ALTERNATIVE THERAPIES TO RELIEVE SYMPTOMS OF MENOPAUSE

A manuscript submitted in partial fulfillment of the requirements for the degree

Masters of Nursing

Family Nurse Practitioner Program

Washington State University

Intercollegiate College of Nursing

Spokane, Washington

By

Traci Pelchat

May 2004
Alternatives Therapies to Relieve Symptoms of Menopause

To the Faculty of Washington State University:

The members of the committee appointed to examine the Intercollegiate College of Nursing research requirements and manuscripts of TRACI MICHELLE PELCHAT find it satisfactory and recommend that it be accepted.

Margaret O Bena
Chair
Barbara Nelson
Lorna Schumann
Abstract

Alternative Therapies to Relieve Symptoms of Menopause

By Traci M. Pelchat

Washington State University, May 2004

Chair: Dr. Margaret Bruya:

Women in menopause experience a plethora of aggravating symptoms. Symptoms range physiologically from hot flashes and depressive symptoms (feeling tense, irritable and depressed) to decreased bone mineral density (Kittell, Kernoff-Mansfield & Voda, 1998). Until recently, hormone replacement therapy (HRT) was the treatment choice for relieving ailing menopausal symptoms. In 2002, the Women’s Health Initiative trial found combination estrogen and progesterone (HRT) to be highly correlative with increased risk for stroke (41%), breast cancer (26%) and cardiovascular disease (29%) (National Heart, Lung & Blood Institute [NHLBI], 2003). For the purpose of this review, a collaboration of evidence-based research on non-HRT therapies has been compiled to provide practitioners and women in menopause a better understanding of which options will help alleviate menopausal symptoms. Phytoestrogen and non-phytoestrogen products have proven to relieve certain menopausal symptoms, namely hot flashes (Freedman & Dinsay, 2000; Somekawa, Chiguchi, Ishibashi & Aso, 2002). Phytoestrogens that may work to relieve hot flashes are found in soy containing products such as isoflavones and tempeh (Somekawa et al., 2001). Non-phytoestrogen products that have been shown to relieve other menopausal symptoms such as depressive symptoms and increase bone density are found in clonidine, melatonin, salmon calcitonin and raloxifene (Freedman & Dinsay, 2000).
# Table of Contents

Signature Page.................................................................ii
Abstract.................................................................................iii
Table of Contents....................................................................iv
List of Tables...........................................................................v
Introduction.............................................................................1
Background..............................................................................3
Framework...............................................................................4
Literature Review.....................................................................6
Phytoestrogens.........................................................................9
Non-Phytoestrogens...............................................................16
Methods Used in Reviewed Studies.........................................22
Implications for Nurse Practitioner.........................................23
Conclusion..............................................................................24
References...............................................................................25
Table 1..................................................................................30
Table 2..................................................................................34
List of Tables

Table 1
Graph of Reviewed Studies: Source, Objective, Design, Sample, Instrument, Validity and Side Effects.................................30

Table 2
Relevant Terms used throughout the manuscript........................................34
Introduction

This manuscript presents an evidence-based review of research on a variety of treatment options, aside from traditional hormone replacement therapy (HRT), for women in menopause. In 2002, the Women's Health Initiative study (WHI) was halted three years early after researchers concluded that combined estrogen and progestin increase women’s risk of stroke, heart attack, breast and ovarian cancer (National Heart, Lung & Blood Institute [NHLBI], 2003). Findings from the Women's Health Initiative trial (WHI), affirmed that 6 million women in the United States were taking HRT, which translates into nearly 6,000 cases of breast cancer overall. Over a 5 year time period of taking HRT, this could mean 30,000 more cases of breast cancer (NHLBI, 2003).

Menopause is defined as the cessation of menstruation due to cease in activity of the ovarian follicles (Paoletti & Wenger, 2003). For the purpose of this manuscript, the definition of menopausal symptoms will also be inclusive of symptoms experienced by women in the period of perimenopause and postmenopause. Perimenopause is defined as irregular menstrual cycles, vasomotor symptoms and mood lability (Shulman & Harari, 2004). The North American Menopause Society has defined perimenopause as “the menopausal transition, plus 1 year after the final menstrual period” (Shulman & Harari, 2004, p.35). Postmenopause is defined as “dating from the final menstrual period, regardless of whether the menopause was induced or spontaneous” (Utian, 2001, p. 400). After several years of being in postmenopause, many women adapt to the decreased amounts of circulating hormones and have less problems with hot flashes and mood lability. However, in all
phases of menopause a woman's risk of heart disease, bone loss and vaginal
dryness increases due to decreased estrogen levels (NHLBI, 2003). The significance
of distressing menopausal side effects has led women to pursue alternative avenues
of therapy that do not involve traditional hormone replacement therapy.

Clinical research data of different treatment options that help to control hot
flashes, depression, cardiac function, improve bone mineral density, vaginal dryness,
and other systemic symptoms brought on by menopause, will be examined. Options
range from soy products and selective estrogen receptor modulators (SERMs), to
narcotic therapies and other alternative therapies. Some of these alternative
therapies include soy-isoflavones, raloxifene, clonidine, salmon calcitonin and
melatonin. This evidence will provide both nurse practitioners and menopausal
women a broader knowledge of different effective therapies that can be utilized to
help with symptoms of menopause. The information obtained from clinical research,
will work to build the practitioner's body of knowledge about therapeutic options for
their patients in menopause.

A comprehensive review of research literature examines different alternative
replacement therapies. These alternative therapies range from soy products
containing phytoestrogens in their molecular make-up to salmon calcitonin,
melatonin, clonidine, and raloxifene. The content of each study is reviewed to
provide an accurate representation about which therapies are useful and which
therapies are not useful. This manuscript also examines subjective data about
women's responses to each alternative therapy regimen for the purpose of better
understanding whether associated symptoms of menopause are successfully
relieved. The Roy Adaptation Model (RAM) is introduced and used as the framework from which to describe the level of adaptation menopausal women must attain in order to establish homeostasis in their changing psychological and physiological environment.

Background

Menopausal women experience aggravating physical, emotional and mental symptoms attributed to menopause (Kittell, Kernoff-Mansfield, & Voda, 1998). Among these symptoms, hot flashes are generally at the top of the list of annoying, distractful and embarrassing physical symptoms (Kittell, et al., 1998). Women in menopause experience other ailing side effects attributed to menopause, such as decreased bone mineral density (BMD), depression, vaginal dryness and a decline in cardiac function. The ailing symptoms of menopause support the need for alternate treatment options that relieve physical symptoms without increasing risk for life threatening diseases.

In the 1960s, estrogen was a popular drug to relieve menopausal symptoms and was marketed without adequate safety testing (Vanderhaeghe, 2003). Soon estrogen became one of the top 10 drugs sold in the United States for treating menopause. By the 1970s, estrogen was found to increase endometrial cancer by 14 times and caused a 30% increase in breast cancer (Vanderhaeghe, 2003). Researchers explored options that would keep estrogen on the market and discovered that opposing estrogen with synthetic progestin would stop
overstimulation of the endometrial lining (Colditz, Hankinson, Hunter, Willett, Manson, & Stampfer, et al., 1995).

The belief that opposing estrogen with progestin is good for women held constant until 1995, when a report in the New England Journal of Medicine confirmed that combined estrogen and progestin increased women’s risk of ovarian and breast cancer (Colditz et al., 1995). This detrimental evidence was re-visited and supported in 2002, when the Women’s Health Initiative study (WHI) halted three years early after researchers concluded that combined estrogen and progestin increase women’s risk of stroke, heart attack, breast and ovarian cancer (NHLBI, 2003).

**Framework**

The Roy Adaptation Model (RAM) acts as a structural guide from which to classify internal and external stimuli that menopausal women experience. Roy categorizes people in four groups according to modes of adaptation; physiologic, self-concept, role-function and interdependence. Roy describes people as having “zones” surrounding their levels of adaptation. Anything that falls inside the zone can be positively adapted to, anything that falls outside the zone will be negatively adapted to (Hanna & Roy, 2001). According to Roy, a person is a bio-psychosocial being interacting with the changing environment. People use both acquired social and innate biological mechanisms to interact and cope with the changing world as with menopause. Women in menopause want to freely exist in a symptom free world. Re-establishing homeostasis will enable menopausal women to return to their normal lives.
Roy suggests that the level of adaptation by the person should work to achieve ways of removing stimuli in order to renew their quality of life. Roy describes health as being a constant state of positive adaptation to external and internal stimuli threatening to disrupt the integrity of the system. A healthy person is one who can positively adapt and avoid destruction of integrity (Hanna & Roy, 2001). There are two parts to self-concept; the physical self and the personal self, the whole is reference to its parts and their relationships to one another (Hanna & Roy, 2001). In order for the person to feel whole, all aspects of the human entity must function in synchrony. The role-function mode is concerned with the roles of the person in relation to the outside world. This mode is focused on social integrity. In relation to menopausal women, role-function is pertinent, because women have a desire to function in social unity with others. Interdependence mode focuses on the mutual exchange of giving and receiving love, respect and value. The goal is for the person to feel at ease and secure in nurturing relationships, enabling the person to both give and receive affection. This mode contributes to both health and wholeness in a person. For menopausal women, obstacles such as depressed mood and irritability can interfere with their basic need for nurturing relationships (Hanna & Roy, 2001).

Roy's concepts can be applied to the mechanism of menopause. The RAM was chosen because the adaptation process is one rendered by women in menopause on a daily basis. Menopause has been described as a stressful life event that involves stimulus such as hot flashes, irritability and mood swings (Kam, Dennehy, & Tsourounis, 2002). Roy's model provides structure for explaining the influence of stimuli and the effect it has on the adaptation ability of women in
menopause. The external and internal stimuli concepts correspond with the sort of stimuli experienced by menopausal women. The model also provides groundwork for how to prepare nursing interventions. The RAM is consistent with the perspective of stressful events that may effect menopausal women. This type of stress is viewed as a direct result of external and internal stimuli that stem from the person and the world around them (Hanna & Roy, 2002). Hot flashes and depressive symptoms are stressful events that result from a combination of stimuli. Knowing ways to prevent stimuli or change adaptation modes will help menopausal women better cope.

Literature Review

Hot flashes are a common aggravating side effect of menopause. North American and European postmenopausal women report the highest number of hot flashes. The hypothesis is that this is due, in part, to consumption of diets low in phytoestrogen containing foods like soy (Somekawa et al., 2001). Of the menopausal women from these two continents, 70-80% report having hot flashes compared to less than 20% experienced by their Japanese, Chinese and Southeast Asian counterparts (Somekawa et al., 2001). The speculation for why there is a decrease in number of hot flashes experienced by postmenopausal women in Asian countries is that their diets contain more naturally occurring, estrogenic compounds like soy, tofu, miso, temph and soy milk (Van de Weijer & Barentsen, 2002).

Kittell et al. (1998) studied women recruited from a Midlife Women's Health Study initiated in 1991 (see Table 1). Women who reported having changes from their normal menstrual bleeding were asked to do a telephone survey. Personal
identifiers were removed from the transcribed text and code numbers were assigned
to all transcripts. Women ranged in age from 41 to 54 (n=61) in the data set. Most
were white, educated and middle class. The interviews lasted between 23 and 110
minutes with a mean of 40 to 45 minutes. Each woman was asked to describe the
changes she was having and how they affected her life. Women expressed hot
flashes as being one of the most “embarrassing, unexpected” side effects of
menopause. Most women detailed this side effect as “a change in appearance that
consisted of turning beet-red and dripping with sweat” (Kittell et al., 1998, p. 619).

Kleijn, Schouw, Wilson, Grobbee & Jacques (2002) studied 964 Caucasian
menopausal women who participated in the Framingham Offspring study (see Table
1). The participants were asked to estimate the daily dietary intake of phytoestrogens
they consumed. Researchers identified food sources that contain phytoestrogens for
the women participating in the study. The concentration of the different
phytoestrogens in each food was scored in 7 categories and multiplied by serving
size. The study revealed western menopausal women to consume only a low 1 mg
of daily dietary phytoestrogens when compared with that of Asian women from Asia
who consume upwards of 20-80 mgs per day (Kleijn et al., 2002). This discovery
may contribute to the observation that Asian women experience less hot flashes
attributed to diet.

The results from the aforementioned study were obtained by examining
offspring of subjects from the longitudinal Framingham Offspring study that ran
between 1948 and 1950. The offspring cohort was examined repeatedly over a 3 to
4 year period. Between 1991 and 1994, 3799 subjects of the offspring cohort
participated in the 5th exam cycle. Of these subjects, 1061 were menopausal women without menses for greater than one year. The researchers only studied menopausal women who filled out a Food Frequency Questionnaire (FFQ) and those who ate a normal balanced diet. Nine hundred and sixty four subjects remained eligible to study the daily consumption of phytoestrogens. The self-administered FFQ was used to assess usual consumption of food. The FFQ contained 130 food items and asked subjects how often they consume these items over the previous year. The 9 responses ranged from "never" to "more than 6 times per day." Each food item in the FFQ was scored by calculating the amount of phytoestrogens that it contained, then values were converted to milligrams per 100 grams. The score of the food items in milligrams was multiplied by the frequency of consumption and then summed for all food groups to obtain individual intake. The determination that Western postmenopausal women consume less than 1 mg per day of phytoestrogens was based on these findings (Kleijn et al., 2002).

Somekawa et al. (2001) found menopausal Japanese women to have a decrease in hot flashes, backaches, heart palpitations and an increase in BMD in women who consume high levels of soy isoflavones (see Table 1). The study consisted of 478 postmenopausal women ages 44 to 80. Enrollment for the study was from January 1998 to January 2000. Women were excluded, if they exercised excessively (more than 2 hours per day), were smokers, alcoholics, had ischemic heart disease, liver disease, diabetes, endocrine diseases, depression, were taking medications that could alter lipid levels, or had a history of carcinoma. Participants were assigned to two groups according to years since menopause. One group
consisted of women in menopause less than 5 years and the other group consisted of women in menopause greater than 5 years. Each group was then broken down into 4 subgroups based on the intake of isoflavones. The amount of isoflavones ranged from the low intake group of 35 mg/day up to the high intake group of over 65 mg/day. Weekly consumption was divided by seven, monthly consumption by 30 and yearly consumption by 365. Prior to the study, lipid profiles, BMD density tests and demographic variables were obtained.

At the conclusion of the 2-year study, researchers identified that the major source of soy came from soybeans. Researchers also concluded that there was a decrease in hot flashes, heart palpitations and an increase in BMD by participants in the higher isoflavone intake group (p=0.05). Differences in serum lipids were not found to be significant in either group. The researchers attribute the improvement of associated menopausal symptoms to a high intake of soy isoflavones (Somekawa et al., 2001).

**Phytoestrogens**

Women who are unwilling to take traditional hormone replacement therapy may view herbal remedies as more natural (Glazier & Bowman, 2001). Non-pharmacologic, alternative therapies that contain concentrations of phytoestrogens are available in both pill form and as food supplements, and both have been shown to decrease hot flashes (Moyad, 2002). Phytoestrogens come from plant extract and pharmokinetically resemble the body’s weakest form of estrogen “estriol” (Moyad, 2002). Phytoestrogens are a group of non-steroidal plant compounds that contain a
phenolic ring, which enables them to bind estrogen receptors in humans. Two estrogenic receptors have been located by researchers; the alpha-receptor and the beta-receptor (Moyad, 2002). Phytoestrogens are considered to be selective estrogen receptor modulators (SERM) that can bind estrogenic receptors and specific DNA sequences in the cell. When phytoestrogens bind numerous alpha and beta estrogen receptors at once, the combination of receptor activation and gene activation causes changes in target cell confirmation. These modifications may amount to physically noticeable changes like decrease in hot flashes and improvement in bone density and cardiac function (Fitzpatrick, 1999).

Phytoestrogens produce their effect on the beta-receptor, because their affinity for alpha-receptors is not nearly as strong (Moyad, 2002). Scientists believe that the increased affinity for the beta-receptor, as opposed to the alpha-receptor, is the reason for the increased benefit by phytoestrogens on the central nervous system, blood vessels and bone (Moyad, 2002). Phytoestrogens also do not exert as much effect on breast and endometrial tissue, because of their poor affinity for the alpha-receptor (Fitzpatrick, 1999).

There are 3 main types of phytoestrogens; isoflavones, coumestans and lignans. Phytoestrogens are found in soy, chickpeas, clover, lentils and beans (Glazier & Bowman, 2001). Phytoestrogens were initially studied for their estrogenic effect in decreasing the risk of breast cancer (Glazier & Bowman, 2001). However, studies by Albertazzi et al. (1998), Albert et al. (2002), Drapier Faure, Chantre, & Mares et al. (2002), and Kam et al. (2002) now affirm phytoestrogens may also be beneficial in relieving vasomotor responses in postmenopausal women.
Albertazzi, et al. (1998) examined the effects of daily dietary soy powder on hot flashes (see Table 1). The study was a 12-week, double blind, parallel, randomized, placebo-controlled trial of 104 postmenopausal women who had a minimum of 7 hot flashes in a 24-hour period in the previous 2 to 4 weeks before the study. Baseline follicle stimulating hormone (FSH) levels were drawn and had to be at least 50 IU/L and baseline estradiol levels had to be less than 35 mg/ml. The eliminating criteria consisted of women taking HRT or any other drugs used to treat hot flashes.

Fifty-one women were randomly assigned to take 60 g/day of soy and 53 women were assigned to take 60 g/day of casein. At the end of the study, postmenopausal women taking the soy supplement had a 45% decrease in daily hot flashes as compared to a 30% decrease in those taking the casein (p<0.01). Twenty-five subjects withdrew from the study due to gastrointestinal side effects. Of the subjects who dropped out of the study 11 were from the soy group and 14 were from the casein group (Albertazzi et al, 1998).

A multicenter, open, prospective, observational and non-randomized study was done in 13 communities in Spain by Albert et al. (2002). The objective was to investigate the efficacy of soy isoflavones in decreasing symptoms derived from lack of estrogen, namely hot flashes. The participants consisted of 146 Spanish women with established menopause. Exclusion criteria consisted of women who use HRT or have used HRT in the previous 6 months, use of vitamin E or raloxifene, and women with a history of breast cancer. Each participant received 35 mg of soy isoflavones per day in two doses for 4 months. Women who averaged 4 to 9 hot flashes per day
had a 47% decrease in hot flashes after taking soy-isoflavones (P<0.003). All other associated menopausal side effects like anxiety, depression, vaginal dryness and bone pain also improved (p<0.003). Two participants discontinued the study because of gastrointestinal problems related to the supplements.

Drapier Faure, et al. (2002) conducted a randomized, double blind, placebo controlled, multicenter, parallel study. In the study, 75 menopausal women suffering from 7 or more hot flashes per day were randomized into two groups (see Table 1). The exclusion criteria consisted of women taking HRT or any other drugs used to relieve menopausal symptoms. A standardized 325 mg soy isoflavone supplement that contained 17.5 mg of total isoflavone or a placebo pill were assigned to each group. Each group took two pills, twice per day, of either the standardized soy supplement or the placebo supplement. After the first four weeks menopausal women taking the soy extract had a 38% decrease in hot flashes over a 24 hour period. At week 8, the women taking the soy supplement experienced a 51% decrease in hot flashes. By 16 weeks, these women were found to have a 61% decrease in hot flashes over a 24-hour period as compared with women in the placebo group who only had a 21% decrease in daily hot flashes. In the study, it does not specify the method of data analysis or if Pearson’s correlation test was used to compare data.

Kam et al. (2002) examined patterns of dietary soy supplements during menopause (see Table 1). The researchers looked at information about type of supplements being taken, prevalence, and rationale for use. A survey tool was distributed to 105, self-identified, eligible, menopausal women attending a Women’s
Health conference. The survey tool asked questions about type of menopausal symptoms, prescription products being used, supplements, and lifestyle modifications done to relieve associated menopausal symptoms. The survey answers were scored in a Likert scale format, where 1 represented an answer of “not satisfied” and 5 represented an answer of “completely satisfied.” The mean age of the cohort was 53.7 years old. The results of the survey discovered that 29% of the study cohort used HRT, 16% used HRT and a dietary supplement containing phytoestrogen, 32% used only phytoestrogen containing supplements and 13% used nothing. Women who used alternative phytoestrogen supplements (i.e. tofu and soy milk) reported a perceived better quality-of-life with regard to relief from hot flashes, vaginal dryness, decreased libido and mood swings. Five participants were excluded due to regular menstrual cycles or a history of a hysterectomy. The data collected was retrospective and self-reported, which left room for “recall bias.”

Bromberger, Meyer, Kravitz, & Sommer (2001) conducted a multiethnic Study of Women’s Health Across the Nation (SWAN) that took place in 7 regions of the United States. The cohort consisted of 16,065 White, Chinese, African American, Hispanic, and Japanese American women from Newark, New Jersey to Los Angeles, California, ages 40-55 years old. Based on use of HRT in the previous 3 months, pregnancy, history of hysterectomy, significant weight loss and illness, 5,123 participants were eliminated. The study was a longitudinal design from 1995-1997 that recorded data on 10,374 women and subjects were obtained by random digit dialing by telephone and by snowball sampling. Participants completed a 15-minute, 12-item survey that collected demographic data, health data and psychologic distress
data at both the beginning of the study and at the conclusion of the study. Results from both the initial analysis and the final analysis revealed that in comparison to Whites, Hispanics and African Americans, the Japanese and Chinese American women reported lower psychologic distress with regard to vasomotor changes (hot flashes), other health and demographic problems (Bromberger et al., 2001). Researchers claim that the results of the study reflect higher amounts of isoflavones in the form of soy in the Japanese and Chinese diets (Bromberger et al., 2001).

Kritz-Silverstein, Von Muhlen, Barrett-Connor, and Bressel (2003) reported that soy has a benefit on cognitive functioning (see Table 1). Participants were part of the Soy and Postmenopausal Health In Aging Study (SOPHIA). The SOPHIA study was a 6 month, double blind, randomized, placebo-controlled clinical trial on 56 women with a mean age of 61 years old. Women in the study were in good health, postmenopausal for at least 2 years and not using HRT. Women were recruited from mass mailings based on voter registration lists, newspaper advertisements and women's health organization functions. Women were randomly assigned to the treatment group or the placebo group. The treatment group received two pills per day each containing 55 mg of soy isoflavones and the placebo group received two identical pills that contained inert ingredients. Baseline questionnaires asked demographic questions, educational level, occupation, race/ethnicity, alcohol and cigarette use and menopausal history. The Beck Depression Inventory (BDI) was used to assess for depression. Once the score was summed for the BDI, women who were considered more depressed were given the Mini Mental Status Exam (MMSE). Both at baseline and 6 months, cognitive function was assessed using the
Trials A and Trials B, Category Fluency and Logical Memory Recall instruments. These instruments measured visualmotor and verbal memory (Kritz-Silverstein et al., 2003).

At the 6 month conclusion of the study, overall mean compliance was 98% in the placebo group and 97% in the treatment group. Women in the treatment group showed more of an improvement on the cognitive tests than those in the placebo group (p=0.03). There was a 23% improvement in the treatment group between baseline and follow up on the Category Fluency test, compared with only a 3% improvement for women in the placebo group. Age and education levels were adjusted accordingly for each test. Due to the relatively short length of the study, scores between baseline and follow up may reflect a “learning effect” and not an actual improvement. In order to achieve a more definitive hypothesis about the benefit of cognitive function while ingesting isoflavones, a longer study of the same magnitude is necessary.

Germain, Peterson, Robinson, and Alekel (2000) examined menopausal symptoms in response to taking a standard isoflavone extract yielded no significant improvement (see Table 1). The study was a double blind, 24-week study that consisted of 69 menopausal women randomized into three groups. The first treatment group ingested isoflavone rich soy protein (80.4 mg/day), the second treatment group isoflavone poor soy protein (4.4 mg/day) and the placebo group ingested whey protein. A menopausal index was used to assess hot flashes at baseline, 12 and 24 weeks. Women kept a menopausal diary for 5 days at baseline, 12 and 24 weeks and were also asked to do a 24-hour urine collection before each 6-
week appointment. Participants were menopausal women with 10 or more hot flashes and night sweats per 24-hour period. The exclusion criteria included women taking HRT, women with chronic diseases and women with a BMI of greater than 31 or less than 20. Women also had to have a FSH level of greater than or equal to 30 UI/L to be participants of the study.

Adherence to treatment and placebo regimens was high, reflected by the urinary excretion of isoflavones. At the conclusion of the study no significant improvement of menopausal symptoms were indicated in the cohort groups treated with soy isoflavones. Repeated measures of analysis of variance indicated no change in treatment effect (p=0.29). The chi square analyses was not indicative of a change in severity of hot flashes from baseline (p=0.97) to follow up (p=0.53) (Germain et al., 2000).

Cumulatively, phytoestrogens have been shown to have a positive effect regarding the symptoms of menopause (Albert et al., 2002). The Food and Drug Administration (FDA) approved the claim that phytoestrogens are good in decreasing risk for heart disease and postmenopausal osteoporosis (Moyad, 2002). The FDA is currently reviewing studies about the benefit of phytoestrogens on menopausal symptoms (Moyad, 2002).

**Non-Phytoestrogen Containing Therapies**

Alternative therapies to relieve symptoms of menopause that do not contain phytoestrogens in their molecular make up have also been studied in clinical trials. Some such therapies include raloxifene, salmon calcitonin, clonidine and melatonin.
These therapeutic modalities have proven beneficial effects on the symptoms of menopause. However, many of the studies did not result in the type of supportive evidence needed to show improvement of the specific symptom in question or effect clinical practice.

Raloxifene has been shown to prevent bone loss, improve serum lipid profiles, and improve cardiac function in menopausal women (Lidor et al., 2002). Raloxifene is a Selective Estrogen Receptor Modulator (SERM) that is considered "devoid" of estrogen-related adverse effects (Lidor et al., 2002).

Setacci et al. (2001) reported a reduction in carotid artery pulse index (PI) (the pressure exerted on the walls of the carotid arteries) in healthy postmenopausal women taking raloxifene (see Table 1). The trial consisted of 66 healthy women in menopause, who had ceased menses for greater than one year. Mean ages of the women ranged from 48-58 years old. None of the women participating had taken thyroid hormones, steroids or raloxifene in the previous 12 months. Women in the trial had normal lipid levels and their blood pressures were in a normal range. Women with known cardiovascular disease were excluded from the trial. Women were randomly divided into 2 groups, Group A (33 participants) received raloxifene treatments of 60 mg/day for 6 months and Group B (33 participants) did not receive any type of therapy. Doppler ultrasonography was performed at the beginning of the trial and again every 2 months throughout the study. After only 2 months into the study participants taking raloxifene showed a marked reduction in PI. After 2 months there was a reduction of 6.1%, after 4 months there was a reduction of 11.2% and at the conclusion of the 6 months there was a 13.2% reduction in PI.
Calcitonin is believed to inhibit bone demineralization by inhibiting bone resorption (Melis et al., 1996). Salmon calcitonin is the most widely used calcitonin. However, oral and injectable routes of administration have a high correlation with side effects and poor compliance (Melis et al., 1996).

A study by Melis et al. (1996) found that combined nasal spray salmon calcitonin (sCT) and intravaginal estriol (E3) have beneficial effects on declining BMD and neurovegetative effects (hot flashes and sweating) (see Table 1). The clinical trial included 214 Italian menopausal women, mean age of 53.2 years old. Women were randomly assigned to one of 4 groups for 12 months of treatment. Participants were excluded based on endometrial thickness of greater than 4 mm, smoking more than 15 cigarettes per day, drinking more than 500 ml of alcohol per day, drinking more than 4 coffees per day, osteopenic diseases and use of HRT. The first group received 0.5/mg of E3 every other day, plus calcium 0.5 mg everyday. The second group received 0.5/mg of E3 every other day, calcium 0.5 mg everyday and sCT 50 IU two times per day. The third group received sCT 50 IU two times per day and calcium 0.5 mg everyday. Lastly, the fourth group received 0.5 mg of calcium everyday. At baseline, 6 and 12, months BMD at the distal 1/10 of the non-dominant radius was measured by dual photon absorptiometry. At baseline, 6 and 12 months bone metabolites were observed by looking at alkaline phosphatase, urinary excretion of calcium by spectrophotometry and urinary excretion of hydroxyproline after hydrolysis by a colorimetric method. At baseline and at the end of treatment participants self reported their 24-hour frequency and intensity of neurovegetative symptoms (hot flashes and sweating).
The trial concluded that sCT 100 IU/day nasal spray and 0.5 mg of calcium increased BMD values. Alone, E3 exerted an effect on bone density, but not significantly. Intravaginal E3 improved hot flashes and sweating without increasing endometrial growth. At the conclusion of the study, there were no side effects reported from E3 or sCT. The combination of intravaginal E3 with sCT may potentiate the relief of symptoms associated with menopause.

Bellipanni et al. (2000) reported an improvement of mood and depression symptoms in Italian menopausal women taking melatonin (see Table 1). The study consisted of 79 premenopausal, perimenopausal and postmenopausal women ranging from 42 to 62 years old. Women were randomly assigned into 2 groups by age (42-49 yrs old) and (50-62 yrs old). Women were selected based on having no relevant pathologies, taking no medications, HRT or herbal remedies. Women had to have healthy lifestyles with a Mediterranean rich diet (fruits, vegetables, fresh fish and limited red meat) and normal sleeping patterns (7 hours per night or more). Data was recorded at baseline, 3 and 6 months. All participants took the capsules at bedtime between 10 and 11pm. Participants measured MEL in saliva every night with a commercial kit donated by Diagnos Techs in Kent, Washington. At the end of the 6 months results were collected from all 79 women.

MEL was found to produce a significant increase of total T3 and T4 after 3 and 6 months, as compared to placebo. MEL was also found to produce a significant decrease in plasma follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the younger group of women. MEL had no significant effect on estrogen and progesterone levels. Participants self reported a significant improvement in mood.
and depression when treated with MEL. Women in both the younger group and older group reported a decrease in hot flashes, palpitations and an improvement in sleep.

Freedman and Dinsay (2000) found that clonidine raised the sweating threshold for symptomatic women experiencing hot flashes (see Table 1). Clonidine is an alpha 2-adrenergic agonist that works at the alpha 2-receptor site and lowers hypothalamic norepinephrine levels, which helps to ameliorate hot flashes. The study consisted of 19 postmenopausal women. Twelve of the participants reported having at least 5 or more hot flashes per day and 7 participants were asymptomatic. All participants were in good health, normotensive, without menses for greater than one year and were not taking HRT. Sixteen of the participants were naturally menopausal and three were not.

Just prior to data collection, women received either an intravenous injection of clonidine (2 ug/kg) or normal saline over a 5-minute period. Data was collected from baseline to 30 minutes and the room temperature was 23 degrees celcius. The room temperature was then increased to 26 degrees celcius and the participant's torsos were covered with hot water pads at 42 degrees celcius. The experiment took place over a 10-minute period of time until the sweating threshold was reached. Analysis of core body temperature was recorded every 30 seconds by using a radiotelemetry pill ingested 90 minutes before data collection. Radiotelemetry signals were detected by a wire antenna placed around the participant's torso. Yellow Springs instruments measured skin temperature. Mean skin temperature was calculated after data collection. Sweating activity was recorded by using a capacitance hygrometer with a 3.5 cm plastic chamber attached over the sternum. Blood pressure was also
measured every 4 minutes. The temperature of the skin, conductance of the skin and sweating activity data were recorded on a polygraph that was digitalized at 100 Hz by an analog-to-digital converter and then data was stored in a computer. The differences in demographic and hormonal data were analyzed by using unpaired t-tests. Physiologic data achieved by the test session was analyzed with repeated measures of analysis of variance. The significance level for all analysis was p<0.05.

The core body temperature data from the placebo session showed the sweating threshold was significantly lower in symptomatic women than in the asymptomatic women. The experiment with clonidine proved to significantly increase the sweating threshold for symptomatic women (p<0.01), but decreased the sweating threshold in the asymptomatic participants (p<0.05). No dramatic changes in skin temperature were observed in the symptomatic or asymptomatic women who had clonidine injections. Systolic and diastolic blood pressures were lower for the participants in the clonidine session versus the placebo session.

Methods Used in Reviewed Studies

Of the studies referenced, none had theoretical frameworks. All the studies had implied frameworks that combined both physiologic and pathologic theories about postmenopausal symptoms and the benefits of alternative therapies. The majority of the studies were designed around the symptoms of menopause in relation to the effect of non-hormone replacement therapies. Kam et al. (2002) used a pathologic description of menopausal symptoms. *Symptoms commonly associated
with menopause include vasomotor changes (night sweats, hot flashes), vaginal dryness, mood and libido changes, bladder control problems and memory loss” (p. 73). After laying the groundwork, the study concludes that these are the symptoms for which people seek alternative therapy. All of the studies used physiologic measurements as the main method of collecting data. Most studies used double blind, randomized, placebo-controlled designs that helped foster the highest level of validity (see Table 1). Some of the studies used questionnaires, available data and records to contribute to the overall method of research. Bromberger et al. (2001) used a Medical Outcomes Study Social Support Survey (MOSSSS) to help exclude extraneous variables that might sway the data. Kleijn et al. (2002) used the Food Frequency Questionnaire (FFQ) to determine how much daily dietary phytoestrogens are consumed by western postmenopausal women. Kritz-Silverstein et al. (2003) used the Beck Depression Inventory (BDI) and the Mini Mental Status Exam (MMSE) to assess depression status of participants.

All of the studies that researched the effect of phytoestrogens on postmenopausal women found that the main adverse reactions of the therapy involved gastrointestinal problems (Albert et al. 2002; Van de Weijer & Barentson, 2002). For this reason, a comprehensive study needs to be done examining the effects of phytoestrogens on the gastrointestinal tract. Further research needs to be conducted on the effects of phytoestrogens in postmenopausal women with hypertension. Since the Food and Drug Administration (FDA) recognizes soy extract as decreasing the risk for heart disease, it would be of interest to know if
phytoestrogens can both decrease blood pressure, as well as relieve menopausal symptoms.

The previous studies discussed in detail the biochemical make-up of phytoestrogens and how they affect pharmokinetics in the body. The only inconsistency in the available research is that the adverse reactions of phytoestrogens have not been fully studied. While examining the effects of phytoestrogens on the gastrointestinal tract, it would be pertinent to check pancreas and liver enzymes to ensure that no organ damage is occurring. This type of physiologic experiment should be conducted in a prospective study, to allow researchers to know the extent to which phytoestrogens affect other organs in the body.

**Implications for Nurse Practitioners**

Menopause is a challenging time in a woman's life both physically and emotionally (Reddish, 2002). Women experience a variety of complex physiologic factors ranging from hot flashes to decreased bone mineral density (Finkel, Cohen, & Mahoney, 2001). Many women look to nurse practitioners for guidance, emotional support and recommendations of options that relieve menopausal symptoms (Finkel et al., 2001). Lack of current knowledge by nurse practitioners may inhibit them from suggesting the best treatment regimen for relieving menopausal symptoms in their patients (Finkel et al., 2001). This manuscript enables nurse practitioners to review a variety of clinically tested therapies that could potentially be recommended to patients for relief of menopausal related symptoms. The information provided to the patient by
the nurse practitioner may decrease patient anxiety and the feeling of having unanswered questions. The nurse practitioner can tailor treatment regimens, such as those that contain phytoestrogens or those that do not, to better meet the patient’s need for relief of menopausal symptoms. Meeting the patient’s treatment needs will help foster a solid patient-provider relationship.

Conclusion

Since the 1960s, the main treatment for hot flashes was HRT. However, researchers from the WHI trial announced in July of 2002, that combination HRT increases the risk of breast cancer, heart attack and stroke (NHLBI, 2003). Shortly after the WHI study was canceled, the Journal of the American Medical Association published a follow up study of 44,241 women who participated in a breast cancer detection study. This study showed women on unopposed estrogen replacement (without progesterone) had an increased risk of ovarian cancer (Meschino, 2002). The risk increased to 3.2% for women who have taken unopposed estrogen for greater than 20 years (Meschino, 2002). For these reasons, researchers are interested in whether non-pharmacological alternatives can adequately manage the physical symptoms of menopause (Freedman & Dinsay, 2000).

A few factors were not included in many of the studies those being gastrointestinal side effects, hysterectomy and oophorectomy status. For this reason, more research needs to be conducted on alternative therapies to help discover a therapy that will be less harmful to women as well as holistically provide homeostasis.
References


*Australian Family Physician, 31*(5) 427-432.


<table>
<thead>
<tr>
<th>Source</th>
<th>Objective</th>
<th>Design</th>
<th>Sample</th>
<th>Instrument</th>
<th>Validity</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert, Altabre, Baro, Buendia, Cabero &amp; Canelo (2002)</td>
<td>To examine the efficacy and safety of phytoestrogen preparation derived from Glycine max in climacteric symptomatology</td>
<td>A multicentric, open, prospective, observational and non-randomized study</td>
<td>146 Spanish women with established menopause</td>
<td>Wilcoxon test was given to make it possible to compare variables between each visit. Blood pressure was analyzed by Student's t-test.</td>
<td>An analysis of covariance was performed and a the significance level was set at P&lt;0.05.</td>
<td>2 participants abandoned the study due to gastrointestinal side effects.</td>
</tr>
<tr>
<td>Albertazzi, Pansini, Bonaccorsi, Zanotti, Forini &amp; De Aloysio (1998)</td>
<td>To examine the effect of dietary soy supplementation on hot flushes.</td>
<td>A 12-week, double blind, parallel, randomized, placebo-controlled trial.</td>
<td>104 postmenopausal women had to have 7 hot flashes in a 24-hour period.</td>
<td>A daily diary was kept to record the number of hot flashes per 24 hours. Kupperman index assessed presence and severity of symptoms.</td>
<td>An analysis of covariance was used to analyze changes from baseline. The test was performed 2-sided at a significance level of P&lt;0.05. A linear regression analysis was performed.</td>
<td>25 participants quit the study due to gastrointestinal side effects. 11= from soy group 14= from casein group</td>
</tr>
<tr>
<td>Bellipanni, Bianchi, Pierpaoli, Bulian &amp; Aloysio (2000)</td>
<td>To examine the effects of Melatonin in perimenopausal and menopausal women.</td>
<td>A randomized, placebo-controlled study.</td>
<td>79 premenopausal, perimenopausal, and postmenopausal women ranging in age from 42-62 were randomly divided into 2 groups.</td>
<td>Questionnaires were given that asked physiology and demographic questions at baseline, 3 and 6 months. A commercial kit was given to measure saliva every night. Measured samples were transferred, centrifuged and a MEL1125 tracer was added and counted by a gamma counter.</td>
<td>Analysis of covariance was measured with a significance level of P&lt;0.05. Significance between means was assessed using paired Student's t-test and ANOVA. Linear regression was performed.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Bromberger, Meyer, Kravitz &amp; Sommer (2001)</td>
<td>To examine the psychologic distress and natural menopause.</td>
<td>A multi-ethnic, randomized, longitudinal, community study.</td>
<td>The cohort was 16,065 Caucasian, Chinese, African American, Hispanic and Japanese American women. 5,123 participants were eliminated based on not meeting study criteria.</td>
<td>15-minute, 12-item survey of demographic, health and psychologic distress questions. Medical Outcomes of Social Support Study to exclude external variables.</td>
<td>Univariate comparisons were made on psychologic distress using t-tests. Multivariate analysis was done on variables and a significance level of P&lt;0.05 was assigned. Analysis of variance was performed.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Participants</td>
<td>Method</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Drapicr Faure, Chaintre &amp; Mares (2002)</td>
<td>To examine the effects of standardized soy extract on hot flushes.</td>
<td>A multicentric, double blind, randomized placebo-controlled, parallel study.</td>
<td>75 menopausal women suffering from 7 or more hot flushes per day.</td>
<td>A special card was filled out daily to record number of hot flashes.</td>
<td>The primary analysis was based on the two-way repeated measures of variance. The test was performed two-sided at a significance level of α=0.05. 4 participants abandoned the study due to treatment inefficacy. 14 abandoned the study from the placebo group due to treatment inefficacy.</td>
<td></td>
</tr>
<tr>
<td>Freedman &amp; Dinsay (2000)</td>
<td>To examine whether Clonidine raises the sweating threshold in symptomatic menopausal women.</td>
<td>A randomized, placebo-controlled trial.</td>
<td>19 postmenopausal women. 12=symptomatic 7=asymptomatic.</td>
<td>Radiotelemetry pill ingested and signals picked up with antenna on torso. Sweating recorded by a capacitance hygrometer. Skin temperature recorded by polygraph digitalized at 100Hz and stored on computer.</td>
<td>Unpaired t-tests measured demographic and hormone data. Analysis of variance was done on t-test results. A significance level was set at P&lt;0.05. None reported.</td>
<td></td>
</tr>
<tr>
<td>Germain, Peterson, Robinson &amp; Alekel (2000)</td>
<td>To examine the effects of isoflavone rich and isoflavone poor soy protein on menopausal symptoms.</td>
<td>A 24-week, double blind, randomized, placebo-controlled trial.</td>
<td>69 menopausal women randomized to one of 3 groups.</td>
<td>A menopausal diary was kept. Urine collection before each visit, and Kruskal-Wallis test used to determine urinary isoflavone excretion.</td>
<td>Statistical analysis was performed by using PC SAS version 6.12. Reported analysis of variance done among treatment groups. Chi square test used to assess differences. The significance level was set at P&lt;0.05. None reported.</td>
<td></td>
</tr>
<tr>
<td>Kam, Dennehy &amp; Tsourounis (2002)</td>
<td>To examine dietary supplement use among menopausal women at a Women's conference.</td>
<td>A self-identified study.</td>
<td>105 self-identified menopausal women answered a survey of question about HRT, supplement use and relief of symptoms.</td>
<td>Survey in Likert scale format.</td>
<td>Pearson's correlation test was used to get a significance level for compared data. None reported.</td>
<td></td>
</tr>
<tr>
<td>Kittell, Kernoff-Mansfield &amp; Voda (1998)</td>
<td>Keeping up appearance: the basic social process of the menopausal transition.</td>
<td>Participants recruited from a Midlife Women's Health Study.</td>
<td>61 women, 41-54 yrs old, were asked to do a telephone interview-survey about menopausal changes.</td>
<td>Telephone survey.</td>
<td>No methods of data analysis identified.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Participants</td>
<td>Measures</td>
<td>Analysis</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Klein, Schouw, Wilson, Grobbee &amp; Jacques (2002)</td>
<td>To examine dietary intake of phytoestrogens on favorable metabolic cardiovascular risk profile in menopausal women.</td>
<td>Recruited from Framingham Offspring Study. Longitudinal design from 1991-1994.</td>
<td>964 Caucasian menopausal women did a questionnaire on daily phytoestrogen intake.</td>
<td>The score of the food items in milligrams was multiplied by frequency of consumption and then summed. The mean intake of phytoestrogens with standard deviation applied.</td>
<td>None reported.</td>
<td></td>
</tr>
<tr>
<td>Kritz-Silverstein, Von-Muhlen, Barrett-Connor &amp; Bressel (2003)</td>
<td>To examine isoflavones on cognitive function in older women.</td>
<td>A 6-month, double blind, randomized, placebo-controlled trial.</td>
<td>56 menopausal women (average age 61-ys old) were randomly assigned to treatment group or placebo group.</td>
<td>Beck Depression Inventory used to assess depression. Mini Mental Status Exam used once depression was noted. Cognitive function was assessed using Trials A and Trials B, Category Fluency and Logical Memory Recall tests.</td>
<td>Statistical analysis done using analysis of the variance. Chi square analysis done for categorical data. The significance level was set at P&lt;.05. All analysis done on SPSS system.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Melis, Cagnacci, Bruni, Falsetti, Jasonni, Nappi, Polatti &amp; Volpe (1996)</td>
<td>To examine the effect of Salmon Calcitonin plus intravaginal estradiol as an effective treatment for menopausal symptoms.</td>
<td>A double blind, randomized, placebo-controlled clinical trial.</td>
<td>214 menopausal women (average age 53.2-ys old) were randomly allocated to one of four groups for 12 months.</td>
<td>Bone mineral density at distal 1/10 of non-dominant radius measured by dual photon absorptiometry. Metabolites observed by examining alkaline phosphatase and calcium in urinary excretion.</td>
<td>Statistical analysis performed by ANOVA.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Setacci, Marca, Agricola, Morgante, Setacci, Cappelli, Petraglia &amp; De Leo (2001)</td>
<td>To examine the effect of Raloxifene on carotid artery pulse index in postmenopausal women.</td>
<td>A double blind, randomized, placebo-controlled clinical trial over 6 months.</td>
<td>66 healthy women in menopause for greater than 12 months, 48-58 yrs old, were randomized into two groups.</td>
<td>Doppler ultrasonography was performed at baseline and every 2 months throughout</td>
<td>Analysis of variance was performed. The significance level was set at P&lt;.05.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Note</td>
<td>Methodology</td>
<td>Analysis</td>
<td>Conclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somekawa, Chiguchi, Ishibashi &amp; Aso (2001)</td>
<td>To examine soy intake related to menopausal symptoms, serum lipids and bone mineral density in Japanese postmenopausal women.</td>
<td>A self-identified, randomized, placebo-controlled, longitudinal trial.</td>
<td>Lipid profiles, bone mineral density tests were performed at baseline and at the conclusion. Questionnaires were given to assess progress throughout.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>478 postmenopausal women ages 44-80 were randomly assigned to one of 4 groups.</td>
<td>Data analysis was performed using the Stat View 5.00 software system. Kruskal-Wallis test was used for continuous variables. Questionnaires were tested by one-way factorial analysis of variance and Scheffe's F test. A significance level was set at P&lt;.05.</td>
<td>None reported.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>