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ORIGINAL ARTICLE

Knowledge and attitude of primary care doctors towards management of postmenopausal symptoms

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KEYWORDS

Knowledge; Primary care physicians; Post-menopausal management

Abstract Background: According to the current recommendations, women with post-menopausal symptoms should be managed. Knowledge and perception of primary care physicians towards management of postmenopausal symptoms are deficient.

Aim: The aim of the present study was to explore knowledge and attitude of primary care doctors towards management of postmenopausal symptoms.

Methods: This study is a cross-sectional survey that was conducted from October to December 2010 in the five health regions in Kuwait. Two centers were selected randomly from each health region. All physicians who were currently working in the selected centers were asked to participate in the study. Out of 209 physicians, 142 agreed to participate and completed a self-administered questionnaire.

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Results: The study revealed that 82.4% of physicians had moderate knowledge about treatment options for postmenopausal symptoms, 88.0% discussed postmenopausal symptoms with their patients, and 45.1% of them either described or referred their patients for hormonal replacement therapy (HRT). The correct answers regarding 10 statements related to the Women Health Initiative finding were ranging from 2.8% to 78.9% which indicated low level of knowledge. Regarding the effectiveness of hormonal replacement therapy in postmenopausal women, the majority of the physicians agreed correctly that HRT is effective in prevention of osteoporosis (87.3%), treatment of vasomotor symptoms (83.7%), and treatment of vulvo-vaginal symptoms (82.4%). There was a variation among physicians opinion about the effectiveness of certain treatment options for managing hot flushes in postmenopausal women.

Conclusion: The results suggest that there is a lack of primary care physicians knowledge and confidence in recognizing signs and symptoms of menopause and in identifying and prescribing appropriate management.
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1. Introduction

Menopause is a physiological event occurring with ovarian failure and marks the end of women's reproductive life.¹ The average age of menopause is 51 years.¹ In 1960, the world population of women aged over 60 was below 250 million, but it is estimated that in the year 2030,^{1,2} billion will be peri or postmenopausal and that this total will increase by 4.7 million a year.² The average woman in the developed world can now expect to spend approximately one-third of her life in postmenopausal state.³

Because of these predicted changes in population structure, physicians are beginning to see that menopause is not a negligible phenomenon but a major public health problem.² Attitudes, perceptions, and expectations are part of the psychosocial phenomenon surrounding menopause.⁴ Women in midlife and health professionals believe that attitude plays a role in the experience of menopause.⁵

Hormonal changes at menopause are associated with numerous physical and psychological symptoms like vasomotor symptoms, sleep disturbances, mood alteration, depression, urinary tract infection, vaginal atrophy, and increased health risks for several chronic disorders including osteoporosis, cardiovascular disease, and loss of cognitive function. Menopausal symptoms are found to be less common in societies where menopause is viewed as a positive rather than negative event.⁴

The Massachusetts women health study did a longitudinal study on more than 2000 women between 45 and 55 years. This study showed that negative attitude towards menopause leads to less favorable mode of climacteric.⁶ This cultural aspect of menopausal symptoms has been discussed in a number of studies among Asian women including Japanese and Chinese population.¹ It is well established that hormonal replacement therapy (HRT) is an effective means of treating postmenopausal symptoms and preventing long term complications, such as osteoporosis.^{7–10} The HRT usage rate is low largely because majority remain poorly informed about this therapy.^{11,12}

Therefore, doctor's knowledge and perception towards menopause and participation in health related activities is expected to be more in primary health care (PHC) centers. The present study was an approach to evaluate primary care physician's knowledge and attitude towards management of postmenopausal symptoms in primary health care centers in Kuwait.

2. Methods

2.1. Setting and design

The health care system in Kuwait is divided into five regional health authorities. PHC is provided by 82 centers served by either family practice physicians (FPs) or general practitioners (GPs). This study is a cross-sectional survey that was conducted from October to December 2010 in the five health regions. The sampling unit used in this survey was the health center. Ten centers were randomly selected from the official national list of all PHC (two from each health region). All PHC physicians who were currently working in the selected centers were asked to participate in the study. Out of 209 physicians, 142 physicians agreed to participate in the study and returned the filled self-administered questionnaires. Participation was optional and verbal consent was obtained prior to conducting the survey. All the necessary approvals for carrying out the research were obtained. The Ethical Committee of the Kuwaiti Ministry of Health approved the research.

2.2. Study questionnaires

The predesigned self-administered questionnaire derived from other published studies dealing with the same topic as well as from our own experience was used to collect the information from the physicians. The administrative time for filling it was 20–30 min. In order to maintain confidentiality, questionnaire was made anonymous. It consisted of two parts. The first part includes personal and working characteristics (age, gender, nationality, marital status, and years at work, specialty, education certificates and jobs). The second part included questions about knowledge and attitude of physicians towards menopause (having enough knowledge about treatment option for postmenopausal symptoms, discussion of postmenopausal symptoms with patients, prescription or referral of patient for HRT, absolute and relative contra indication for HRT in menopause).

2.3. Statistical analysis

The Statistical Package for Social Sciences (SPSS-17) was used for data processing. Simple descriptive statistics were used

 Table 1
 General characteristics of participating physicians and their work features.

Characteristics	No.	%
Age (year)		
< 35	26	18.3
35-	52	36.6
45-	48	33.8
≥55	16	11.3
Gender		
Males	86	60.6
Females	56	39.4
Nationality		
K	26	18.3
NK	116	81.7
Education		
Bach	53	37.3
master	63	44.4
PHD or board	26	18.3
Marital status		
Single	16	11.3
Married	122	85.9
Divorced	4	2.8
Experience (year)		
< 5	13	9.2
5-10	31	21.8
>10	98	69.0
Specialty		
GP	111	78.2
FP	31	21.8
Total	142	100.0

(mean \pm standard deviation for quantitative variables, and frequency with percentage distribution for categorized variables).

3. Results

Out of 219 distributed questionnaires, 142 were returned back with 64.8% response rate. Table 1 describes the general characteristics of participating physicians. Their mean age ranged from 25 to 66 years was a mean of 43.3 \pm 9.1 years, more than 80% of them were above 35 year of age. Males were predominating females (60.6% versus 39.4%). Most of physicians (81.7%) were non-Kuwaiti and 69.0% of them had 10 or more years of experience as PHC physicians. According to specialty, 78.2% were GPs and 21.8% were FPs. Nearly about two-third of the participating physicians have master, PhD or Board certificates (62.7%).

Table 2 reveals that 6.3% of participating physicians said that they had poor knowledge about treatment options for postmenopausal symptoms and 82.4% declared that they had moderate knowledge. The majority of them (88.0%) stated that they have ever discussed postmenopausal symptoms with their patients. Among them, only 45.1% described or referred their patients for HRT.

Among those physicians who prescribed or referred patients for HRT, 50.0% did these for treatment of vasomotor symptoms, 37.5% attributed that for prevention or treatment of osteoporosis, while the minority did this for prevention of

Table 2	Physicians	knowled	lge and	attitud	e toward	ls postmen-
opausal	management					

Variable	No.	%
Knowledge about treatment option for post	menopausal	symptoms
I have no knowledge	9	6.3
I have moderate knowledge	117	82.4
I have good knowledge	16	11.3
Discussion of postmenopausal symptoms w	ith your pat	ients
No	17	12.0
Yes	125	88.0
Prescription or referral of any patient for it therapy	hormonal re	placement
No	78	54.9
Yes	64	45.1
Symptoms for which physician referred pat HRT	tients for or	prescribed
Treatment of vasomotor symptoms	32	50.0
Prevention of cardiovascular disease	5	7.8
Prevention or treatment of osteoporosis	24	37.5
Treatment of cognitive symptoms	3	4.7
Treatment of cognitive symptoms	64 ^a	100.0
Subtotal	•••	

cardiovascular disease or treatment of cognitive symptoms (7.8% and 4.7%, respectively)

Table 3 Illustrate the correct answers regarding 10 statements related to the Women Health Initiative finding. When the physician asked about the effect of prescribing estrogen plus progestin, only 12.7% answered correctly increased heart attack from multiple chooses. Only 2.8% chose correctly the increased risk of heart attack as a result of prescribing estrogen alone. According to FDA recommendations on hormonal therapy. 36.6% choose approved estrogen therapy for relief of moderate to severe hot flashes as correct choice. However, 31.0% of the physicians chose patients on combine HRT have increased risk of breast cancer after average 2-5 years correctly. Only 12.0% of the physicians chose correctly that FDA did not approved lower dose single tablet of prempro, containing 0.45 estrogen and 1.5 progestin for prevention of coronary heart disease or other cardiovascular disease. Severe liver disease, history of uterine fibrosis and venous thrombosis were chosen correctly as absolute contra indication for HRT in menopause by 78.9% of the physicians. On the other hand, only 21.8% chose correctly undiagnosed vaginal bleeding as relative contraindication for HRT in menopause. Regarding side effects, only 3.5% chose correctly severe abdominal pain as common side effect to HRT and 35.9% chose correctly severe depression as uncommon side effect to HRT. Moreover, 29.6% chose sexual desire is decreased after the menopause as correct answer.

Regarding physicians opinion about the effectiveness of HRT in postmenopausal women, the majority of the physicians agreed correctly that HRT is effective in prevention of osteoporosis (87.3%), treatment of vasomotor symptoms (hot flashes) (83.7%) and treatment of vulvo-vaginal symptoms (82.4%). On the other hand, around one-third of the physicians correctly disagreed that HRT is effective in prevention of chronic heart disease (28.1%), stroke (35.9%), treatment of dementia or Alzheimer (36.6%), skin wrinkles (33.1%), and increasing sexual

Table 3	Proportion of physicians an	swered correctly certain statements	for management of menopausal symptoms.

Women Health Initiative findings	No.	%
 Compared with placebo, prescribing estrogen plus progestin resulted in increased heart attack 	18	12.7
 Compared with placebo, prescribing estrogen alone resulted in increased risk of heart attack 	4	2.8
 According to FDA recommendations on hormonal therapy, estrogen therapy (combined or alone) approved for relief of moderate to severe hot flashes 	52	36.6
- Patients on combine hormonal replacement therapy (HRT) have increased risk of breast cancer after average 2–5 years	44	31.0
- FDA did not approved lower dose single tablet of prempro, containing 0.45 estrogen and 1.5 progestin for prevention of coronary heart disease or other cardiovascular disease	17	12.0
- Absolute contra indication for HRT in menopause is: severe liver disease, history of uterine fibrosis, venous thrombosis	112	78.9
- Relative contraindication for HRT in menopause is: undiagnosed vaginal bleeding	31	21.8
- Common side effect to HRT is: severe abdominal pain	5	3.5
- Uncommon side effect to HRT is: severe depression	51	35.9
- Which of the following statement is correct? Sexual desire is decreased after the menopause	42	29.6
Total	142	100.0

Physician opinion	No.	%
Hormonal replacement therapy		
in postmenopausal women is effective for		
Prevention of osteoporosis	124	87.3
Prevention of CHD	40	28.2
Prevention of stroke	51	35.9
Treatment of dementia or Alzheimer	52	36.6
Treatment of skin wrinkles	47	33.1
Increasing sexual drive	31	21.8
Treatment of vasomotor symptoms (hot flashes)	119	83.8
Treatment of vulvo-vaginal symptoms	117	82.4
Effective managing for hot flashes		
in postmenopausal women		
SSRI and venlafaxine (Effexor)	44	31.0
Clonidine (Catapres)	18	12.7
Soy isoflavones	13	9.2
Red clover	12	8.5
Black cohosh	14	9.9
Belladonna/ergotamine tatrate/phenobarbital	17	12.0
combination		
Dong quai	11	7.7
Evening primrose oil	7	4.9
Gabapentin (neurontin)	29	20.4
Ginseng	22	15.5
Mirtarzapine (Desyrel)	16	11.3
Vitamin E	28	19.7
Wild yam	16	11.3
Behavioral/life style modification	78	54.9
Others	5	3.5
Total	142	100.0

 Table 4
 Proportion of physicians with correct opinion

drive (21.8%). Regarding physicians opinion about the effectiveness of certain treatment options for managing hot flashes in postmenopausal women, SSRI and venlafaxine (Effexor), belladonna/ergotamine tatrate/phenobarbital combination, gabapentin (neurontin), and behavioral/life style modification were chosen correctly as effective options by 31.0%, 12.0%, 20.4%, and 54.9%, respectively by the physicians. On the other hand, clonidine (Catapres), soy isoflavones, red clover, black cohosh, dong quai, evening primrose oil, ginseng, mirtarzapine (Desyrel), vitamin E, and wild yam were chosen correctly by lower proportions of physicians as not effective options for managing hot flashes in postmenopausal women as shown in Table 4.

4. Discussion

Menopause induces a lot of disturbances in the body that the woman is most often not aware of.¹³ Post-menopause is the stage in a woman's life that follows menopause. It is generally believed that the post-menopausal phase begins when 12 full months have passed since the last menstrual period.¹ It is accompanied by decreases of certain hormone production leading to a group of symptoms, bone loss, and the risk of heart disease. Although practice guidelines on HRT have been developed and several physician surveys and review articles have been published on the topic, there are few clear cut recommendations on when to prescribe HRT, which pretreatment investigations to conduct, which regimens to prescribe, how long HRT should be prescribed or what schedule of surveillance should be followed.^{14–21} In agreement with that, 82.4% of PHC physicians participating in this study declared that they had moderate knowledge about treatment options for postmenopausal symptoms. Moreover, although 88.0% of the physicians discussed postmenopausal symptoms with their patients, only about half of them either described or referred their patients for HRT. Our findings indicate that 50.0% of the physicians did these for treatment of vasomotor symptoms, 37.5% attributed that for prevention or treatment of osteoporosis, while the minority did this for prevention of CVD or treatment of cognitive symptoms (7.8% and 4.7%, respectively). These finding indicated that the vast majority of physicians are not familiar with the benefits of HRT described in the medical literature and practice guidelines (protection against osteoporosis, fractures and CAD) and risks from long-term use (endometrial and breast cancer).

Most agreement in the literature appears to be about the benefits of estrogen in preventing osteoporosis and fractures.^{4–16} There is some question about the benefits in preventing coronary artery disease (CAD). Observational studies

suggested that the risk of CAD among estrogen users was about 30%-50% the risk among women not using estrogen.^{17,18} However, in a subsequent randomized controlled clinical trial involving women with CAD, the rate of CAD events was not reduced.¹⁹

The majority of the respondents considered the prevention of osteoporosis and the presence of risk factors for osteoporosis as important or very important reasons for prescribing HRT. The results of the Women's Health Initiative (WHI) study of hormone therapy in post-menopausal women, published in 2002, have prompted many women and primary care physicians to reconsider the use of estrogen and progesterone hormone therapy to alleviate hot flashes.²⁰ In that study, 16,608 healthy, post-menopausal women with an intact uterus were randomized to receive therapy with conjugated equine estrogens plus medroxyprogesterone acetate, or placebo.²⁰ The results of the current study about the correct answers regarding 10 statements related to the Women Health Initiative finding revealed lower level of knowledge for all items except for the item related to absolute contra indication for HRT in menopause where, more than three quarters of physicians (78.9%) answered correctly severe liver disease, history of uterine fibrosis, venous thrombosis.

Doctors were not confident prescribing this type of therapy and considered it a specialized form of treatment that requires investigations.¹³ Thus, most of the physicians surveyed were consistent with the epidemiological literature¹⁸ and practice guidelines,^{15,16,21} which recommend combined HRT for women who have an intact uterus and are at risk of endometrial cancer.

Although observational studies have consistently shown that estrogen protects against CAD,^{17,18} a recent randomized, blinded, placebo-controlled trial involving menopausal women with CAD found that a combined estrogen–progestin regimen did not reduce the overall rate of CAD events.¹⁹ Although that trial assessed HRT as secondary prevention, its findings will probably result in a re-evaluation of the role of estrogen in the prevention of heart disease.²² Similarly, the majority of the participating physicians agreed correctly that HRT is effective in prevention of osteoporosis (87.3%), treatment of vasomotor symptoms (hot flashes) and treatment of vulvo-vaginal symptoms. On the other hand, a round one-third of the physicians correctly disagreed that HRT is effective in prevention of CHD, stroke, treatment of dementia or Alzheimer, skin wrinkles, and increasing sexual drive.

Regarding physicians' opinion about the effectiveness of certain treatment options for managing hot flashes in postmenopausal women, one-third of physicians in the present study agreed that SSRIs and venlafaxine (Effexor), a serotonin and norepinephrine reuptake inhibitor, as effective options for managing hot flashes in post-menopausal women. Other studies have shown an absolute risk reduction (ARR) in hot flashes of 19–60% with these agents compared with placebo.^{23,24}

Clonidine (Catapres) has been found to reduce hot flashes by 12.7%. Similarly other studies reported a decrease by 15– 20% (ARR) compared with placebo.^{25,26} Another study, in which clonidine was administered transdermally in 30 postmenopausal women, showed that clonidine decreased the number and the severity and duration of hot flashes compared with placebo.²⁶

PHC physicians have evaluated the effectiveness of soy isoflavones as tablets, capsules, and liquids in management of hot flashes in lower proportion (9.2%). A small pilot study of

the effects of soy isoflavones in 39 menopausal women reported a 20% ARR in hot flashes weekly compared with placebo.²⁷ Other studies have shown no difference in effectiveness between isoflavones and placebo.^{28,29}

The American College of Obstetricians and Gynecologists (ACOG) states that soy and isoflavones may be helpful in the short-term treatment of vasomotor symptoms. However, given the possibility of their interacting with estrogen, these agents should not be considered free of potential harm for women, particularly those who have an estrogen-dependent cancer.³⁰

Only 8.5% of the physicians reported the effectiveness red clover, like soy, contains isoflavones, which act as agonist/ antagonists on estrogenic receptors. In two small pilot studies, ^{31,32} researchers compared red clover with placebo in postmenopausal women and found no difference in effectiveness of reducing hot flashes. In a randomized study with 252 menopausal women, researchers compared two different commercial red clover products with placebo. All groups reported significant declines in hot flashes compared with baseline, but neither of the red clover products demonstrated superiority over placebo.³³

Black cohosh shows promise for treatment of hot flashes, but study results are inconsistent.^{34–36} Black cohosh is the most studied and perhaps the most popular herb for treatment of hot flashes. Typically, it is not used on a long-term basis. However, in the current study, black cohosh was reported as an effective management by 9.9% of the physician. A study in which 97 menopausal women were randomized to estrogen, black cohosh, or placebo showed black cohosh to be as effective as estrogen and superior to placebo in decreasing hot flash symptoms.³⁴ ACOG states that black cohosh may be helpful in the short-term treatment of women with vasomotor symptoms.³⁰

In consistent with other studies, other agents also have been used for the treatment of hot flash symptoms in menopause, including belladonna/ergotamine tartrate/phenobarbital combination, dong quai, evening primrose oil, gabapentin (neurontin), ginseng, mirtazapine (Remeron), trazodone (Desyrel), vitamin E, and wild yam, but there are few published data on their effectiveness. Belladonna/ergotamine tartrate/phenobarbital combination and gabapentin were more effective than placebo in reducing hot flashes in two small clinical trials. However, larger clinical studies are needed to support these initial findings.^{37–45}

5. Conclusion

The study revealed a general lack of knowledge about menopause and HRT. Better education about menopause and its management for healthcare providers in PHC is needed regarding the long-term risks associated with menopause and the role of HRT so that physician can take health decisions, which may results in improvement in quality of life of these women.

References

- Pam HA, Wu MH, Hsu CC, Yao BL, Huang KE. The perception of menopause among women in Taiwan. *Maturitas* 2002;41:269–74.
- Lee JY, Suh CS. The attitudes of postmenopausal women towards hormone replacement therapy (HRT) and effects of HRT on lipid profiles. In: Proceedings of the first consensus meeting on menopause in East Asian region, May 26–30, Geneva, Switzerland; 1997.

- 3. Avis NE. Women's perceptions of menopause. *Eur Menopause J* 1996;**3**:80–4.
- Cowan G, Warren LW, Young JL. Medical perceptions of menopausal symptoms. *Psychol Women* 1985;9:3–14.
- Avis NE, Mckinly SM. A longitudinal analysis of women's attitudes towards the menopause, results from the Massachusetts Women Health Study. *Maturitas* 1991;13:65–79.
- Shafi S, Samad Z, Syed S, Sharif A, Khan MA, Nehal US. Hormone replacement therapy menopause with a better future – A survey of views on hormone replacement therapy (HRT). J Pak Med Assoc 2001;51:450–3.
- Obel EB, Munk Jensen N, Svenstrup B, Bennet P, Micic S, Henrik-Nielsen R. A two year double blind controlled study of the clinical effect of combined and sequential postmenopausal replacement therapy and steroid metabolism during treatment. *Maturitas* 1993;16:13–21.
- Ettinger B, Genant HK, Cann CE. Long term estrogen replacement therapy preventing bone loss and fracture. *Ann Int Med* 1985;102:319–24.
- Maharaj NR, Gangaram R, Moodley J. The Menopause, hormone replacement therapy and informed consent: are women in an under resourced country adequately aware? *J Obstet Gynecol* 2007;27:300–4.
- Horner E, Fleming J, Studd J. A study of women on long-term hormone replacement therapy and their attitude to suggested cessation. *Climacteric* 2006;9:459–63.
- Lam PM, Leung TN, Haines C, Chung TK. Climacteric symptoms ad knowledge about HRT among Hong Kong Chinese women aged 40–60 years. *Maturitas* 2003;45:99–107.
- Nir-Caein R, Nahum R, Yogev Y, Rosenfeld J, Fisher M, Kaplan B. Ethnicity and attitude towards menopause and hormone replacement therapy in Northern Israel. *Clin Exp Obstet Gynecol* 2002;29:91–4.
- Elaine CH. Improving health care providers' knowledge, attitudes, and practices in reproductive health in rural romania. Project Concern International/Romania 2004:5–37.
- 14. Feig DS. Prevention of osteoporotic fractures in women by estrogen replacement therapy. *Canadian task force on the periodic health examination. The Canadian guide to clinical preventive health care.* Ottawa: Canadian Medical Association; 1994. p. 620–31.
- Society of Obstetricians and Gynaecologists of Canada. The Canadian Menopause Consensus Conference. J Soc Obstet Gynaecol Can 1994;16:1643–97.
- Postmenopausal hormone prophylaxis. In: US preventive services task force. Guide to clinical preventive services. Baltimore: Williams & Wilkins; 1996. p. 829-43.
- 17. Bush TL, Barrett-Connor E. Non-contraceptive estrogen use and cardiovascular disease. *Epidemiol Rev* 1985;7:80–104.
- Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–37.
- Hully S, Grady D, Bush T, Furberg C, Herrington D, Riggs B. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–13.
- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy menopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.
- American College of Physicians. Guidelines for counseling postmenopausal women about preventive hormone therapy. *Ann Intern Med* 1992;117:1038–41.
- Petitti DB. Hormone replacement therapy and heart disease prevention. Experimentation trumps observation. *JAMA* 1998;280:650–2.

- Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003;289:2827–34.
- Weitzner MA, Moncello J, Jacobsen PB, Minton S. A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. *J Pain Symptom Manage* 2002;23:337–45.
- Goldberg RM, Loprinzi CL, O'Fallon JR, Veeder MH, Miser JA, Mailliard JA, Michalak JC, Dose AM, Rowland KM, Burnhan NL. Transdermal clonidine for ameliorating tamoxifeninduced hot flashes. *J Clin Oncol* 1994;12:155–8.
- Nagamani M, Kelver ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol* 1987;156:561–5.
- Scambia G, Mango D, Signorile PG, Anselmi Angeli RA, Palena D, Gallo D. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. *Menopause* 2000;7:105–11.
- Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril* 2003;**79**:1112–7.
- Van Patten CL, Olivotto IA, Chambers GK, Gelmon KA, Hislop E, Templeton E. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. *J Clin Oncol* 2002;20:1449–55.
- American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Use of botanicals for management of menopausal symptoms. Obstet Gynecol 2001;97(suppl):S1–11.
- Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. *Climacteric* 1999;2:79–84.
- Baber RJ, Templeman C, Morton T, Kelly GE, West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. *Climacteric* 1999;2:85–92.
- Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study. JAMA 2003;290:207–14.
- Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 2003;44(suppl 1):S67–77.
- Hernandez Munoz G, Pluchino S. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. *Maturitas* 2003;44(suppl 1):S59–65.
- 36. Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizome): a 6month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based Med 2002;11:163–74.
- Bergmans MG, Merkus JM, Corbey RS, Schellekens LA, Ubachs JM. Effect of Bellergal Retard on climacteric complaints: a double-blind, placebo-controlled study. *Maturitas* 1987;9:227–34.
- Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A doubleblind, placebo-controlled trial. *Fertil Steril* 1997;68:981–6.
- Chenoy R, Hussain S, Tayob Y, O'Brien PM, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994;308:501–3.
- 40. Guttuso Jr T, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;**101**:337–45.
- 41. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a doubleblind, placebo-controlled trial. Swedish Alternative Medicine Group. *Int J Clin Pharmacol Res* 1999;19:89–99.

- 42. Waldinger MD, Berendsen HH, Schweitzer DH. Treatment of hot flushes with mirtazapine: four case reports. *Maturitas* 2000;**36**:165–8.
- Pansini F, Albertazzi P, Bonaccorsi G, Zanotti L, Porto S, Dossi L. Trazodone: a non-hormonal alternative for neurovegetative climacteric symptoms. *Clin Exp Obstet Gynecol* 1995;22:341–4.
- Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495–500.
- 45. Komesaroff PA, Black CV, Cable V, Sudhir K. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. *Climacteric* 2001;4:144–50.