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EFFECTS OF THE EVENING PRIMROSE OIL ON WOMEN'S MASTALGIA: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Paying attention to women's health is important. The majority of women usually suffer from mastalgia. Herbal medicine is more compatible with human body and has fewer side effects because the drugs are natural. Evening Primrose Oil is a novel treatment for the relief of cyclic (premenstrual) and non-cyclic breast pain. The aim of the review is to assess the efficacy of evening prime rose oil (EPO) on mastalgia. Electronic databases (Google scholar, PubMed, Scopus, the Cochrane Library, SID, Iran Medex, Magiran, Medlib and Irandoc) were searched from 1990 up to January 2015 for published randomized controlled Trials (RCTs). Only randomized controlled trials involving Evening Primrose Oil and other drugs agents for mastalgia were included. Background information of the study, participants' characteristics, and study outcomes were collected out of 143 relevant publication trials, 10 RCTs met the inclusion criteria. Evening Primrose oil showed beneficial effects on Mastalgia in comparison with other drugs used for treatment, which had side effects. It seems that evening Primrose oil can be first line of treatment in mild mastalgia without any side effects. However, efficacy of EPO for moderate to severe mastalgia remains doubtful. Therefore, further studies are required to improve our understanding of management of patients with symptoms of mastalgia.

Keywords: Evening Primrose Oil, Randomized controlled trials, Mastalgia

INTRODUCTION

Mastalgia or breast pain is the most common symptom among patients visiting the breast clinic (Mansel *et al.,* 2004). The majority of women usually suffer from mastalgia. It may occur at monthly intervals (cyclical) or may not follow any patterns (noncyclical). A cyclic pain is the most common type of breast pain. It may be caused by normal monthly changes in hormones (Rosolowich *et al.,* 2006) and has been reported in 50% of women who visit surgical clinics for breast symptoms (Hughes, Mansel & Webster 1989). The management of mastalgia consists of classification into various patterns, re-assurance, drug therapy in severe cases and, rarely, surgery. Differentiation of cyclical and non cyclical pattern on a simple pain chart is useful for objective assessment of pain severity, selection of approved drug therapy, and subsequent monitoring of response is necessary (Maddox & Mansel, 1981). A large number of agents have tried for the treatment of cyclical and non-cyclical breast pain. Since drugs had side effects, people became interested in herbal medicine used in mastalgia which are non-steroidal anti-inflammatory gels, iodides and plant derivatives like Evening Primrose Oil (EPO). There is a considerable debate about the choice of best agent for initial management of mastalgia (Halaska *et al.,* 1999).

EPO is omega-fatty-acid-rich oil containing both linolenic acid (LA) and gamma-linolenic acid (GCA). EPO contains 74% linoleic acid, 11% oleic acid, 6% palmitic acid, 2% stearic acid and 9% GLA (Maddox, 1981). According to research, women with breast pain have low levels of gamma-linolenic acid (GLA) and its metabolites dihomogammalinolenic acid and arachidonic acid. Efamol Pure Evening Primrose Oil contains GLA-gamma-linolenic acid. Treatment with Efamol Pure Evening Primrose Oil raises levels of GLA

and its metabolites towards normal and probably relieves breast pain by attenuating the effects of ovarian hormones and prolactin without changing their levels in blood (Horrobin & Manku 1989). It seems that Pure Efamol Evening Primrose Oil is a novel treatment for the relief of cyclic (premenstrual) and non-cyclic breast pain (Mansel, Pye & Hughes, 1990). Many discussions have already taken place about the choice of best agent for initial management of mastalgia. So far no systematic review has evaluated the effects of EPO on mastalgia, except a meta-analysis by Srivastava *et al.,* (2007). He conducted a meta-analysis on randomized controlled trials comparing Bromocriptine, Danazol, Evening primrose oil (EPO) and Tamoxifen with placebo on mastalgia. This meta-analysis consisted 8 articles and the part related to EPO was updated. Therefore this review has been done to investigate published randomized trials of EPO which is used in the treatment of mastalgia. The result of this study indicates that Bromocriptine, Danazol and Tamoxifen all offer significant relief from mastalgia. Reliable data regarding direct comparison of above medicine is not available. Tamoxifen is associated with least side effects, so it should be the drug of first choice. According to Srivastava *et al.*, (2007), EPO is ineffective and should not be used. Moreover it must be noted that breast pain may or may not be related to menstruation or hormone use. As, the most women experience breast pain and tenderness before their menstruation or after hormone use, this review focused on mastalgia accompanied with menstrual or hormone use. Since it was more commonly observed in women and no systematic review had been conducted on the effects of EPO on mastalgia, therefore the aim of this study is to assess the efficacy of Evening Primrose Oil (EPO) on mastalgia.

MATERIALS AND METHODS

Study selection:

Studies which met the following criteria were included in the systematic review:

1. Randomised Controlled Trials (RCTs)
2. Evaluating efficacy of Evening Primrose Oil (EPO) on mastalgia

Trials on agents other than EPO were excluded.

Data extraction

For each study, the authors extracted the following data according to a pre-defined checklist: first author, year of publication, age of participants, study design, study duration, and sample size. In crossover trials the result on initial phase (i.e. before cross-over) was used for the analysis of reports.

Methodological quality assessment:

The quality of randomized controlled trials was independently assessed by two authors using Oxford Centre for Evidence- Based Medicine Checklist for RCTs quality.

RESULTS

Search results:

The search of the electronic databases identified 143 articles for screening. A total of 10 papers met the inclusion criteria. The process of the search and selection of RCTs is described in Figure 1.

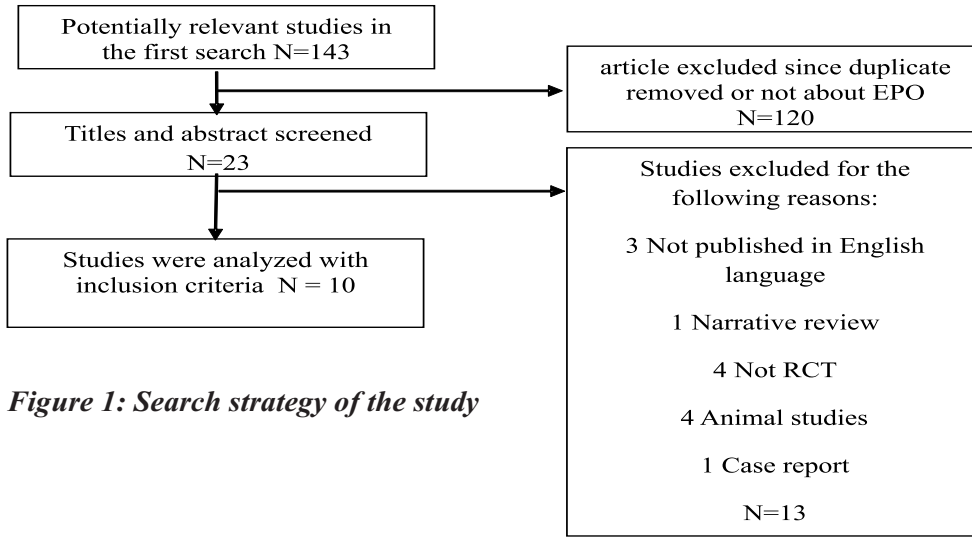

Figure 1: Search strategy of the study

Characteristicsoftheselectedstudies:125

A total of 143 studies were identified. About 120 studies were excluded because the titles and abstracts werenotrelevanttoourpreviewand10studies were included in the systematic review. Quantitative analysis was carried out to determine the effect on mastalgia. The characteristics of the selected studies are summarizedin Table 1.

Table 1: Summary of trials of four on EPO vs Placebo

Author, Country, Year	Age of participants	Study design	Treatment duration (month)	Drop out%	Randomiz-ation technique	Treatment Blinding	Type of Intervention N=	Type of control N=	Cyclic and non-cyclic mastalgia	Conclusion
Blommers *et al*. Nederland (2002)	37	RCTS (parallel factorial)	6	10 %	Yes	Double-blind	Evening primrose oil N=30	Fish oil N=30	Cyclic	All groups showed a decrease in pain. Neither Evening Primrose Oil (P = .73);nor fish oil (P = .28) offered clear benefit over control oils in the treatment of mastalgia.
Colling *et al.*, Sweden, 1993	30-45	RCTS (Crossover)	10	28	Yes	Double-blind	Evening primrose oil N=27	Placebo (paraffinoil) N=22	Cyclic	Treatment with essential fatty acids is ineffective therapy for PMS. No statistically significant differences between groups (p > 0.05).
Fathizadeh *et al.*, Iran, 2008	18-40	RCTS (semi-experime ntal	3	7.5	Yes	Single-blind	Evening primrose oil N=31	Vitamin E N=30	Cyclic	Evening Primrose Oil decrease the severity of pain and it is more effective and better than the known and common vitamin E medicine (p < 0.001).
Gateley *et al.*, CARDIFF-UK (1992)		RCTS	4	15 %	No	No blinding	Evening Primrose Oil N=85	Danazol: N=145 Bromocriptine:	Cyclic	Overall 92% of patients with cyclical mastalgia and 64% of patients with non-cyclical mastalgia can obtain a linically useful response using a combination of danazol, bromocriptine or Evening Primrose Oil. unless the severity of symptoms requires a rapid response, Evening Primrose Oil
Goyal and Mansel. UK.2005	18-55	RCTS (parallel, multicent er study)	8	-	Yes	Double-blind	4 arm multicentre 555 women in44 centres	placebo-controlled	Non-cyclic	Gamolenic acid was not shown to be superior to placebo. (P = 0.850 in blinded phase (P = 0.217) in open phase). GLA was shown to be safe in long-term use.
Katiyar *et al.*, Singhpur, (2012)	15 – 55	RCTS (Crossover)	12	23 %	No	No. blinding	Evening Primrose Oil N=26 IN CYCLICAL MASTALGIA, N=12 IN NON CYCLICAL MASTALGIA	Danazol N=37 Tamoxifen N=24 Bromocriptine N= 19	Cyclic	Danazol seems to be best available drug for both cyclical and non cyclical mastalgia. However, Tamoxifen approaches the same efficacy in both groups; in fact it has a better response in non cyclical mastalgia group. EPO is better drug for young and for women who do not
Mohammed K Mohammed, Iraq, 2010	17-48	RCTS	3		No	No blinding	Group1 (Evening Primrose Oil) N=35	Group2 (Diclofenac Sodium (Olfen)N=35	Non-cyclic	Topical NSAI Diclofenac Sodium gel is safe, relatively quick in action with reliable patient compliance and compares favourably with an established recommended first-line treatment for mastalgia; namely EPO. (P- value= 0.000001)
SUGHRA PARVEEN *et al*., 2007	18-35	An open, non-randomiz ed, comparati ve study	3	-	No	No blinding	Evening primrose oil N=50	Danazol N=50	Non-cyclic	Danazol offers good pain control in mastalgia but with distressing side effects, where as Oil of Evening Primrose (OEP) also showed good pain control but without much distressing side effects.
Pruthi *et al.* USA (2010)	40	RCTS	6	51 %	Yes	Double-blind	Evening Primrose Oil N=11	Vitamin E N=11 Vitamin E+EPO N=9	Cyclic	Vitamin E, EPO , and EPO in combination with vitamin E may improve cyclical mastalgia. (EPO:P=0.18,VIT E:P=0.10, EPO+VIT E: P= 0.16)
Thakur *et al.* Srinagar. (2009)	17-40	prospecti ve study ,	6	12.35	No	No blinding	Evening Primrose Oil N=89	-	Cyclic	Cap. Evening Primrose oil can be used as first line of treatment in mild to moderate mastalgia; however, its efficacy for moderate to severe mastalgia remains doubtful.

The effect of Evening Primrose Oil (EPO) on mastalgia Comparing

Evening Primrose Oil (EPO) with medical treatment

Four trials (Gateley *et al*.,1992, Parveen, 2007, Mohammed, 2010, Katiyar, Nigam, & Omar, 2012) compared EPO with drug treatment (Danazol and Bromocriptine and diclofenac).

The First study by Gateley *et al.*, (1992) included 414 patients in two groups, 324 with cyclical mastalgia and 90 with non-cyclical mastalgia, to receive a therapeutic trial of drug treatment at least for 2 months or 4 months in the case of Evening Primrose Oil (danazol 200 mg daily, bromocriptine 5 mg daily or Evening Primrose Oil 6x500 mg capsules daily). A clinically useful response was obtained in 115 (79%) for those treated with danazol, 51 (54%) with bromocriptine and 49 (58%) with Evening Primrose Oil. Overall 92% of those with cyclical mastalgia and 64% with non-cyclical mastalgia showed a clinically useful response to the therapy. Danazol was the most effective drug, while bromocriptine and Evening Primrose Oil had equivalent efficacy. Fewer side effects complain where reported about using Evening Primrose Oil compared with danazol or bromocriptine.

The Second study by Parveen *et al.*, (2007) included 100 female patients with moderate to severe breast pain who visited the out-patient Surgical Department, Karachi. After clinical evaluation, investigations and informed consent, all patients were assigned to two groups alternatively. Mastalgia in all patients was gauged before and during the treatment according to the Cardiff Breast pain Score (CBS). Group-I (n=50) received Danazol 100mg bid per oral and Group-II (n=50) Efamol (Oil of Evening Primrose) 500mg b.i.d per oral for three months. The authors visited all patients at the 4^{th} and 12^{th} weeks. The overall response showed that Danazol was 76% **more effective** in contrast to EPO treatment 68% with. But the group treated with with Danazol showed 32% distressing with reversible side effects as compared to 12% in case of EPO which were neither distressing nor reversible. Danazol offered good pain control in mastalgia but with distressing side effects, whereas Oil of Evening Primrose (EPO) showed good pain control but without much distressing side effects.

The third trial by Mohammed (2010) compared anti-inflammatory drug (NSAID) and Evening Primrose Oil (EPO). After three months of treatment, out of 35 patients who were treated with topical NSAI gel, 96.5% had clinically significant response compared with 45.7% of 35 patients treated with EPO. Two patients (5.7%) in EPO group had side effects compared to side effects in NSAI gel group. Response to NSAI gel was reported earlier than EPO. About 82.8% of patients accepted the cost of NSAI gel treatment versus 85.7% in EPO.

Katiyar, Nigam & Omar (2012) evaluated female patients between 15– 55 years of age with breast pain complain. Local examination in all of the patients and Mammography in patients above 35 years of age was done. All patients coming to OPD on the first 15 Days of month took Evening Primrose Oil (500 mg 2 cap) twice a day for two months. All of them in next half were treated with danazol (200mg /day) for two months. Patients were called to OPD every 15 day to assess the response and also to check whether the patient was appropriately following the treatment. A total of 104 patients complaining of severe breast pain were examined during the span of 12 months (November 2011 – October 2012). In cyclical mastalgia in the first line therapy, the obtained effective response was 4.6% with EPO (3gm/day) compared to 68% cases with Danazol (200mg/day). However in non cyclical mastalgia the levels were 16.66% and 33.33% for EPO and danazol respectively. After the use of third drug (crossover of groups) a response of 45.45% was seen in patients with cyclical mastalgia and 30.76% in non cyclical mastalgia. About 15 out of 80 patients were resistant to hormonal manipulation. He concluded that EPO is a better drug for girls and women who do not want their period to be disturbed.

Comparing Evening Primrose Oil (EPO) with placebo

Three trials (Collins *et al.*, 1993; Blommers *et al.*, 2002; Goyal, Robert & Mansel, 2005) compared EPO with fish oil.

Colling *et al.*, carried out a randomized, double-blind, cross over trial, on 49 women 30-45 years who had PMS over ten menstrual syndrome. He divided them to two groups, group 1 (N=27) with Efamol and another (N=22) with placebo (paraffin, oil tablet). Then he continued randomizing to four cycles of active treatment with EPO and placebo, with a cross over after the fourth cycle. He concluded EPO did not reduce premenstrual symptom (breast discomfort and swelling). In EPO group, breast discomfort was

reduced from 3.1 to 2.9 but in placebo group there was no decrease. So no statistically significant differences between groups were seen.

Blommers *et al.*, (2002), randomly divided one hundred twenty women into four groups: (1) fish oil and control oil, (2) Evening Primrose Oil and control oil, (3) fish and evening primrose oil, and (4) both control oil during 6 months. Corn oil and corn oil with wheat germ oil were used as control oil. After 6 months, he analyzed the change in the percentage of days with breast pain. The obtained result showed useful response on the reduction of days with pain with 12.3% for Evening Primrose Oil and 13.8% for its control oil (P=0.73); 15.5% for fish oil and 10.6% for its control oil (P= 0.28).

Goyal, Robert & Mansel, (2005), carried out a double-blind, placebo-controlled, parallel group, multicenter study on 555 women with moderate to severe mastalgia. They randomized them to four treatment groups to receive (a) gamolenic acid (GLA) and antioxidants, (b) placebo fatty acids and antioxidants, (c) GLA and placebo antioxidants, and (d) placebo fatty acids and placebo antioxidant, for four menstrual cycles. They followed eight menstrual cycles of open treatment in which all patients received GLA, but continued to be randomized to active or placebo antioxidants as in the preceding parallel phase. Diary, pain cards and linear analog charts were used for assessment of response. They showed a reduction in breast pain in all four treatment groups. There was a substantial improvement in the placebo fatty acids groups (response rate of 40%), but no significant differences among the four treatment groups.

Comparing Evening Primrose Oil (EPO) with vitamin E

Two trial (Pruthi *et al.*, 2010; Fathizadeh, 2008) compared EPO with vitamin E and placebo. Pruthi *et al.*, conducted double-blind, randomized, placebo-controlled trial on 55 women with premenstrual cyclical breast discomfort randomly assigned to one of four oral treatment for six-month: vitamin E (1, 200 IU/day), EPO (3,000 mg/day), vitamin E (1,200 IU/day) plus EPO (3,000 mg/day), or double placebo. The primary outcome measure was a change in breast pain, measured by the modified McGill Pain Questioner at time of enrolled and after six months among 45 patients. Intent -to-treat analysis (pretesting and post testing) showed a difference in pain improvement with the treatments of EPO (p=0.005), vitamin E (p=0.04), and EPO plus vitamin E (p=0.05), but no difference with placebo (p=0.93). Results from two-sample t-test showed no significant decrease in cyclical mastalgia individually for the three treatment groups compared with the placebo group (EPO, p=0.18; vitamin E p=0.10; and EPO plus vitamin E, p=0.16).The data were also analyzed with the separation test by Aikin, which showed a trend toward a reduction of cyclical mastalgia with vitamin E and EPO both individually and in combination. He proposed daily dose of 1,200 IU vitamin E, 3,000 mg EPO, or together with the same dosage, for 6 months may decrease the severity of cyclical mastalgia .

Fathizadeh *et al.*, (2008) carried out a single-blind semi-experimental study on 66 women of 18-40 years of age suffering from periodical breast pain. Among them, 31 were given Evening Primrose Oil and 30 in vitamin E group. Sampling method was a simple random. She assessed severity of pain with Cardiff chart before and after one month of intervention. The result showed that numbers was more than 14 considered as severe pain, 7-14 as average pain; and less than 7 was no pain. At the end of the second month, she randomly divided the participants into two groups; one group received 3 g oral evening primrose oil and the other 600 mg oral vitamin E three times during a day. She showed a significant difference in the severity of pain before and after the intervention in both groups. Before the intervention, severe and moderate pain among 41.9% and 58.1% in the evening primrose oil group and it decreased to 3.2% and 35.2%, respectively after intervention (p<0.001). In the vitamin E group, 36.7% had severe pain and 63.3% had moderate pain before the intervention and it decreased to 23.3% and 50%, respectively after the intervention (p=0.04). $\chi 2$ test showed that before the intervention both groups had the same severity of pain and there was no significant difference between them (p=0.788). After using drugs, there was a significant difference between the severity of pain in the two groups, but the pain decreased more in Evening Primrose Oil group (p<0.05).

Evening primrose oil (EPO)

Thakur *et al.*, (2009) studied 89 female patients with breast symptoms, out of which 11 patients didn't follow-up, at the surgical out-patient department of SKIMS, Srinagar. He assessed the patients and treated

them by reassurance, low fat diet, methyl-xanthine restricted diet and dietary supplementation of Evening Primrose Oil 1000 mg/day. Then he assessed the response with visual analog pain score after 3 and 6 months. Approximately 74.44% of patients responded to the treatment, whereas 26.66% showed no response.

DISCUSSION

Our study was a systematic review of the available literature to assess the efficacy of Evening Primrose Oil (EPO) on women`s mastalgia. This review showed a very slight change in breast pain by EPO. But as EPO did not have any side effects, it can be used as the first line of treatment in mild to moderate mastalgia.

The effect of Evening Primrose Oil (EPO) with medical treatment on mastalgia

Four trials (Gateley *et al.*, 1992; Parveen *et al.*, 2007; Mohammed, 2010; Katiyar, Nigam & Omar, 2012) involving a total of 598 participants, investigated the efficiency of EPO on cyclical and non-cyclical mastalgia comparing with drug treatment (Danazol and Bromocriptine and diclofenac). Two studies (Gateley *et al.*, 1992; Parveen, *et al.*, 2007) showed that patients with mastalgia obtained a clinically useful response to therapy though this response was lower in EPO than danazol. Due to lesser side effects complain in EPO than for Danazol patients, it seems that can be effective on mastalgia (Gateley, 1992; Parveen, 2007).

One study (Mohammed, 2010) compared anti-inflammatory drug (NSAID) to Evening Primrose Oil (EPO) on mastalgia and showed that topical NSAID gel had clinically significant response compared with EPO. Another study (Katiyar, 2012) compared EPO with Danazol and showed that EPO is a better drug for girls and women who do not want their period to be disturbed. To sum up, it seems that EPO is effective in relieving mastalgia because of no side effects, however, future RCTs are needed with consistent statistical methods to further support the current evidence.

Comparing Evening primrose oil (EPO) with vitamin E

Two studies, involving a total of 102 participants, investigated the effect of EPO and vitamin E.

One study (Pruthi *et al.*, 2010) showed a trend toward a reduction of cyclical mastalgia with vitamin E and EPO individually and in combination. He concluded that vitamin E and EPO in combination for 6 months may decrease the severity of cyclical mastalgia. Another study (Fathizadeh *et al.*, 2008) showed a significant difference between the severity of pain in the two groups (EPO and vitamin E), however this reduction was more in EPO than vitamin E. Future studies to evaluate the effect of EPO with larger sample size and comparing it with vitamin E should also be taken into account.

Comparing Evening primrose oil (EPO) with placebo

Three trials (Collins *et al.*, 1993; Blommers *et al.*, 2002; Goyal, Robert & Mansel, 2005) involving a total of 664 participants, compared EPO with placebo. All of them showed that there were no statistically significant differences between EPO and placebo. To sum up it seems that more clinical trials are needed to evaluate the adjunct effect of EPO.

Evening primrose oil (EPO)

One study (Thakur *et al.*, 2009), involving a total of 89 participants showed that EPO can be used as the first line of treatment in mild to moderate mastalgia. However, its efficacy for moderate to severe mastalgia remains doubtful. Therefore, further studies are required to improve our understanding of breast pain and management of patients with moderate to severe symptoms of mastalgia.

The current systematic review was limited in several aspects: The number of RCTs was limited. Some articles had small sample size and weak methodology. A potential limitation of this review is that some of the included studies had different control groups that we couldn't be sure about efficacy of evening prime rose oil with other medications. Because of these limitations, the results of our systematic review should be interpreted with caution.

This systematic review provides an overview of current evidence on the efficacy of Evening Primrose Oil (EPO) for mastalgia among women. The strength of our review is the comprehensive and systematic literature search for identifying relevant publications. Each trial detailed, and outcome measures were used for this review report. Furthermore, we included Randomised Controlled Trials, which assessed efficacy of EPO on mastalgia by examining evaluations with a comparison group, which seems important. The point that some of the trials were conducted in large sample size was another positive aspect of the research.

On the basis of the findings of this review it can be said that, there is presently insufficient evidence to recommend the use of EPO in the treatment of breast pain. Further studies are needed to show whether this drug can replace synthetic and chemical medicine but it seems that EPO is a better medicine for girls and women who do not want their period to be disturbed. Therefore it is reasonable of a clinical setting to offer these lines of treatment for women with severe cyclical mastalgia for a short-period trial with Evening Primrose Oil.

CONCLUSION

In conclusion it can be said that while EPO did not cause a considerable decrease in mastalgia compared to medical treatment or placebo, but its use was associated with a reduction in the cyclical breast pain severity. This study indicates that Oil of Evening Primrose doesn't show any distressing side effects. While the available data do not support the recommendation of EPO for relief of mastalgia compared to medicine, some patients may benefit its use in reducing mastalgia as it seem to be well tolerated and has few side-effects. As the current data is inconclusive, further study of EPO for the relief of mastalgia is suggested.

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