Alternative treatments for menopausal symptoms

Systematic review of scientific and lay literature

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ABSTRACT

OBJECTIVE To review the scientific literature on common alternative remedies for treatment of symptoms attributed to menopause and to contrast this with available lay literature.

QUALITY OF EVIDENCE Scientific articles were identified by searching MEDLINE, CINAHL, and HEALTH databases from 1966 to mid-1997 for English-language articles. More than 200 references were reviewed; 85 were selected for citation based on specific reference to alternative medicine for symptoms commonly attributed to menopause (eg, hot flashes), to the effects of changing estrogen levels (eg, irregular menses, vaginal dryness), and to reported side effects of the treatments.

MAIN FINDINGS The scientific literature was categorized under the headings nutritional supplements, herbal remedies, homeopathic remedies, and physical approaches. Some scientific evidence of the safety and efficacy of alternative treatments during menopause was uncovered, with the strongest evidence emerging in favour of phytoestrogens, which occur in high concentrations as isoflavones in soy products.

CONCLUSIONS In available controlled studies, the strongest data support phytoestrogens for their role in diminishing menopausal symptoms related to estrogen deficiency and for possible protective effects on bones and the cardiovascular system. Randomized controlled trials, standardization of dosage, and accurate safety and efficacy labeling are required to ensure proper use of alternative remedies.

RÉSUMÉ

OBJECTIF Analyser les ouvrages scientifiques sur les médecines douces communément utilisées dans le traitement des symptômes de la ménopause et en comparer le contenu avec celui des publications populaires disponibles.

QUALITÉ DES DONNÉES La sélection d'articles scientifiques en anglais s'est faite au moyen d'une recherche dans les bases de données MEDLINE, CINAHL et HEALTH, entre 1966 et le milieu de 1997. Plus de 200 articles ont été examinés, dont 85 ont été retenus aux fins de citation en raison des références précises sur les thérapies d'appoint pour traiter les symptômes associés communément à la ménopause (comme les bouffées de chaleur), sur les effets des changements du taux d'œstrogène (comme l'irrégularité des menstruations, l'assèchement des muqueuses vaginales) et sur les effets secondaires rapportés à la suite des traitements.

PRINCIPALES CONCLUSIONS Les ouvrages scientifiques ont été classés sous les rubriques suivantes: suppléments nutritionnels, plantes médicinales, remèdes homéopathiques et approches physiques. On a dégagé certaines preuves scientifiques de la sécurité et de l'efficacité des thérapies d'appoint durant la ménopause, la plus probante étant en faveur des phytoestrogènes qui se trouvent en fortes concentrations sous forme d'isoflavones dans les produits du soja.

CONCLUSIONS Dans les essais contrôlés disponibles, les données les plus probantes sont favorables aux phytoestrogènes en raison du rôle qu'elles jouent dans l'atténuation des symptômes de la ménopause associés à la carence en œstrogène et de ses effets possibles de protection des os et du système cardiovasculaire. Des essais aléatoires contrôlés, la normalisation des dosages et l'étiquetage exact en matière de sécurité et d'efficacité sont nécessaires pour assurer un usage approprié des médecines douces.

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anagement of menopause has received increased attention in recent years, as a consequence both of the growing interest in women's health and of the greater num-

ber of women entering the menopausal years.¹ Fear and dislike of possible side effects and long-term risks of hormone replacement therapy (HRT), disenchantment with conventional medicine, and belief in the safety of "natural" products are factors that have contributed to increased use and acceptance of alternative and complementary medicine.^{2,3*}

According to Health Canada's recent National Health Survey,⁴ at least 15% of Canadians aged 15 and older have sought alternative medical health care. Despite the wide use of alternative medicine, little is known about the safety and efficacy of alternative treatments.

This review examines evidence from controlled studies of use of alternative therapies by women experiencing symptoms attributed to menopause. Its purpose is to familiarize family physicians with scientific support for the alternative therapies their patients are using, with the information their patients are exposed to in the lay literature, and with the topics that require further clinical trials.

Despite evidence supporting the benefits of HRT, only 11% to 15% of Canadian postmenopausal women currently use HRT.⁵ Of those who begin HRT, less than 50% continue beyond 1 year.⁶ Although evidence supports the benefits of estrogen in reducing the risk of osteoporosis⁷ and coronary vascular disease,⁸ using HRT for prevention does not appear to be a high priority for women.⁹ Most women use it only for relief of vasomotor symptoms attributed to menopause.⁵

Review of 7000 letters received by the menopause information and support publication, *A Friend Indeed*, revealed reasons women elect not to take HRT. These included regarding menopause as a natural transition, not perceiving osteoporosis or cardiovas-

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References originating from non-academic books and non-peer-reviewed journals and magazines are identified by * throughout.

cular disease as a personal threat, unwillingness to tolerate side effects (such as vaginal bleeding), belief that estrogen is not safe, and fear of cancer. ^{10*} A study of women's perceptions of HRT also revealed that women do not want to commit to its long-term use and that unsatisfactory communication with physicians results in a lack of confidence in HRT. ¹¹ Reasons for discontinuing HRT include return of unacceptable vaginal bleeding, other side effects, fear of long-term complications, cost, and lack of encouragement from physicians to try various HRT regimens for a "better fit." ^{12,13*}

Interest in use of complementary and alternative remedies for managing menopausal symptoms has increased exponentially in the last 5 years. 10*,11,14 This interest is fueled by growing media coverage and lay literature on the topic and by claims often made without scientific evidence. 11,15* Providers of complementary medicine are perceived to offer a more personalized and user-friendly service. 16

METHODS

Data were obtained by searching the MEDLINE, CINAHL (Nursing and Allied Health), and HEALTH (Health Planning and Administration) databases from 1966 to mid-1997. Lay literature was obtained through the Health Reference Centre, a consumer database in the Metropolitan Toronto Reference Library, as well as from recent articles and books referenced in the Toronto public library system and recommended by alternative health care providers.

Articles with reference to symptoms commonly attributed to menopause (eg, hot flashes) or to topics related to changing estrogen levels (eg, irregular menses, vaginal dryness) were included. A preliminary search involved combining the key word "menopause" with "alternative medicine," "complementary medicine," "plants-medicinal," "herbs," "medicine—herbal," "medicine—traditional," "phytosterols," "phytoestrogens," "isoflavones," "diet," "nutrition," "vitamins," "minerals," "homeopathy," "naturopathy," "acupuncture," "electroacupuncture," "acupressure," "chiropractic," "massage," "massage therapy," "relaxation techniques," and "exercise." Additional articles were obtained through references cited in articles previously identified. The search was restricted to English literature. The lay literature was also searched to determine what women are reading on alternative therapies for menopause and to compare this with the available scientific literature.

RESULTS

Alternative methods for coping with symptoms attributed to menopause cluster into nutritional supplements, herbal remedies, homeopathic remedies, and physical approaches.

Nutritional supplements

Following national dietary guidelines should ensure that women in the menopausal years receive adequate nutrients.¹⁷ This includes choosing a variety of foods and getting adequate calcium; choosing high-fibre and low-fat foods for their protective effects against cardiovascular disease and cancer; and limiting intake of salt, alcohol, and caffeine.¹⁸ Additional calcium and vitamin D might have osteoprotective effects for menopausal women, especially those at high risk for osteoporosis.¹⁹

Phytoestrogens, naturally occurring compounds found in many foods (including cereals, legumes, and grasses), deserve special mention due to evidence of their estrogenic effect in postmenopausal women.²⁰ Phytoestrogens are defined as plant substances that are functionally similar to 17β-estradiol or that produce estrogenic effects. There are several classes, including isoflavones, lignins, coumestans, and resorcyclic acid lactones.²⁰ Isoflavones generally occur in legumes, with the highest concentrations in soybeans and soy products.²⁰

The estrogenic effect of phytoestrogens on postmenopausal women was established in a study that observed the maturation of the vaginal epithelia of 25 women after 6 weeks' supplementation with soya (isoflavones) and linseed (lignins).21 A subsequent randomized, double-blind study of 58 postmenopausal women given daily supplements of either 45 g of soy flour or 45 g of wheat flour for 12 weeks showed that soy flour produced a more rapid and continuous reduction (40%) in hot flashes compared with wheat flour (25%) (P<.001 for both).22 A study of isoflavonoid and endogenous estrogen levels in Japanese, American, and Finnish women's urine found that the Japanese women excreted far more isoflavonoids in their urine than the other two groups did, and that isoflavonoid estrogens were excreted in 100-fold to 1000-fold greater amounts by the Japanese women than endogenous estrogen was excreted by all groups.²³ The authors suggested that the Japanese women's high levels of dietary isoflavonoid phytoestrogens might partly explain why hot flashes and other menopausal symptoms are much less frequent among the Japanese.24

The biologic effects of isoflavonoid phytoestrogens can vary with age because of their proposed mechanism of action.²⁵ The relative potency of phytoestrogens is, at most, only 2% that of estradiol (E2).²⁶ Thus, in premenopausal women with high concentrations of circulating estrogens, isoflavonoids must compete for sites on estrogen receptors.²⁵ Since most of these sites are occupied by estrogen, when isoflavonoids do bind there is a net weakly antiestrogenic effect because their activity is much lower than that of estrogen. In postmenopausal women with much lower endogenous circulating estrogen, isoflavonoids can occupy more estrogen receptor sites, and since they have some estrogenic activity, they increase total estrogens in these women.

The estrogenic effects of phytoestrogens might decrease risk of osteoporosis and fracture.²⁷ Genistein, one of the important isoflavones, was recently reported to have identical effects to conjugated equine estrogens in maintaining bone mass in ovariectomized rats.²⁸ Ipriflavone, a synthetic isoflavone, was also found to maintain bone density in premenopausal women given gonadotropin-releasing hormone agonists,²⁹ and to maintain or increase bone density in postmenopausal women.³⁰

The cardioprotective effects of phytoestrogens have recently been under study also. A meta-analysis of the effects of soy consumption on lipid levels concluded that total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels can be significantly reduced by three servings of soy products daily, with phytoestrogens accounting for 60% to 70% of the effects.³¹

Although studies on the safety of phytoestrogens are few, phytoestrogen consumption through legumes is assumed to be safe as part of a balanced diet, since legumes have provided humans with their main source of protein for thousands of years.³² The scientific literature most frequently attributes phytoestrogenic properties to soybeans and soy products. In addition to soy products, the lay literature identifies several herbs as containing phytoestrogens, including dong quai and black cohosh.^{33*} We were unable to find any studies that confirmed this.

Table 1³⁴⁶¹ shows some of the more popular nutritional supplements used by women in the climacteric. Despite abundant popular claims, randomized placebo-controlled studies are required to demonstrate the efficacy of bioflavonoids in menopause. Vitamin E and evening primrose oil were found to have no benefit over placebo.

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Herbal remedies

About \$15 million of the \$400 to \$500 million profits earned annually by the Canadian health food industry come from the sale of herbal medicines. 62 Because herbal medicines are legally classified as foods in North America, only limited scientific literature is required or available on their action, safety, and interactions with other drugs.⁶⁰ While some herbs might be pharmacologically and clinically effective, they are not necessarily free from toxicity and side effects nor can we be sure that they will not interact with prescription medications. 63 Health problems from herbs can also result from contamination, adulteration, and misidentification of products.⁶⁴ Herbs can have nonspecific chronic effects, such as hepatitis, that are hard to associate with the cause. 65 Because of the reputed estrogenlike activity of some herbs, menopausal women might be exposing themselves to unpredictable amounts of unopposed estrogen.66*

Table 1. Nutritional supplements used to alleviate menopausal symptoms

SUPPLEMENT	SCIENTIFIC LITERATURE	WHAT YOUR PATIENTS MIGHT BE READING	
Bioflavonoids	No known nutritional or medical need for bioflavonoids. ³⁴	Bioflavonoids are recommended for hot flashes, 40*.41* mood swings, 41*.42* insomnia,	
	Randomized crossover study of eight ovariectomized women showed that grapefruit juice (containing three bioflavonoids) might increase bioavailability of administered 17β -estradiol and estrone. ³⁵	vaginal dryness, ^{42-44*} and heavy vaginal bleeding. ^{42*}	
	In vitro, chalcones, flavonones, and flavones bind to and activate nuclear estrogen receptors in cell-free extracts. ³⁶		
	In vitro evidence of flavonoid prevention of LDL oxidation. ³⁷		
	Cross-cultural correlational study suggests average flavonoid intake partly contributes to differences in coronary heart disease mortality across populations ³⁸ ; randomized clinical trial needed to support claims that flavonoids protect against atherosclerosis. ³⁹		
Vitamin E (tocopherol)	Uncontrolled studies in 1940s found vitamin E effective for hot flashes ^{45,46} ; later placebo-controlled study found no efficacy. ⁴⁷	Vitamin E is recommended for hot flashes, ^{40*,41*,42*,48*} mood swings, ^{41*} vaginal dryness ^{41*,42*} ; reputed to enhance effect of estrogen. ^{43*,49*}	
	Reported side effects are dermatitis, vaginal bleeding, hemorrhagic luteal cyst. ⁴⁶		
Evening primrose oil (EPO) (Oil of Oenothera biennis)	Randomized, double-blind, placebo-controlled study of 56 menopausal women with hot flashes found no benefit over placebo in treating menopausal flushing. Meta-analysis found five randomized placebo-controlled trials for treatment of premenstrual syndrome, but no evidence of efficacy. 51	Oil from seeds relieves PMS ^{61*} and hot flashes. ^{49*}	
	Recommended for premenstrual syndrome (PMS), ^{52,53} including cyclical mastalgia ⁵⁴ ; earlier trials reported success with PMS treatment, ⁵⁵ but recently no differences were found between EPO and placebo in crossover trial of 38 women with PMS. ⁵⁶		
	Contains gamma linolenic acid, precursor of prostaglandin PGE ₁ . ⁵⁰		
	Reported side effects are inflammation, thrombosis, immunosuppression, ⁵⁷ nausea, ^{50,58} diarrhea. ⁵⁸ Contraindications are epilepsy, ⁵⁹ mania, ⁵⁹ anticoagulants, ⁵⁹ phenothiazines. ⁶⁰		

Table 2^{40,41,43,44,48,49,52,67,69,70,97} lists some of the more popular herbs used for menopausal symptoms, as well as their known effects and safety considerations. No randomized placebo-controlled studies have been reported in the available English literature to support any of the many claims of herbal treatments for menopausal symptoms.

Homeopathic remedies

According to the theory on which homeopathy is based, illness can be cured by very small doses of drugs that would in large doses produce symptoms in healthy people similar to those of the disease.98 The effect of the drug is believed to be enhanced by repeated mechanical shock at each stage of preparation in a series of dilutions. 99 Some homeopathic remedies are attenuated beyond Avogadro's number, so that in theory none of the original substance remains. Despite such minute quantities of reputedly active substance, homeopathic products are considered drugs in Canada under the Food and Drugs Act; each remedy requires a Drug Identification Number. 98 Since homeopathic remedies are considered non-toxic and generally free of side effects, homeopathy is currently an unregulated profession that can be practised by naturopaths, other health care providers, or lay people designating themselves as "homeopaths."98

Homeopathy views menopausal problems as long-term imbalances that require constitutional treatment. The three most commonly prescribed homeopathic remedies for menopausal symptoms are lachesis (derived from South American bushmaster snake venom), pulsatilla (derived from the perennial windflower, *Anemone pulsatilla*), and sepia (derived from cuttlefish ink). 40*,41*,100-102*

Due to lack of known mechanism for homeopathic remedies, ¹⁰³ numerous studies have been conducted to determine whether the effects of homeopathy are placebo responses. ^{99,104} We found no double-blind, placebo-controlled evidence to show homeopathic drugs as more effective than placebo.

Physical approaches

Although properly randomized controlled clinical trials have not yet been conducted to assess the effectiveness of physical ways of obtaining relief from menopausal symptoms, treatments such as exercise, acupuncture, massage therapy, and chiropractic are often used.⁵ Exercise has an important role in enhancing well-being, promoting

mobility, preventing and treating a variety of diseases, ¹⁰⁵⁻¹⁰⁶ and providing osteoprotection and cardioprotection. ¹⁰⁷ One study of the effects of exercise on the frequency of postmenopausal hot flashes found that moderate to severe hot flashes occurred in 21.5% of a group of postmenopausal women belonging to an athletic club compared with 43.8% of women in a large control group who did not exercise in a structured manner. ¹⁰⁸ This study, however, used a questionnaire completed by a self-selected group without controls for socioeconomic status and other variables.

Numerous anecdotes report the effectiveness of exercise in alleviating menopausal symptoms. Another limited questionnaire study did not find any demonstrable effect of energy expenditure on hot flashes. 109 The only study examining the effects of acupuncture on menopausal symptoms was found in a Swedish journal. 110 According to the English translation, both superficial needle position and electrostimulated acupuncture resulted in a decrease in hot flashes in both groups; however, without a placebo group, the results of the study are meaningless. Chiropractic, massage therapy, acupressure, and relaxation techniques might be effective in stress management,⁵ but we could find no studies examining their effects on menopausal symptoms. Further study is required to determine whether specific physical approaches are effective in alleviating symptoms attributed to menopause.

Conclusion

Many alternative remedies, including nutritional, herbal, homeopathic, and physical, for treating menopausal symptoms were reviewed to identify the scientific evidence on their efficacy and safety. The strongest evidence emerged in favour of phytoestrogens for their role in diminishing menopausal symptoms related to estrogen deficiency and for their possible osteoprotective and cardioprotective effects. Long-term effects of increased phytoestrogen intake, however, are unknown.

While anecdotal information about the effectiveness of herbal remedies in alleviating menopausal symptoms is plentiful in the lay literature, scientific data are usually lacking, and there are risks for side effects and drug interactions. Homeopathy is growing in popularity as anecdotal success stories abound in the lay literature and media; but scientific data are insufficient to indicate that these

HERB	SCIENTIFIC LITERATURE	WHAT YOUR PATIENTS MIGHT BE READING		
Black cohosh (Cimicifuga racemosa)	Luteinizing hormone-suppressive effects observed in menopausal women and ovariectomized rats. ⁶⁷	Recommended for hot flashes, 40°.44°.69°.70° excessive vaginal bleeding, 41° depression, 69° nervous tension, 71°		
	No evidence of estrogenic effect in study of uterine growth in immature mice and vaginal cornification in ovariectomized rats. ⁶⁸	menstrual pain, and irregularity. 44*.48*.70* May result in endometrial hyperplasia if unopposed with progesterone. 48*		
Blue cohosh (Caulophyllum thalictroides)	Alkaloids (eg, methylcysteine) and glycosides (eg, caulosaponin) appear to contribute to its physiologic activity. ⁵²	Blue cohosh is recommended for hot flashes, ⁴⁰ ' spasms, ⁴⁸ ' and as a menstrual inducer. ⁴⁸ '		
	Reported side effects are methylcysteine elevates blood pressure and stimulates respiration and intestinal motility, and caulosaponin constricts coronary blood vessels and induces intestinal spasms in animals. ⁵²			
Chasteberry (Vitex agnus castus)	Found to have a dopaminergic effect and to be effective for hyperprolactinemia. ^{72,73}	Chasteberry is recommended for hot flashes, 40*.41*.44*.49* dry vagina, 44* depression. 70*		
	A case report described one woman having symptoms of mild ovarian hyperstimulation syndrome in the luteal phase following ingestion. ⁷⁴			
	Reported side effect was an itchy rash. ⁷⁵			
Dong quai (Angelica sinensis)	Seven different coumarins (acting as vasodilators and antispasmodics) have been identified; insufficient clinical evidence to support effectiveness as an estrogenic or therapeutic agent. 52	Dong quai is recommended for hot flashes, 40*.41*.44*.67*.79* and for uterine spasm, dry vagina, and palpitations.44* Reputed to have estrogenic effects.48*.70*		
	Decreased prothrombin time following cotreatment of rabbits with warfarin and dong quai indicates need for precautionary advice for patients who self-medicate with dong quai while taking chronic warfarin treatment. ⁷⁶	Reputed side effects are breast enlargement and tenderness ^{44*,80*} and menstrual flooding. ^{44*,48*} Dong quai is not recommended for women with fibroids, ^{44*} fever, ^{81*} excessive menstrual flow, ^{44*,81*}		
	A double-blind, randomized, placebo-controlled trial of 71 women indicated that dong quai is no more helpful than placebo in relieving menopausal symptoms and does not alter endometrial thickness, vaginal maturation, or estrogen levels. ⁷⁷	and women using ASA or blood thinners regularly. ^{44*}		
	Ferulic acid, phenolic compound in dong quai, showed inhibitory effect on spontaneous movement of rat uteri in situ. ⁷⁸			
Ginseng (Panax ginseng)	Active ingredients are triterpenoid saponins. ⁵²	Ginseng is reputed to increase energy levels, ^{49*} metabolic rate, ^{49*} estrogen production, ^{70*,79*} and immune function. ^{49*,70*}		
(I ana ginseng)	Estrogenic activity uncertain ^{52,82} ; possible estrogenic effect due to chemical similarity of ginsenosides to estrogens. ⁸³ Case report of postmenopausal bleeding attributed to vaginal	Recommended for hot flashes, 44*,49* stress, 44*,49* and headaches.44*		
	application of ginseng cream's estrogenlike effect.84	Reported side effects are hypertension, 44*,86* vaginal bleeding, 44*		
	Double-blind, non-placebo-controlled study of a multivitamin complex supplemented with and without ginseng extract demonstrated significant improvement in quality of life in ginseng group, as reported in a questionnaire. ⁸⁵	Contraindications include asthma or emphysema due to histamine-liberating action, 87* hypertension, 70* difficulty sleeping. 44*		
Hops (Humulus lupulus)	Belong to Cannabinaceae Hemp family, closely related to marijuana; known as a neurosedative. 88	Hops are recommended for water retention, 44*,89*,90* insomnia, 40*,91* suppressed or painful periods, 89*		
	Reported to relax smooth muscle and possess estrogenic and antiandrogenic activity ⁸⁸ (no clinical study in English found).	relaxation. ^{90*} Reputed to contain estrogen precursors. ^{89*,90*}		
	Reported side effects are central nervous system effects on brewery workers. ⁸⁸	Reported side effects include decreased libido 90 ° and skin irritation. 90 °		
Licorice (Glycyrrhiza glabra)	Glycyrrhizin in licorice has structure and physiologic effects similar to aldosterone and desoxycortisone. 52	Licorice is recommended as a hormone balancer and anti-inflammatory agent. ^{44*}		
	Reported side effects are increased serum sodium, decreased serum potassium, raised arterial and venous pulse pressures, 92 and headaches. 52	Reputed to have estrogenic activity. ^{70*,94*} Contraindications include hypertension, ^{70*,95*} and kidner		
	Negative effects of licorice found to be dose-related and more frequent in women. ⁹⁸	disease.91		
Wild yam (Dioscorea villosa)	Does not contain natural progesterone, but a chemical procedure converts components of Mexican wild yam into progesterone. 96	Recommended for hot flashes, 41* excessive vaginal bleeding, 41*,70* inflammation. 70* Progesterone can be extracted as an alternative to		
		HRT. 43*,70*,79*		
	•	May increase libido. ^{97*}		

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Key points

Despite widespread use of alternative treatments for menopausal symptoms, good scientific evidence supporting their safety and efficacy is sparse. In published controlled trials, phytoestrogens, which occur in soy products, seem to have the greatest evidence for a role in diminishing menopausal symptoms.

remedies are superior to placebo. Well-controlled studies are needed to prove that specific physical approaches to obtaining relief from menopausal symptoms are safe and effective. Although some scientific evidence about the safety and efficacy of alternative treatments was found in this review, that evidence was usually inconclusive.

There are obvious limitations to this search, which could not review all lay literature on the topic, studies or abstracts in foreign languages, and unpublished data. Further searches of European and other databases might provide additional scientific evidence supporting alternative therapies and warning of specific adverse effects.

The role of alternative and complementary remedies as placebo, defined as any treatment deliberately used for nonspecific psychological and psychophysiological effect,¹¹¹ and regarded as a form of treatment without demonstrable substance,¹¹² must be considered when evaluating their effectiveness. Researchers suggest that the extent of the true placebo effect depends on, among other factors, the attitude of health care providers toward treatment of patients, patients' suggestibility, and the type of treatment.¹¹³

An American survey uncovered the fact that 72% of patients using alternative therapies did not tell their physicians. 114 While most physicians are not trained in alternative medicine, it is important that they ask patients about alternative remedies to check for possible side effects, toxic effects, and incompatibility with pharmacologic treatment. 60,115*

This review indicates that, despite widespread use of alternative treatments, scientific evidence supporting the efficacy and safety of most complementary treatments for relief of menopausal symptoms is sparse. Double-blind, randomized placebo-controlled trials demonstrating the short-and long-term effects of these treatments are needed. In addition, regulation of content, standardization of dosage, and accurate labeling of safety and efficacy are required to increase professional and public confidence in these products.

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2.5 mg. 5 mg and 10 mg

Antihyoertensive Agent/Dibydrogyridine Calcium Changel Blocks

INDICATIONS AND CLINICAL USE PLENDIL (telodipine) is indicated in the treatment of mild to moderate essential hypotension. PLENDIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable aborese effects. PLENDIC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause senious adverse effects. Combination of PLENDIL with a thisacide diuretic or a beta-blocker has been found to be compatible and short and an additive antihypertensive effect. Safety and efficacy of concurrent use of PLENDIL with other antihypertensive egrets has not been established.

CONTRAINDICATIONS PLENDIL (felodipine) is contraindicated in:

1) Patients with a known hypersensitivity to felodipine or other dihydropyridines.

1) a value of childhearing potential, in pregnancy, and during lectation. Felal malformations and adverse effects on pregnancy have been reported in animals. Teratogenic Effects. Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of costilaction of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropriotine class. Similar fetal anomalies were not observed in rats given leddquie, in a learnatogy study in optomologus monkeys, no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses. Non-territopenic Effects. In a study on fertility and general reproductive performance in rats, prolongation of parturition with the groups treated with doses of 9.6 mg/kg/dday and above. Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits and repressed during lactation. Similar changes in the mammary glands were not observed in it as or monkeys.

WARNINGS Congestive Heart Failure. The safety and efficacy of PLENDIL (telodipine) in patients with heart failure has not been established. Caution should, therefore, be exercised when using PLENDIL in hypertensive patients with compromised ventricular function, particularly in combination with a bea-blocker. Acute hemodynamic studies in a small number of patients with New York Heart Association Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects. Hypotension, Nyhocaridal Ischemia. PLENDIL may, occasionally, precipitate symptomatic hypotension and rarely synopee. It may lead to reflex achycardia which, particularly in patients with severe obstructive coronary artery disease, may result in myocardial ischemia. Careful monitoring of blood pressure during the initial administration and fittration of felodipine is recommended. Care should be alast to avoid hypotension especially in patients with a history of cerebrovascular insufficiency, and in those taking medications known to lower blood pressure. Beth-Biochar Withdrawal. PLENDIL gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blockers. Durithow Obstruction. PLENDIL should be used with caution in the nessers of fised let westigen artifly medication rithe modernacion.

PRECAUTIONS Peripheral Edema. Mild to moderate peripheral edema was the most common adverse event in the clinical trials. The incidence of peripheral edema was dose-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction. Use in Elderly Patients. Patients over 65 years of age may have elevated plasma concentrations of felodip require lower doses of PLENDIL (see ACTION AND CLINICAL PHARMACOLOGY -Pharmacokinetics1). These patients should have their blood pressure monitored closely during initia administration and after dosage adjustment of PLENDIL. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION - Use in the Elderly). Use in Patients with Impaired Liver Function. Patients with impaired liver function may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of PLENDIL (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics1). These patients should have their blood pressure monitored closely during initial administration and after dosage adjustment of PLENDIL. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION - Use in Patients with Impaired Liver Function). Gingival Hyperplasia. PLENDIL can induce gingival enlargement in patients with pronounced gingivitis and parodontitis. However, such changes may be reversed by measures of good oral hygiene and mechanical debridement of the teeth. Pregnancy and Lactation. See CONTRAINDICATIONS. Use in Children. PLENDIL is not recommended in chi efficacy in children have not been established. Interaction with Grapefruit Juice. Published data shows that through inhibition of cytochrome P-450, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of dihydropyridine calcium channel blockers. In view of the absolute bioavailability of PLENDIL, the potential for a significant increase in pharmacodynamic effects exists (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics'). Therefore, the consumption of grapefruit juice prior to or during treatment with PLENDIL should be avoided. Drug Interactions. As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P-450 system, mainly via the CYP 3A4 isoenzyme. Coadministration of felodipine with other drugs which follow the same route of biotransformation may result in altered bioavailabili felodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered felodipine to maintain optimum therapeutic blood levels. Drugs known to be inhibitors of the cytochrome P-450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin. Drugs known to be inducers of the cytochrome P-450 system include: phenobarbital, phenytoin, rifampin, Druos known to be biotransformed via P-450 include: benzodiazepines, flecamide, imipramine, propafenone, terfenadine, theophylline. Enzyme Inhibitors. Cimetidine: In healthy volunteers pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C... of felodinine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine. Erythromycin: Concomitant treatment with erythromycin has been shown to cause an increase in felodipine plasma levels. Enzyme Inducers. Phenytoin. Carbamazenine and Phenoharbital: In a pharmacokinetic study maximum plasma concentrations of felodipine were considerably lower in ptic patients on long-term anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in healthy volunteers. The mean area under the felodipine plasma concentration-time curve was also reduced in epileptic patients to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be red in these patients. Alcohol: Alcohol can enhance the hemodynamic effects of felodipine. Beta-Adrenoceptor Blocking Agents: A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and

C_{max} of metoprolol, however, were increased approximately 31 and 36 percent, respectively. In controlled clinical trials, howeve, bet-blockers including metoprolol were concurrently administered with felodiptine and were well blotested. *Diporativ* When pieve oncombinative with felodiptine as conventional tablets the peak plasma concentration of digoxin was significantly increased. With the extended release formulation of felodiptine there was no significant change in peak plasma levels or AUC of digoxin. *Other Concomitant Therapy*: In healthy subjects there were no clinically significant interactions when felodiptine was given concomitantly with indomethacin or spirronolactore.

ADVERSE REACTIONS in 861 essential hypertensive patients treated once daily with 2.5 mg to 10 mg PLEMDIL (feliodipine) as monotherapy in controlled clinical trials, the most common clinical adverse events were peripheral edien and headone. Adverse events that coursel with an incidence of 1.5% or greater at any of the recommended doses of 2.5 mg to 10 mg once a day, without regard to causality, are listed by dose in Table 1 below. These events are reported from controlled clinical trials with patients who were randomized to either a fixed close of PLEMDIL to tritated from an initial dose of 2.5 mg or 5 mg once a day. A dose of 20 mg once a day has been evaluated in some clinical studies. Although the antihippentresistive effect of PLEMDIL is increased at 20 mg once a day, there is a disproportionate increase in adverse events, especially those associated with vasaelitatory effects (see DOSAGE AND ADMINISTRATION).

Table 1. Percent of patients with adverse events in controlled trials of PLENDIL (N=861)* as monotherapy without regard to causality (incidence of discontinuations shown in

parentheses).				
Body System	Placebo	2.5 mg	5 mg	10 mg
Adverse Events	N=334	N=255	N=581	N=408
Body as a Whole				
Peripheral Edema	3.3 (0.0)	2.0 (0.0)	8.8 (2.2)	17.4 (2.5)
Asthenia	3.3 (0.0)	3.9 (0.0)	3.3 (0.0)	2.2 (0.0)
Cardiovascular				, ,
Palpitation	2.4 (0.0)	0.4 (0.0)	1.4 (0.3)	2.5 (0.5)
Warm Sensation/Flushing	0.9 (0.3)	3.9 (0.0)	6.2 (0.9)	8.4 (1.2)
Digestive				
Nausea	1.5 (0.9)	1.2 (0.0)	1.7 (0.3)	1.0(0.7)
Dyspepsia	1.2 (0.0)	3.9 (0.0)	0.7 (0.0)	0.5 (0.0)
Constipation	0.9 (0.0)	1.2 (0.0)	0.3 (0.0)	1.5 (0.2)
Hervous				
Headache	10.2 (0.9)	10.6 (0.4)	11.0 (1.7)	14.7 (2.0)
Dizziness	2.7 (0.3)	2.7 (0.0)	3.6 (0.5)	3.7 (0.5)
Paresthesia	1.5 (0.3)	1.6 (0.0)	1.2 (0.0)	1.2 (0.2)
Respiratory				
Upper Respiratory Infection	1.8 (0.0)	3.9 (0.0)	1.9 (0.0)	0.7 (0.0)
Cough	0.3 (0.0)	0.8 (0.0)	1.2 (0.0)	1.7 (0.0)
Skin	, ,		` '	
Rash	0.9 (0.0)	2.0 (0.0)	0.2 (0.0)	0.2 (0.0)
• O		I	· NOU ` ´	

Some patients have been exposed to more than one dose level of PLENDIL Adverse events that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical trials at the recommended dosage range of 2.5 mg to 10 mg once a day are listed below. These events are listed in order of decreasing severity within each category regardless of relationship to PLENDIL therapy: Body as a Whole: Chest pain, facial edema, flu-like illness; Cardiovascular: Tachycardia, premature beats, postural hypotension, bradycardia; Gastrointestinal Abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation, cholestatic hepatitis ngival hyperplasia, salivary gland enlargement; *Metabolic*: ALT (SGPT) increased; *Musculoskeletal* Arthralgia, muscle cramps, mvalgia: Nervous/Psychiatric: Insomnia, depression, anxiety disorders v. nervousness, somnolence, decrease in libido, tremor, confusion; Respiratory; Dyspnea epistaxis; Dermatologic: Pruritis, erythema multiforme, erythema nodosum, urticaria photosensitivity reactions: Special Senses: Visual disturbances: Urogenital: Impotence, urinary frequency, urinary urgency, dysuria, polyuria. Serious adverse events reported from controlle clinical trials and during marketing experience (incidence <0.5 percent) were myocardial infarction hypotension, syncope, angina pectoris, arrhythmia and anemia. Isolated cases of angioedema have een reported. Angioedema may be accompanied by breathing difficulty. Laboratory tests: For the following laboratory values statistically significant decreases were observed; bilirubin, red blood count, hemoolobin, and urate. Statistically significant increases were found in erythrocyte sedimentation rate and thrombocyte count. In isolated cases, there were increased liver enzymes. None of these changes were considered to be of clinical significance

DOSAGE AND ADMINISTRATION PLENDIL should be swallowed whole and not crushed or chewed. The usual recommended initial dose is 5 mg once daily see DOSAGE AND ADMINISTRATION — Use in the Elderly, and — Use in Patients with Impaired Liver Function). Depending on the patients response, the dosage should be adjusted accordingly. Dose adjustment, if necessary, should be done at intervals of not less than two weeks. The maintenance dosage range is 2.5 mg to 10 mg once daily. In chinical trisis, doses above 10 mg daily showed an increased blood pressure response but a disproportionately higher incidence of peripheral edema and other vasodilatory adverse events. Modification of the recommended dosage is usually not required in patients with renal impairment. Use in the Elderly Patients over 65 years of age may develope elevated plasma concentrations of felodipine. A starting dose no higher than 2.5 mg once daily is recommended. A dosage of 10 mg daily should not be exceeded (see PRECAUTIONS – Use in Elderly Patients). Use in Patients with Impaired Liver Hondle Patients with impaired Liver Intotion may develop elevated plasma concentrations of felodipine. A starting dose no higher than 2.5 mg once daily is recommended. A dosage of 10 mg daily should not be exceeded (see PRECAUTIONS – Use in Patients with Impaired Liver Function.)

AVAILABILITY PLENDIL tablets are extended release, film-coated tablets, containing felodipine i strengths of 2.5 mg, 5 mg and 10 mg.

PLENDIL 25 mg Tablet: A yellow, circular, biconvex film-coated tablet, engraved $\frac{A}{h}$ on one side and 25 on the other. PLENDIL 5 mg Tablet: A pink, circular, biconvex film-coated tablet, engraved $\frac{A}{h}$ on one side and 5 on the other. PLENDIL 10 mg Tablet: A red-brown, circular, biconvex film-coated tablet, engraved $\frac{A}{h}$ on one side and 10 on the other.

Each tablet strength is available in blister packages (30's) and in 10 x 10 unit dose blister packages NOTE: These extended release tablets must not be divided, crushed or chewed.

† Full Product Monograph available on request

PLENDIL® is a registered trademark of Astra Pharma Inc., Mississauga, Ontario L4Y 1M4.

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