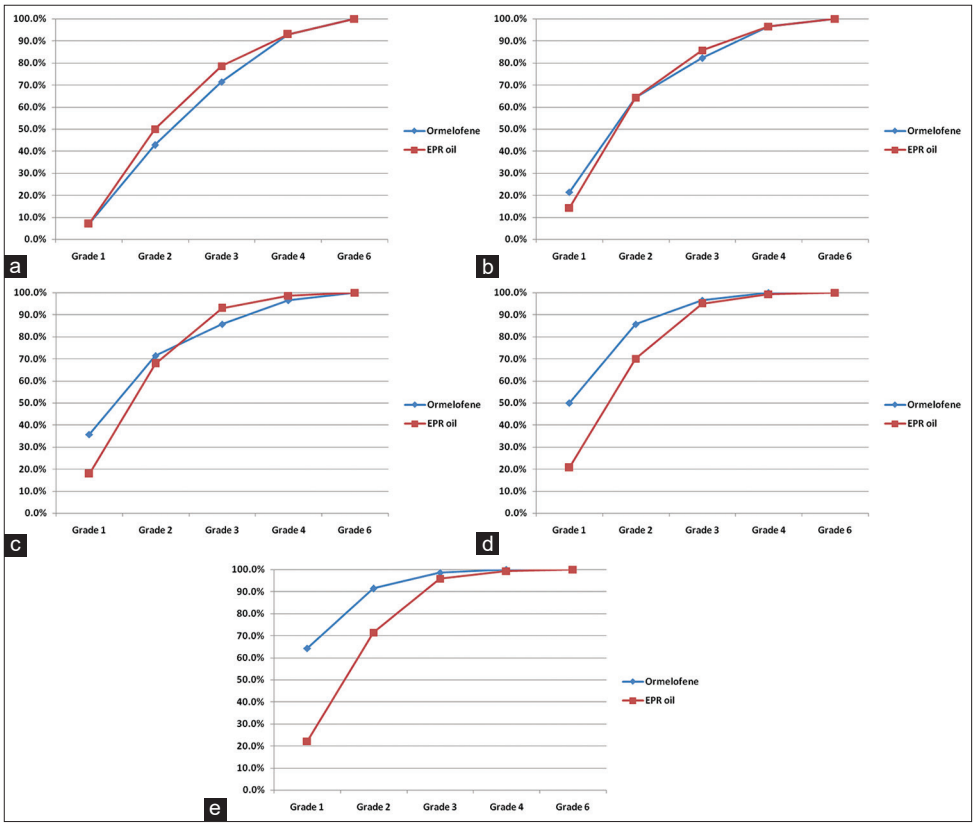


**Figure 2:** Cumulative percentage of breast nodularity grading in ormeloxifene versus EPR oil. (a) At the beginning, (b) at the end of 1st month, (c) at the end of 2nd month, (d) at the end of 3rd month, and (e) at the end of 6th month

still the gold standard and more fruitful in combination with USG and FNAC.[10] Evening primrose oil (*Oenothera biennis*), derived from evening primrose seeds, is a rich source of omega-6 essential fatty acids. It is commonly used as an alternative therapy in mastalgia and ANDI. Bayles and Usatine in 2009 noted that, though well tolerated, most trials have come up with not so satisfactory results.[11] Nigam et al., in a comparative study of the effects of ormeloxifene with evening primrose oil for mastalgia, showed a more prominent VAS score reduction with ormeloxifene by the end of 2nd and 3rd month in comparison to evening primrose oil.[8] Gara et al., showed in their study that ormeloxifene-$C_{30}H_{35}O_3N.HCL$, a selective estrogen receptor modulator, is basically used as an oral contraceptive.[12] Traded first as SAHELI is novel formulation by CDRI, Lucknow and included in the National Family Welfare Program, is relatively free from side effects such as nausea and vomiting. Dhar et al., included 60 patients in a pilot study in 2007 where he found ormeloxifene to be a safe drug with almost complete disappearance of nodularity as well as mastalgia.[13] Nigam et al., in 2018, studied centchroman with evening primrose oil in benign breast diseases and found centchroman to have an excellent safety profile as well as being highly cost effective.[8] Our study shares similar findings with results that clearly indicate ormeloxifene to be a superior alternative to evening primrose oil and at the same time being more cost effective. Safety profile observed with ormeloxifene was also excellent.

### Limitations of the study

This is an observational study that we have conducted and with a small sample size. Larger sample sizes with adequate randomization are required to have a final verdict on the best drug to treat fibroadenosis of the females of the reproductive age group.

## CONCLUSION

Cyclical and non-cyclical mastalgia are very common presenting problems among females throughout the reproductive age. Both ormeloxifene and evening primrose oil are being used in treatment of mastalgia. However, patients on ormeloxifene offer early and better sustained relief of mastalgia and breast nodularity without discernible increase in side effect profile. The effectiveness coupled with the safety profile of ormeloxifene scored much better when compared with evening primrose oil in this study. In the treatment of fibroadenosis, ormeloxifene therefore is more effective as well as cost effective drug than evening primrose oil; however, larger trials are needed to finally conclude.

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**Authors' Contributions:**
**AB-** Concept, design of study and primary draft preparation; **DM-** Interpretation of results, statistical analysis and manuscript preparation; **TM-** Review of literature; **SC-** Concept, preparation and revision of manuscript.

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