

Premenstrual Syndrome

Premenstrual syndrome (PMS) and related menstrual disorders are common sources of misery among menstruating women. Symptoms range from mild to severe enough to interfere with family and social activities and work (Frackiewicz EJ et al 2001).

Identifying PMS can sometimes be difficult because it covers such a wide range of symptoms. It is estimated to affect up to 50 percent of menstruating women, with symptoms sometimes beginning among young women aged 16 to 18 and peaking when women are in their 20s and 30s (Cleckner-Smith CS et al 1998). Symptoms of PMS tend to decrease with age (Freeman EW et al 2004), ceasing with menopause. Women who continue to experience PMS symptoms at an older age are also more likely to experience menopausal symptoms (Freeman EW et al 2004).

PMS can affect a number of systems and produce a wide variety of symptoms:

- *Psychological symptoms.* Tension, depression, irritability, fatigue, panic, phobia
- *Nervous system symptoms.* Migraine, seizures, headaches, dizziness, fainting
- *Symptoms affecting the skin.* Acne, boils, hives
- *Symptoms affecting the muscles and joints.* Backache, joint pains, edema
- *Respiratory symptoms.* Asthma, allergies (Redmond AM et al 2004)
- *Symptoms affecting the head and neck.* Sinusitis, sore throat, hoarseness
- *Urinary symptoms.* Bladder infections
- *Gastrointestinal symptoms.* Bloating, gas, food cravings
- *Symptoms affecting the breast.* Tenderness, swelling

A more severe form of PMS is called premenstrual dysphoric disorder (PMDD). This disorder occurs in 2 to 9 percent of menstruating women. Although the symptoms of PMDD and PMS are similar, they are much more severe in PMDD. In fact, PMDD is characterized by symptoms that are severe enough to interfere with personal relationships, especially in the marital and family area (Freeman EW et al 2004).

Unfortunately, traditional medicine is not especially well equipped to deal with PMS. There are no unique physical findings or lab tests that can diagnose PMS and few drugs that achieve consistent results without side effects. If symptoms are mild, most women are told to use over-the-counter painkillers (usually containing ibuprofen) and make dietary and lifestyle changes. In more serious cases, including PMDD, antidepressants are sometimes prescribed.

Hormone-based birth control pills are also frequently recommended to produce a state of anovulation (lack of ovulation). Until recently, however, evidence concerning their effectiveness was mixed. Studies involving a new form of synthetic progesterone (progestin) have shown some benefit. However, Life Extension recommends that women take natural progesterones or phytoestrogens derived from plants rather than synthetic progestin or estrogen.

Life Extension has also uncovered a number of nutrients that address underlying deficiencies associated with premenstrual syndrome and excess levels of prostaglandins, which have been linked to symptoms of PMS. Chief among the alternative therapies for PMS is calcium, which has been used for more than 70 years in the treatment of menstrual disorders. Other therapies include magnesium, vitamin E, vitamin B6, and extract from fruit of the chaste tree.

THE MENSTRUAL CYCLE, HORMONES, AND PMS

A normal menstrual cycle is characterized by the regular rise and fall of sex hormones, most importantly estrogen and progesterone, culminating in menstruation. The cycle is usually divided into four phases:

- *Follicular phase.* During this phase, a rise in follicle stimulating hormone causes several follicles (each containing an egg) to begin growing on the surface of the ovary. Under the influence of the pituitary luteinizing hormone, these follicles secrete estradiol, a form of estrogen. This estrogen discourages production of follicle stimulating hormone by a negative feedback mechanism, causing a slowdown in growth of the follicles. The estrogen also encourages endometrial (uterine lining) tissue to build up in preparation for a fertilized egg. Eventually, one follicle emerges as the dominant follicle.
- *Ovulation.* In this phase, the dominant follicle bursts, releasing an egg into the fallopian tube. This phase is caused by a burst in the production of luteinizing hormone. Ovulation usually occurs around day 14 in the cycle, but the timing varies from

woman to woman. Once the egg is in the fallopian tube, it is available for fertilization.

- *Luteal phase.* After the egg has been released, the remaining follicle tissue is known as the corpus luteum. During the next two weeks of the menstrual cycle, the corpus luteum secretes an increasing amount of progesterone to prepare the body for early pregnancy and reception of a fertilized egg. If the egg is not fertilized, levels of progesterone decline.
- *Menstruation.* Menstruation is characterized by low levels of both progesterone and estrogen. It occurs when the egg has not been fertilized. In this phase, the built-up portion of the uterine wall sloughs off and passes through the vagina as blood, mucus, and tissue remnants. This sloughing off is caused by contraction of the arterioles that supply the thickened endometrium with blood, as well as the contraction of endometrium smooth muscular wall. These muscular contractions cause cramping and are under the control of cyclooxygenase (COX) enzymes. COX enzymes are nonselectively inhibited by over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs).

Among women with PMS, some form of hormonal dysfunction occurs during the luteal phase. However, PMS is still not well understood, and many theories have been proposed to explain the underlying symptoms. In fact, the clinical diagnosis of PMS wasn't even established until the last 15 years or so. Until then, there was significant disagreement as to whether PMS existed as a legitimate medical condition.

A number of novel theories have been put forward to help explain PMS. There is evidence that in severe cases, symptoms associated with severe menstrual disorders are caused by a derangement of serotonin, an important neurotransmitter that regulates mood and behavior (Clayton AH et al 2006).

Evidence also suggests decreased sensitivity of brain gamma-aminobutyric acid (GABA)-alpha receptors, increased sensitivity of brain motor cells, and disturbances of the hypothalamic-pituitary-adrenal axis, which controls stress hormone levels (Smith MJ et al 2003; Sundstrom I et al 1998; Rabin DS et al 1990). GABA-alpha is an inhibitory neurotransmitter associated with relaxation and a decrease in anxiety.

Together, these effects might account for some of the mood and motor problems so commonly seen in PMS. There is also evidence that PMS runs in families, and women with PMS also tend to have a personal or family history of alcohol abuse and mood-related psychiatric disorders (Berga S 2005). Also, women with a history of sexual abuse were found to be more likely to suffer from severe PMS. In fact, studies have shown that up to 95 percent of women who experienced sexual abuse, often at early ages, were likely to suffer from PMS (Golding JM et al 2000).

Finally, prostaglandins, hormone-like chemicals that control various bodily functions, may play a role in PMS. Prostaglandins are known to promote smooth muscle contraction and blood vessel dilation, both of which are essential to the normal menstrual cycle. Studies have shown that prostaglandin excretion is disordered in women with PMS compared with women without PMS (Piccoli A et al 1993). Prostaglandin production appears to be significantly lower in the late luteal phase of women with PMS compared with controls, based on a study of 20 women with PMS and 12 controls, while prostaglandin production is much higher in the follicular phase and early luteal phase (Koshikawa N et al 1992).

HORMONE MODULATION AND MENSTRUAL SYNDROMES

The influence of hormones on PMS and menstrual syndromes has been studied extensively, often with conflicting results. Women typically suffer from PMS during the luteal phase of their menstrual cycle, which is characterized by increasing levels of progesterone and fluctuating levels of other steroid hormones. Hoping to unravel the connection between hormones and premenstrual symptoms, researchers have studied women with PMS to see whether they have abnormal levels of various hormones compared with women without PMS. In one study, researchers found that 20 women with PMS had higher levels of dehydroepiandrosterone and free testosterone during the luteal phase of menstruation, along with reduced levels of allopregnanolone, than did 20 controls (Lombardi I et al 2004). Allopregnanolone is a metabolite of progesterone and is an active neurosteroid that has been shown to affect mood and behavior.

Many studies have examined the role of hormone therapy, using conventional estrogen-progestin (synthetic progesterone) contraceptives, to control symptoms associated with PMS. These hormone preparations are used to induce a state of anovulation (no ovulation), which allows women to bypass the hormonal fluctuations that occur during ovulation and thus the accompanying symptoms (Mayo Clinic 2005). Unfortunately, evidence of their effectiveness is mixed.

Some women attempt to control their symptoms with progestins, or synthetic progesterone. These drugs have consistently failed to show good results. In recent years, however, a progestin called drospirenone has been introduced for the treatment of PMS. Drospirenone is derived from a source (17-alpha spironolactone) different from the progestins usually used in oral contraception. It has antiminerlocorticoid activity and is thus not associated with weight gain and fluid retention, unlike some other hormone preparations.

Early results with an oral contraception formulation including drospirenone have been encouraging. Multiple studies, examining both PMS and PMDD, have been conducted using this combination. Overall, these studies have shown that drospirenone reduces

bloating, cramps, breast tenderness, and other side effects (Rapkin A 2003). A drospirenone-containing pill called Yasmin® has been effective in treating PMDD (Rapkin A 2003). In early 2006, a spin-off of this pill, called Yaz®, was introduced as an oral contraceptive. Yaz® contains drospirenone in combination with ethinyl estradiol (3 mg drospirenone/20 mcg ethinyl estradiol) and showed benefit similar to Yasmin®.

When it comes to hormone modulation to control symptoms of PMS, Life Extension advocates a more natural approach than can be achieved with synthetic estrogens and progestins. Natural, safe progesterones are derived from yams and can be used in place of progestins. In addition, phytoestrogens, or estrogen-like compounds derived from plants, have shown some efficacy in relieving PMS symptoms. In one recent double-blind, placebo controlled, randomized study, phytoestrogens derived from soy were examined for their ability to reduce symptoms of PMS. After two months, researchers reported that the women in the study experienced reduced headache, breast tenderness, cramps, and swelling during periods when they took the soy products compared with periods when they took placebo (Bryant M et al 2005).

The hormone melatonin, which is usually associated with sleep and insomnia, may also play a role in alleviating the symptoms of PMS and PMDD. Melatonin is involved in a variety of mood and anxiety disorders and is intimately related to sex hormones and other hypothalamic-pituitary-adrenal-axis hormones. Studies have shown that levels of melatonin are low among women with PMDD (Parry BL et al 1989).

NUTRITIONAL THERAPY

Calcium and vitamin D. Calcium has a long history in the treatment of PMS and menstrual disorders (Abraham GE 1983). In fact, its use in symptom relief stretches back to the 1930s, when women suffering menstrual cycle problems routinely took supplemental calcium. Since then, this “folk” remedy has been tested in clinical trials with positive results.

In a study performed at Columbia University in New York, calcium supplementation was found to be a simple and effective treatment for premenstrual syndrome (Thys-Jacobs S et al 1998). After calcium supplementation for three consecutive menstrual cycles, healthy menstruating women reported a 48-percent reduction in total PMS-related symptoms compared with menstruating women receiving placebo during the same period (Thys-Jacobs S et al 1998).

A review study performed at Columbia found that women who received calcium coupled with vitamin D experienced significant relief from psychological and physical symptoms of PMS. This review confirmed for the investigators that PMS represents a clinical manifestation of calcium deficiency (Thys-Jacobs S 2000; Thys-Jacobs S et al 1995).

Magnesium. Among its many functions, magnesium plays a role in maintaining parathyroid function and hormone production (Ganong W 2003). Magnesium deficiency has been implicated as a cause of premenstrual symptoms (Abraham GE et al 1981).

Another double-blind, randomized study investigated the effects of oral magnesium on premenstrual symptoms (Facchinetti F et al 1991). This study found significant changes on the Menstrual Distress Questionnaire, a measurement of menstrual distress, in patients who had taken magnesium for two menstrual cycles (Facchinetti F et al 1991).

Zinc. Researchers at the Baylor College of Medicine in Houston, Texas, found that patients with PMS had lower levels of zinc and higher levels of copper during the luteal phase of menstruation than menstruating women without PMS. The researchers concluded that zinc deficiency occurs in PMS patients during the luteal phase of menstruation, and elevated copper further reduces the availability of zinc in PMS patients during the luteal phase (Chuong CJ et al 1994).

Vitamin B6 (pyridoxine, pyridoxal, pyridoxamine). A meta-analysis was performed to evaluate the efficacy of vitamin B6. Researchers reviewed nine placebo-controlled, published trials representing 940 patients with premenstrual syndrome in May 1999. Their conclusions showed that up to 100 mg vitamin B6 daily is likely to be beneficial in treating premenstrual symptoms and premenstrual depression (Wyatt KM et al 1999).

In 1987, researchers conducted a double-blind controlled study on the effects of vitamin B6 supplementation on premenstrual symptoms experienced by 55 women who reported moderate to severe premenstrual mood changes. Study results suggested that vitamin B6 improved premenstrual symptoms related to autonomic reactions (e.g., dizziness and vomiting) and behavioral changes (e.g., poor performance and decreased social activities) (Kendall KE et al 1987).

Vitex. Extracts of the fruits of the chaste tree (*Vitex agnus castus*) are widely used to treat premenstrual symptoms. Double-blind, placebo-controlled studies indicate that one of the most common premenstrual symptoms, breast tenderness, is beneficially influenced by this extract, also called chasteberry. In addition, numerous studies indicate that vitex extracts have beneficial effects on other psychic and somatic symptoms of PMS (Wuttke W et al 2003).

A group of German researchers studied the effects of chaste tree extract versus placebo in a group of women diagnosed with PMS.

Both prior to and after the treatment period, women were asked to report their symptoms of PMS and the degree of severity. The researchers evaluated the changes in reported symptoms. More than 50 percent of the women experienced a reduction in their PMS-related symptoms. The results of this study prompted the German government to allow Vitex agnus castus to be approved for menstrual irregularities, breast pain, and premenstrual complaints (Schellenberg R 2001).

In a study comparing the efficacy of chasteberry extract with that of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), on mood disorders associated with PMDD, patients responded well to both fluoxetine and chasteberry extract. However, chasteberry proved better than fluoxetine at improving physical symptoms (Atmaca M et al 2003).

Researchers investigated the efficacy of using chasteberry extract to reduce breast pain related to PMS. In a placebo-controlled, randomized study, chasteberry extract was effective and well tolerated as a treatment agent for cyclical breast pain (Halaska M et al 1998).

Ginkgo biloba. In a clinical study, Ginkgo biloba was effective at reducing symptoms of anxiety and headaches. A total of 165 women ages 18 to 45 were given 160 mg ginkgo extract or placebo daily from day 16 of one menstrual cycle to day 5 of the next. Symptoms of fluid retention, particularly breast tenderness, were improved, as were psychological parameters (Tamborini A et al 1993).

Vitamin E. Vitamin E is a powerful antioxidant and free radical scavenger that protects the integrity of the cellular membranes in the body. Researchers investigated the impact of D-alpha-tocopherol, a form of vitamin E, on women suffering from PMS. A daily treatment with 400 IU D-alpha-tocopherol was administered for three monthly cycles. A significant improvement in physical symptoms was noted in participants treated with D-alpha-tocopherol (London RS et al 1987).

Theanine. Tea contains a unique amino acid, known as theanine, that can lessen the effects of PMS. Theanine readily crosses the blood-brain barrier and exerts subtle changes in biochemistry. An increase in alpha waves has been documented, and the effect has been compared to getting a massage or taking a hot bath. Theanine does not cause drowsiness, and unlike tranquilizers, it does not interfere with the ability to think. Studies of green tea, which contains a high quantity of theanine, have shown that when given to rats, theanine modulated the release of dopamine in the brain (Yamada T et al 2005). Theanine is now available as a dietary supplement in the United States.

NATURAL METHODS TO MODULATE SEROTONIN

Among women with severe PMS, prescription antidepressants called SSRIs are frequently prescribed. These medications inhibit the uptake of serotonin, thus making more of it available. Serotonin is an important neurotransmitter that is involved in the regulation of mood.

Tryptophan is a precursor of serotonin that is sometimes used by alternative physicians to treat depression by increasing the amount of serotonin. Based on this, it is logical to assume that tryptophan would also be effective among women with PMS, and indeed, it has been shown to significantly reduce symptoms if administered during the luteal phase (Freeman FW 2004).

Similarly, the supplement 5-hydroxytryptophan may help relieve symptoms by increasing the production of serotonin. 5-Hydroxytryptophan is the direct precursor to serotonin. It is the intermediate step between tryptophan and serotonin. Although 5-Hydroxytryptophan has not been studied in PMS, it has been studied in the treatment of depression (Turner EH et al 2006).

Finally, the herb Saint-John's-wort is sometimes recommended for premenstrual syndrome. Saint-John's-wort (*Hypericum perforatum*) has gained attention as a natural antidepressant because of its role in serotonin modulation. It appears to work by multiple mechanisms, each of which is relatively weak on its own but contributes to the herb's overall effectiveness. These mechanisms include inhibiting monoamine oxidase-A and -B activity and inhibiting the uptake of serotonin, dopamine, and noradrenaline (Butterweck V 2003). In one case study, a patient with PMDD who was unable to tolerate standard antidepressant treatment was given 900 mg Saint-John's-wort daily and experienced substantial improvement in her symptoms (Huang KL et al 2003). Another observational study examined the use of Saint-John's-wort among women with PMS. Participants took 300 mg Saint-John's-wort daily, standardized to contain 900 mcg, for one menstrual cycle. The women experienced improvements in all their symptom scores (Stevinson C et al 2000).

THE ROLE OF FATTY ACIDS IN PMS

Omega-3 fatty acids. Fatty acids play a role in mediating prostaglandins (Horrobin DF 1983). Supplementation with the right proportions of fatty acids can maximize the production of anti-inflammatory prostaglandins (E1 and E3) while suppressing pro-inflammatory prostaglandin E2 and leukotriene B4. In addition to avoiding saturated fats and high glycemic foods that contribute to chronic inflammation, eating omega-3 foods, which provide eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can help control inflammation by bringing balance to the essential fatty acids. In clinical studies, supplementation with omega-3 fatty acids reduced symptoms associated with PMS, including cramps (Sampalis F et al 2003; Harel Z et al 1996). Flax seed oil, which is derived from flax, is rich in alpha-linolenic acid. In the body, alpha-linolenic acid is converted into EPA, providing another possible source of EPA.

Gamma-linoleic acid. Gamma-linoleic acid (GLA) is a long-chain polyunsaturated fatty acid found in evening primrose oil and borage seed oil. Like levels of omega-3 fatty acids, levels of GLA are abnormal among women with PMS. For example, one study found that levels of linoleic acid are normal or elevated in women with PMS, but the levels of gamma-linoleic acid, a metabolite of linoleic acid, are low. This implies a problem with the conversion of linoleic acid to gamma-linoleic acid (Brush MG et al 1984).

CONVENTIONAL TREATMENT

Conventional treatment for mild PMS usually focuses on NSAIDs, which reduce smooth muscle contractions and cramping. In addition, some of the drugs that have shown benefit, such as benzodiazepines, have risk for addiction and abuse.

Antidepressants. Antidepressants such as SSRIs are commonly used for the depression associated with PMS and PMDD (Freeman EW et al 2004; Baldessarini R 2001). Serotonin reuptake inhibitors that are commonly used to treat PMS include Prozac® (fluoxetine) and Zoloft® (sertraline) (Berga S 2005). These drugs typically require a two- to three-week phase-in period before they reach maximum effectiveness. If they are prescribed, they should be used continuously until both patient and physician agree to stop using them, and then they should be phased out gradually. They cannot be used on an “as needed” basis. Side effects associated with SSRIs include nausea, diarrhea, tremor, weight loss, and headache.

Benzodiazepines. This class of medications is used to induce sedative, muscle-relaxant, and anticonvulsant effects (Baldessarini R 2001). Benzodiazepines have effects similar to allopregnanolone, a metabolite of progesterone that acts at the brain receptor sites at which benzodiazepines operate. Alprazolam is a commonly prescribed benzodiazepine. However, these drugs have a serious risk of addiction and abuse.

NSAIDs. Over-the-counter (OTC) medicines such as ibuprofen (Motrin®) and naproxen sodium (Aleve®) are commonly used to ease uterine cramping and breast tenderness (Mayo Clinic 2005). These drugs inhibit prostaglandin synthesis (Neal M 2002).

Others. Bromocriptine, an ergot alkaloid that blocks the release of prolactin from the pituitary gland, is often given to treat breast tenderness associated with PMS (Meden-Vrtovec et al 1992).

LIFESTYLE CHANGES TO REDUCE PMS SYMPTOMS

Stress reduction. Stress reduction is important to reduce symptoms of PMS and PMDD. One study determined that women with significant PMS symptoms had more stress and a lower quality of life than women with low-grade or no PMS symptoms (Lustyk M et al 2004). Stress has an effect on the hypothalamic-pituitary-adrenal axis by causing an increase in “stress” hormones with wide-ranging effects throughout the body (Young EA et al 2002).

Women who suffer from high PMS may benefit from psychotherapy, massage therapy, yoga, and other alternative methods to reduce stress.

Smoking cessation. In a study of behavior and lifestyle factors associated with menstrual symptoms, researchers found that cigarette smoking was the lifestyle factor most highly associated with all types of measured menstrual symptoms and cycle disorders (Kritz-Silverstein D et al 1999). Many strategies are available to help people quit, including group therapy, nicotine replacement patches, gums, hypnosis, and support lines.

Exercise. Exercise seems to help reduce PMS symptoms. Both aerobic and other forms of exercise appear to be helpful (Fugh-Berman A et al 2003). Exercise also helps reduce weight. Although obesity is not consistently associated with menstrual symptoms, endometrial hyperplasia and other gynecological disorders are associated with overweight and obese women. Women who suffer from PMS and other menstrual disorders and who are overweight should seriously consider a weight reduction program. Mineral supplementation with chromium picolinate, which helps stabilize blood sugar levels, has been shown to help women who suffer from PMS reduce their cravings for sugar. Chromium picolinate has also been found to help with weight reduction (Bell SJ et

al 2002). For more information, see the chapter Obesity.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Women who suffer from PMS are encouraged to reduce stress if possible. Methods might include massage or cutting back on activities whenever their PMS arises. Daily exercise and weight loss (if necessary) might also help. In addition, the following supplements are suggested for women suffering from PMS:

- **Magnesium**—160 to 250 milligrams (mg) magnesium two times daily. The last dose should be taken at bedtime.
- **Calcium**—1200 to 2000 mg daily, divided into two doses, the last to be taken at bedtime
- **Vitamin D**—400 to 1000 international units (IU) vitamin D daily
- **Zinc**—30 mg daily
- **Vitamin E**—400 IU alpha-tocopherol, including at least 200 mg gamma tocopherols
- **Progesterone cream**—1/4 teaspoon twice daily, starting on day 12 of the menstrual cycle and continuing up to day 28
- **Melatonin**—300 mcg nightly is recommended, increasing to 10 mg if necessary
- **Soy isoflavones**—55 to 110 mg daily
- **GLA**—285 to 1425 mg daily in two divided doses
- **EPA/DHA**—1400 mg EPA and 1000 mg DHA daily
- **Flax seed oil with lignans**—1 to 3 tablespoons daily
- **Vitex berry extract**—(standardized to 0.5 percent) a minimum of 625 micrograms (mcg) Angusides once or twice daily
- **Ginkgo biloba extract**—120 mg daily
- **Theanine**—100 to 200 mg daily to induce a state of relaxation
- **Tryptophan**—500 to 1000 mg once or twice daily on an empty stomach
- **Saint-John's-wort**—women with PMDD: up to 900 mg daily; women with PMS: 300 mg standardized extract daily. NOTE: Please read the safety caveats at the end of this chapter.

Many women may also benefit from drospironone, a progestin that has been effective in reducing symptoms of PMDD and PMS. Drospironone is not associated with weight gain and fluid retention. It is available in combination birth control pills, including Yasmin® and Yaz®, both of which are available by prescription.

PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at www.LifeExtension.com.

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at www.LifeExtension.com.

PREMENSTRUAL SYNDROME SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-alkali syndrome, nephrocalcinosis, or renal insufficiency.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Flaxseed

- Flaxseed has blood-thinning, anticlotting properties.
- Discontinue using flaxseed before any surgical procedure.
- Consult your doctor before taking flaxseed if you have hemophilia or if you take warfarin (Coumadin).
- Flaxseed can cause gastrointestinal symptoms such as nausea and diarrhea.

Ginkgo biloba

- Individuals with a known risk factor for intracranial hemorrhage, systematic arterial hypertension, diabetes, or seizures should avoid ginkgo.
- Do not use prior to or after surgery.
- Avoid concomitant use of ginkgo with NSAIDS, blood thinners, diuretics, or SSRI's.
- Gastrointestinal symptoms (nausea and diarrhea) may occur.
- Allergic skin reactions may occur.
- Elevations in blood pressure may occur.

GLA

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

L-Tryptophan

- Do not take L-tryptophan if you have carcinoid tumors.
- Do not take L-tryptophan while taking monoamine oxidase inhibitors (MAOIs) (type A) or within 2 weeks of discontinuing MAOIs.
- Do not take L-tryptophan with any antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants or MAOIs.
- Do not take L-tryptophan with serotonin 5-HT receptor agonists, including naratriptan, sumatriptan and zolmitriptan.
- Do not take L-tryptophan if you have ischemic heart disease (e.g., a history of myocardial infarction, angina pectoris or documented silent ischemia), coronary artery spasm (e.g., Prinzmetal angina), uncontrolled hypertension or any other significant cardiovascular disease.
- L-tryptophan can trigger excess serotonin formation in tissues other than the target organ and cause significant adverse reactions.?
- L-tryptophan can cause nausea, diarrhea, loss of appetite, vomiting, difficulty breathing, pupil dilation, abnormally sensitive reflexes, loss of muscle coordination, blurry vision and cardiac dysrhythmia.

Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a "heavy head," or gastrointestinal symptoms such as nausea and diarrhea.

Progesterone

- Do not take progesterone if you could be pregnant or are breastfeeding.
- Consult your doctor before taking progesterone if you have cancer of the reproductive organs.

Saint John's Wort

- St. John's wort can increase sensitivity to sunlight. To avoid a sunburn while taking St. John's wort, minimize your exposure to the sun.
- St. John's wort can cause bloating and constipation.

Vitamin D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix

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