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12-2009

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Evening Primrose Oil

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Evening primrose oil (*Oenothera biennis*) is a commonly used alternative therapy and a rich source of omega-6 essential fatty acids. It is best known for its use in the treatment of systemic diseases marked by chronic inflammation, such as atopic dermatitis and rheumatoid arthritis. It is often used for several women's health conditions, including breast pain (mastalgia), menopausal and premenstrual symptoms, cervical ripening, and labor induction or augmentation. However, there is insufficient evidence to make a reliable assessment of its effectiveness for most clinical indications. The current evidence suggests that oral evening primrose oil does not provide clinically significant improvement in persons with atopic dermatitis, and that it is also likely ineffective for the treatment of cyclical mastalgia and premenstrual syndrome. However, most trials to date have significant methodologic flaws and must be considered preliminary. The use of evening primrose oil during pregnancy is not supported in the literature and should be avoided. Evening primrose oil is generally well tolerated, with reported minor adverse effects, including gastrointestinal upset and headaches. Optimal dosing standards and treatment regimens await clarification in adequately powered clinical trials. (*Am Fam Physician*. 2009;80(12):1405-1408. Copyright © 2009 American Academy of Family Physicians.)

Evening primrose oil (EPO), is obtained by cold expression or solvent extraction from the seeds of the evening primrose plant (*Oenothera biennis*).¹ Native to North and South America and now widespread throughout Europe and parts of Asia, this biennial plant is also known by the names tree primrose, sun cups, sundrops, king's cure-all, fever plant, evening star, and night willow-herb. Native Americans valued its mucilaginous stem and leaf juices as topical remedies to soothe cutaneous inflammations, whereas poultices of the plant were used to treat bruises and minor wounds.² Internally, the leaves were used for gastrointestinal ailments and sore throats. Oral EPO is best known for its more recent use in the treatment of systemic diseases characterized by chronic inflammation, such as atopic dermatitis, eczema, and rheumatoid arthritis. The oil also is used for several women's health conditions, including breast pain (mastalgia), menopausal and premenstrual symptoms, cervical ripening, and labor induction or augmentation. Although consistent, quality data currently do not exist, EPO is being investigated in the treatment of a wide range of additional disorders, including diabetes

mellitus, cancer, asthma, preeclampsia, schizophrenia, and attention-deficit/hyperactivity disorder.

Pharmacology

The seeds of the evening primrose are rich in omega-6 essential fatty acids (EFAs), including linoleic acid and gamma-linolenic acid (GLA). The therapeutic effects of EPO are attributed to the direct action of its component EFAs on immune cells,³ as well as their indirect effect on the synthesis of eicosanoids (e.g., prostaglandins, cytokines, cytokine mediators).⁴ Dietary omega-3 and omega-6 EFAs can reduce the effects of highly unsaturated fatty acids in tissues and eicosanoid actions, which have been implicated in various inflammatory and immunologic pathogenesises.⁴

Uses and Effectiveness

ATOPIC DERMATITIS

Although EPO (sold under brand names such as Epogam and Efamast) was previously licensed in the United Kingdom as a prescription treatment for atopic dermatitis, marketing authorization was withdrawn in 2002 because of a lack of evidence of effectiveness. A systematic review examining 11

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
EPO has not been proven effective in the treatment of atopic dermatitis, except perhaps for a very modest benefit in itch or pruritus after one to two months of use.	B	5, 6	Systematic review of small RCTs; inconsistent and limited-quality trials
Early evidence suggests that EPO is likely ineffective for the treatment of cyclical mastalgia and symptoms of menopause or premenstrual syndrome.	B	7-10	Systematic review of small RCTs; inconsistent and limited-quality trials
Current evidence is insufficient to assess the usefulness of EPO in the treatment of diabetic neuropathy and rheumatoid arthritis.	B	11-14	Small RCTs; inconsistent and limited-quality trials

EPO = evening primrose oil; RCTs = randomized controlled trials.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

randomized controlled trials (RCTs) found no clear evidence of clinical benefit for topical or oral EPO for atopic dermatitis.⁵ A later meta-analysis found that Efamol had a clinically modest but statistically significant beneficial effect on itch and pruritus in patients using it for four to eight weeks who were not also taking potent oral steroids.⁶ However, the meta-analysis included several unpublished, industry-sponsored trials that were excluded previously. Many of the studies had significant methodologic limitations, including small numbers; inadequate randomization; unclear blinding; and heterogeneity of dosing, duration, and patient characteristics.

MASTALGIA, MENOPAUSE, AND PREMENSTRUAL SYMPTOMS

A systematic review of treatments for cyclical mastalgia found only three double-blind, placebo-controlled trials of EPO and one multicenter trial of GLA (an active ingredient of EPO).⁷ The latter trial, which was of excellent quality, found that GLA was not superior to placebo, with or without additional antioxidant vitamins and minerals.⁸ Pooling the four studies, the authors found no significant effect of EPO on mean pain scores compared with placebo.⁷ There is insufficient evidence to recommend the use of EPO in the treatment of mastalgia.

Only one randomized, double-blind, placebo-controlled multicenter trial has studied the effects of EPO in menopausal women (n = 56).⁹ For a duration of six months, the participants took four capsules twice daily that contained either EPO (0.5 g EPO and 10 mg natural vitamin E per capsule) or placebo. The EPO showed no benefit in treating menopausal flushing compared with placebo. A systematic review of four small, low-powered trials found that doses of EPO ranging from 3 to 6 g daily were not effective in improving overall symptoms of premenstrual syndrome (PMS)

compared with placebo.¹⁰ Therefore, current evidence does not support a role for EPO in the management of menopause or PMS.

OTHER CONDITIONS

Although evidence to date is limited, several small studies suggest that GLA may be useful in patients with mild to moderate diabetic neuropathy who achieve only partial relief from prescription drugs.¹¹⁻¹³ However, larger methodologically sound studies are needed to confirm this assertion, and it is unclear whether such data may be extrapolated to EPO supplements. A Cochrane review comparing GLA (derived from evening primrose, borage, or black currant seed oil) with placebo in the treatment of rheumatoid arthritis found that current evidence is insufficient to make a reliable assessment of effectiveness.¹⁴ EPO is applied vaginally by many midwives to accelerate cervical ripening, shorten labor, and decrease the incidence of post-term pregnancies.¹⁵ However, no clinical RCTs support this use.

Interactions, Adverse Effects, and Contraindications

EPO is generally well tolerated, with reported minor adverse effects including gastrointestinal upset (e.g., abdominal pain, indigestion, nausea, softening of stools) and headaches.^{2,16,17} Two case reports involving only five patients in the 1980s raised speculation that EPO may exacerbate epilepsy or reduce the threshold for seizures in patients being treated with phenothiazines for schizophrenia.^{18,19} Although caution was advised for patients taking phenothiazine neuroleptics or anticonvulsants, neuroleptics themselves can induce seizures.

The effects of EFA supplementation during pregnancy and lactation remain largely unknown, and their use cannot be recommended. Extensive but transient petechiae and ecchymoses have been reported in a newborn infant whose mother took a total of 6.5 g of EPO during

the week before giving birth.²⁰ The oral use of EPO during pregnancy may also be associated with a more protracted phase of labor and an increased incidence of premature rupture of membranes, arrest of descent, oxytocin (Pitocin) administration, and vacuum extraction.²¹ Additional concerns have been raised about adverse effects of EPO supplementation on conditions including platelet aggregation, cholesterol, and blood pressure,²²⁻²⁷ although there is insufficient evidence to assess these concerns.

Dosage and Preparations

Commercial preparations of EPO are available in capsule or liquid form. A single standardized 1-g capsule of a common formulation, Efamol, contains 0.62 g linoleic acid, 0.08 g GLA, and 0.062 g oleic acid. Products may also be identified according to percent content of EFAs (e.g., 70% linoleic acid, 9% GLA).²⁸ In clinical trials, adult oral dosing for atopic dermatitis has ranged from 0.16 g to 0.64 g of GLA per day in divided doses, with treatment periods ranging from three to 16 weeks.⁶ Oral dosing in trials of children with atopic dermatitis has ranged from 0.08 g to 0.32 g GLA per day in divided doses.⁶ In trials of EPO for diabetic neuropathy,¹¹ 0.36 g to 0.48 g GLA daily for six months has been used, and 0.5 g EPO containing 0.04 g GLA and 0.01 g vitamin E has been used for the treatment of cyclical mastalgia.⁸ More condition-specific dosing recommendations are available at Natural Medicines Comprehensive Database (<http://www.naturaldatabase.com>) and Natural Standard (<http://www.naturalstandard.com> [subscription required]), although the evidence supporting effectiveness is limited or weak. EPO products should be stored out of direct sunlight in light-resistant containers in a refrigerator to prevent rancidity.

Final Comment

EPO is widely used for conditions such as mastalgia, menopause, atopic dermatitis, and arthritis, although there is surprisingly little evidence to support these uses. Most studies to date have significant limitations, including small sizes, possibly active placebos, high attrition rates, and use of concomitant second-line therapies. EPO theoretically holds promise for a wide range of conditions, given its involvement in the metabolism of prostaglandins and leukotrienes; investigation of

Table 1. Key Points About Evening Primrose Oil

Effectiveness	Likely ineffective, based on preliminary evidence (small randomized controlled trials): atopic dermatitis (except perhaps for modest improvement in itch or pruritus); mastalgia; menopause; premenstrual syndrome Insufficient evidence: diabetic peripheral neuropathy; rheumatoid arthritis
Adverse effects	Minor gastrointestinal adverse effects, including abdominal pain, nausea, increased bowel movements, and diarrhea; headaches
Interactions	Evidence for avoiding use with phenothiazine neuroleptics or anticonvulsants is limited and anecdotal Evidence is also insufficient to recommend avoiding use with other drugs, including: antihypertensive agents or pressors; anticoagulants or antiplatelet agents; nonsteroidal anti-inflammatory drugs; herbs or supplements that might affect platelet aggregation
Dose	Varies depending on brand; available in capsule and liquid form
Cost	\$11 to \$48 for a four-week supply, depending on brand and dosage
Bottom line	Widely used with little proven effectiveness, but safe when used in recommended doses for up to six months

its effectiveness and mechanism of action is still in its infancy. However, well-designed clinical trials that are adequately powered are necessary to validate or refute the clinical claims made for EPO, and optimal dosing standards await clarification. *Table 1* lists the effectiveness, safety, tolerability, and cost of EPO.

Members of various family medicine departments develop articles for "Complementary and Alternative Medicine." This is one in a series coordinated by Sumi Sexton, MD, and Benjamin Kligler, MD, MPH.

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Author disclosure: Nothing to disclose.

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