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HRT:
Options for Menopausal Vasomotor Symptoms

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Introduction

The most common climacteric symptom among post-menopausal women is the occurrence of hot flashes, affecting approximately 80% of women, and requiring 40% of those women to seek medical attention.[1] These symptoms last 1 to 5 years in 64% of women, with a median length of 4 years.[2] Because the occurrence of these symptoms is associated with decreased levels of estrogen, logical treatment approaches have involved replacement of estrogen. Two types of estrogen have been commonly prescribed, and include conjugated equine estrogen (CEE) and a combination form of CEE with medroxyprogesterone acetate (MPA), with therapy depending on hysterectomy status. Recent findings have redefined the role of hormone replacement therapy (HRT), forcing practitioners to seek other options for the primary prevention of chronic diseases common in post-menopausal women, and alternatives for the treatment of post-menopausal symptoms. The purpose of this article is to highlight the risk versus benefit of HRT, and provide both pharmacological and non-pharmacological alternatives for the management of hot flashes in post-menopausal women.

Women's Health Initiative

The Women's Health Initiative (WHI) was designed to assess the long-term risk/benefit ratio of estrogen replacement therapy (ERT) and HRT in disease prevention in healthy, post-menopausal women. The study had two components: one which randomized patients with a reported hysterectomy to receive either CEE or placebo, and a second component which randomized women with no history of hysterectomy to receive either placebo or a combination of 0.625mg CEE and 5mg MPA (Prempro). Coronary heart disease (CHD) was the primary outcome measured, with a primary adverse outcome of invasive breast cancer. A Global Index was also compiled to assess other risk/benefits, and included additional outcomes such as stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture and death due to other causes. The HRT component was terminated early, due to statistically significant increases in the risk of cerebral vascular disease, stroke, pulmonary thromboembolism, and invasive breast cancer. These risks outweighed the benefits of HRT, which include decreased incidences of hip fractures and colon cancer.

Findings from the WHI created several clinical dilemmas for practitioners. Cited benefits of ERT/HRT include favorable effect on the lipid profile, particularly increasing HDL, and the prevention of osteoporosis. Lipid-lowering effects were believed to be associated with stabilization or prevention of CHD. It is now established that HRT has no clinical role in the reversal of established CHD, as determined by HERS II, or in the prevention of CHD in health women as determined by the WHI.[3] Superior alternatives are available for patients using ERT/HRT for the prevention of osteoporosis. Patients requiring ERT or HRT for the treatment of vasomotor symptoms associated with menopause are still a challenge for clinicians. How-

ever, other options are supported in scientific literature as being beneficial in hot flash reduction.

Non-pharmacological Options

Non-pharmacological options for the management of hot flashes revolve around lifestyle changes and the addition of dietary supplements. Lifestyle modifications target the avoidance of triggers known to precipitate the hot flashes. Suggestions include dressing appropriately so layers of clothing can be removed should the patient begin to experience warmth, and sleeping in a cool room for patients who suffer from frequent night sweats. Patients should avoid getting too warm while indoors by limiting hot beverages and foods such as soup. Alcohol and spicy foods can cause vasodilatation, triggering hot flashes in many patients, and therefore should be avoided whenever possible.[1] Patients should be instructed on diversion techniques such as taking slow, deep breaths, to prevent the occurrence of hot flashes and lessen their severity.[4]

A diet high in soy or soy supplementation may assist with management of hot flashes. Soy has been advocated as an alternative to HRT in patients with contraindications, or for patients searching for natural alternatives. Soybeans are a rich source of isoflavones, a class of phytoestrogens structurally similar to estrogen derivatives and Selective Estrogen Receptor Modulators (SERMs).[5]

Several studies have compared the use of soy versus placebo in reducing hot flash frequency and severity. Both soy and placebo have demonstrated statistically significant reductions in hot flash frequency and severity, however, no statistically significant differences have been noted between the two.[6,7] Decreases in frequency average 20% with soy products and placebo, although some studies have demonstrated a 45% reduction with soy products versus a 30% reduction with placebo.[1,5] One studied noted patients on soy began seeing relief of vasomotor symptoms within 2 weeks, while those on placebo did not experience relief for an average of 4 weeks.[7] No recommended doses of soy currently exist, however, the most common dose in clinical studies was a product with 90 mg isoflavones given daily, which was well tolerated with no side effects.[6]

Black Cohosh, also known as Actaea racemosa, is an herb native to Eastern North America. Historical use has been for a variety of conditions ranging from diarrhea to use as an antidote for snake bites, while contemporary use focuses on the treatment of menopausal symptoms.[8] Clinical studies with Remifem (a standardized extract of black cohosh) have demonstrated efficacy for alleviation of menopausal complaints, specifically hot flashes. One clinical study compared Remifem (40 mg BID) to estriol (1 mg QD) and CEE (1.25 mg QD). All treatment groups showed positive results, with no significant difference between groups.[8] In a second study, Remifem 40 mg BID was compared to CEE 0.625 mg and placebo for a duration of 12-weeks. Significant improvements were seen in somatic parameters of those patients receiving the Remifemin, compared to those treated with estrogen or placebo.[8] A third clinical study assessed the effective dose of black cohosh. Patients were randomized to receive either 20 mg or 40mg BID of Remifemin. Decreases in symptom scores were seen with each dose, but no statistical difference was noted between groups, leading to a recommended dose 20 mg BID.[8] The most common side effect experienced by patients was gastric discomfort. A lack of toxicology studies led the German Commission E to the recommendation not to exceed 6 months of use.

The use of soy and black cohosh have been associated with a 20% reduction in hot flashes, which is not comparable to the 70% reduction of symptoms seen with HRT.[5] This limits their use to those patients who are highly susceptible to experiencing a placebo effect or those patients experiencing mild hot flashes. Other limitations regarding these products, include; limited knowledge of the precise active ingredients, the minimal effective dose, and lack of standardization.[5] Other therapeutic options are indicated for patients who do not experience relief with these products.

Pharmacological Options

Pharmacological options for the treatment of hot flashes are based on proposed pathophysiology theories regarding their etiology. Estrogen is believed to play a role in hot flashes, but poor correlation between blood estrogen levels and the frequency and severity of hot flashes exists, suggesting other mechanisms are involved.[1] Two proposed mechanisms frequently discussed in the literature

involve the neurotransmitters norepinephrine (NE) and serotonin (5-HT).

Clonidine

Evidence suggests that NE plays a significant role in the prevalence of hot flashes. Studies show increased brain NE levels in symptomatic women, which rise when a hot flash occurs.[2] NE results in peripheral vasodilatation, heat loss and a subsequent decrease in core body temperature. This effect is provoked with central injection of yohimbine (an a_2-adrenergic antagonist), and relieved with injection of clonidine (Catapress®), (an a_2-adrenergic agonist), suggesting that NE plays a role in thermoregulation mediated through alpha-2 adrenergic receptors.[2]

The effects of clonidine on hot flashes are believed to be mediated by a reduction in NE release, subsequently raising the sweating threshold while lowering the shivering threshold.[2] Clinical trials demonstrate that clonidine significantly increases the length of heating time required to induce a hot flash, while decreasing the total number of hot flashes.[2] Two dosage forms have demonstrated success in decreasing hot flash frequency, severity and duration: transdermal patches and oral tablets. One clinical trial compared transdermal administration of clonidine 0.1mg to placebo. Clonidine was associated with decreased patient reports of hot flash frequency (80% vs 36% placebo), decreased severity (73% vs 29% with placebo) and decreased duration of hot flashes (67% vs 21%) with p-values of <0.04, <0.04, and <0.03, respectively.[9] A second trial compared oral clonidine 0.05 mg twice daily to placebo, and 4 separate studies were carried out. Since no statistically significant differences were observed between studies, results were averaged. The frequency, severity and duration of attacks were decreased in 78%, 89%, and 88% of patients, respectively, compared to 50%, 53%, and 50% decreases with placebo ($p<0.05$, paired t-test).[10] Both studies demonstrated no significant effects on blood pressure, and determined the required dose for post-menopausal symptoms to be lower than the dose needed for the treatment of hypertension.[9,10]

Caution should be exercised when administering clonidine to patients with severe coronary disease, recent MI, cerebrovascular disease or impaired hepatic or renal function. Because clonidine is classically used as an anti-hypertensive, patient blood pressure and pulse should be monitored. Common adverse events include drowsiness, dizziness, dry mouth, constipation, and orthostatic hypotension. Patients should be advised not to abruptly discontinue therapy, because rebound hypertension may occur.

Antidepressants

Some antidepressants have been evaluated for treatment of hot flashes in women post-breast cancer treatment, with a history of breast cancer or a concern regarding the use of estrogen because of their risk for developing breast cancer. Antidepressants have demonstrated more significant reductions in hot flash frequency and severity compared to other options such as isoflavones, black cohosh or clonidine. Anti-depressants are believed to work via their effects on serotonin (5-HT), a neurotransmitter associated with hot flashes.

Two Selective Serotonin Reuptake Inhibitors (SSRIs) have shown benefit in postmenopausal women in reducing hot flashes, fluoxetine (Prozac®) and paroxetine (Paxil®). Fluoxetine 20 mg has been compared with placebo in a double-blind randomized cross-over study. Hot flash scores, defined as frequency x average severity, were decreased by 50% compared to a 36% reduction in the placebo arm ($p=0.35$)[11] The superiority of fluoxetine was verified by cross-over analysis. Paroxetine has also demonstrated effectiveness in reducing hot flash frequency and severity. Patients received paroxetine 10 mg daily for one week, followed by four weeks at 20 mg daily. Treatment with 20mg paroxetine reduced hot flash frequency 56%-79%, with a mean reduction of 67%, and reduced the hot flash severity score by 66%-85%, with a mean reduction of 75%.[12] Both SSRIs were well tolerated, with somnolence being the main adverse event.

The largest published study assessing the use of an antidepressant for the management of hot flashes involves the use of venlafaxine (Effexor®). In the venlafaxine dose-seeking trial, venlafaxine was evaluated at doses of 37.5, 75 and 150 mg/day compared to placebo. Overall, the median decrease in hot flash scores was significantly greater in all three venlafaxine groups vs placebo ($p<0.0001$).[13]

The study found a 27% reduction in the average daily hot flash score in patients receiving placebo, and a 37% reduction in patients receiving 37.5 mg daily (p=0.008).[13] Patients receiving 75 mg demonstrated a 61% reduction, a statistically significant difference when compared to the 37.5 mg group (p=0.03), and no significant difference existed between the 75 mg and 150 mg groups.[13] The use of venlafaxine was associated with dry mouth and appetite suppression. Dosing recommendations for the treatment of hot flashes have been made based on the findings of this study. Therapy should be initiated at a dose of 37.5 mg daily for 1 week.[13] If symptom control is not optimal, the dose may be increased to 75 mg daily. Doses greater than this are not recommended since they provide no additional benefit, and increase the occurrence of side effects.

Conclusion

Before prescribing HRT, patients should demonstrate a clear and strong indication for therapy and the risk versus benefits should be evaluated. In patients prescribed HRT for the management of postmenopausal symptoms, several safer alternatives exist. The most studied and effective non-hormonal therapy for hot flashes is venlafaxine at a dose of 75 mg daily, in an extended-release form.[13] Patients who are currently on HRT should be tapered off therapy to lessen the chance of rebound hot flashes. The clinical implications for women on ERT have not yet been defined, however, practitioners may chose to err on the side of caution. Patients who can not tolerate other options and require HRT should be carefully monitored short term. Long-term use over 2 years should be rigorously monitored, and the risk-benefit ratio reassessed often.

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Accutane® update

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Introduction

Acne vulgaris affects 80% of the population between the ages of 12 and 25.[1] There are various over-the-counter (OTC) and prescription medications available to treat acne, but only one has shown significant effects in treating severe acne. The FDA approved Accutane® (isotretinoin) in May 1982, for the treatment of severe recalcitrant nodular acne.[2,3] In the last 8 years, there has been a 250% increase in the number of dispensed prescriptions for isotretinoin in the United States.[4] This data also reveals an increase in the use of isotretinoin for mild to moderate acne.

Acne vulgaris is an inflammation of the pilosebaceous unit. Acne is capable of producing psychological and physical scarring. A prospective clinical study examined the early use of isotretinoin in acne treatment and demonstrated the beneficial effect in minimizing acne scarring.[5] This article will discuss the pharmacology, dosing, adverse effects, clinical trials, and new prescribing guidelines for isotretinoin.

Pharmacology/Pharmacokinetics

Isotretinoin (13-cis-retinoic acid) is an oral retinoid that mediates intracrine and paracrine cell differentiation, proliferation, apoptosis, and reproduction. The primary action of isotretinoin is a reversible inhibition of sebum production through a reduction in the size of sebaceous glands and possible inhibition of follicular keratinization.[2] Only isotretinoin exerts such an effect on sebum production. Isotretinoin is an effective compound capable of treating severe acne because it is the only one that affects all etiological factors of acne: sebum production, comedogenesis and colonization with Propionibacterium acnes.[6]

The pharmacokinetics of isotretinoin do not seem to differ with gender. Absorption of isotretinoin is incomplete; however, bioavailability can be enhanced by taking it with food or milk. Peak plasma concentrations are attained within 3 hours. Unlike vitamin A, isotretinoin does not accumulate in the liver. Isotretinoin is 99.9% bound to plasma proteins, and is metabolized in the liver to 4-oxo-isotretinoin. It is unknown whether this metabolite has pharmacologic activity. The half-life of isotretinoin is 10-20 hours. The metabolites are eliminated via renal pathways, while unchanged drug appears to be excreted in the feces through biliary elimination.[2]

Dosing

The recommended dosage range for isotretinoin is 0.5-1.0mg/kg/day, by mouth, given in two divided doses for 15-20 weeks. Maximum recommended daily dose is 2mg/kg. A safe dosage has not been established in children. The age in which isotretinoin can be safely given is unclear. Specific guidelines for dosage adjustments in hepatic and renal impairments are not available; it appears that no dosage adjustments are needed.[2]

Adverse Effects

The use of isotretinoin has been associated with reports of adverse events. Two trials examined the difference in adverse events in once daily dosing verses twice daily dosing of isotretinoin. Demographics are summarized in Table 1. In the first trial, 67 patients received isotretinoin at 1mg/kg in a single dose with food for 16-20 weeks. The patients were asked to evaluate adverse effects at weekly visits. The patients rated the severity of each event on a 10cm visual analog scale (VAS) with 0 being not present and 10 being extremely noticeable. In the second trial, 300 patients received isotretinoin at 1mg/kg in 2 equally divided doses with meals. The incidence of adverse effects, in both trials, is seen in Table 2. Chelitis persisted for up to 95.8% of the therapy period and was the biggest concern among patients.[7]

Liver function tests and cholesterol levels should be evaluated on a monthly basis during isotretinoin therapy. As many as 5% to 25% of patients

Table 1. Summary of Demographic Data[7]

Characteristic	Trial 1 (n=69)	Trial 2 (n=300)
Sex		
Male (%)	31(45)	174(58)
Female (%)	38(39)	126(42)
Age (y)		
Mean	22.9	21.6
Median	21	20
SD	7.6	6.8
Range	13-43	13-50
Height (cm)		
Mean	171.2	172.7
Median	172	172
SD	9.7	9.4
Range	152-192	144-203
Weight (kg)		
Mean	69.4	71.6
Median	67	69.3
SD	15.6	14.5
Range	41-120	41-125

show abnormalities in liver function tests, but most of these cases present with no histologic liver change.[11] Elevations in triglyceride levels occur in 25% to 45% of patients.[11] In both trials, serum triglyceride values increased by 0.99 to 1.441 mmol/L over baseline to 2.11-1.670 mmol/L at week 20. In both groups the mean variation was within the normal range. Both treatment groups were not associated with increased risk of cardiovascular problems or pancreatitis.[7]

Between the years 1982 and 2000, 37 cases of suicide have been reported while taking isotretinoin.[11] The population most commonly treated with isotretinoin (12-18 year olds) are at increased risk for depression and suicide. The number of suicides reported does not exceed what is expected, given the suicide rate in the United States.[11] A prospective and retrospective study of isotretinoin concludes that there is not an increased risk for depression, suicide, or other psychiatric problems associated with isotretinoin use.[10] Because there are few trials that have evaluated at the psychiatric effect of isotretinoin, a conservative approach has been adopted, including FDA warnings. Also it is important that physicians advise patients, especially those with a history of depression, to report changes in mood or behavior.[11]

Table 2. Incidence of adverse events by body systems[7]

Body System	Percentage of patients with adverse events	
	Trial 1 (n=69)	Trial 2 (n=300)
All body systems	100	97.6
Skin and subcutaneous disorders	100	92
Gastrointestinal[a]	100	93
Respiratory[b], thoracic, and mediastinal disorders	62	70.7
Disorders of eye[c]	73	57
Infections and infestations	9	26
Neurologic disorders[d]	29	16.3
Musculoskeletal, connective tissue, and bone disorders	20	14.3
General disorder	3	4.7
Injury and poisoning	1	10.7
Psychiatric disorders	0	0.3
Reproductive system and breast disorders	7	3
Disorders of immune system	0	2.3
Disorders of metabolism and nutrition	0	1
Cysts	0.7	0.3
Cardiac disorders	0	1
Disorders of ear and labyrinth	0	0.7

[a] Includes cheilitis, [b] Includes dry nose and epistaxis, [c] Includes dry and irritated eyes, [d] Includes headaches

The most serious adverse event associated with isotretinoin is congenital abnormalities. When a pregnant woman exposes a fetus to isotretinoin, 25% to 30% of pregnancies will show malformations.[11] The most commonly reported malformations include craniofacial, cardiac, thymic and central nervous system structures.[11] The severity of fetal malformation has led to new prescribing procedures for isotretinoin, including the *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T).

Clinical Trials

A randomized, double blind, placebo controlled trial examined 33 patients with treatment resistant cystic and conglobate acne. This study tested the efficacy of isotretinoin versus placebo. Criteria for inclusion into the study required at least 10 inflamed deep dermal or subcutaneous acne cysts of at least 4mm diameter. All patients had discontinued their conventional acne treatment for at least one month before entry into the study. No other acne therapy was allowed during the 4-month treatment period. The number of cysts present de-

Table 3. Grading of facial acne scars according to scar type

Ice-pick macular atrophic		Hypertrophic keloid	
number	scar grade	number	scar grade
(1-5)	1	(1-3)	2
(6-10)	2	(4-7)	4
(11-25)	3	(>7)	6
(26-50)	4		
(51-100)	5		
(>100)	6		

termined efficacy of treatment. Patients assigned to the placebo group were comparable in age, sex, and number and distribution of lesions to those patients who received isotretinoin.[14]

At the 1-month observation period, the mean number of cystic lesions in the 17 patients receiving the placebo had increased by 33%. Eight patients receiving placebo had a mean increase of 61% in their lesion count, and were switched to isotretinoin. The remaining 9 patients had a mean increase in lesions of 58%. Five of the 9 patients were dropped from the study and were switched to isotretinoin. Two patients had slightly fewer lesions after 2 months. Of these 2 patients, one received isotretinoin by mistake. During placebo therapy, there was an overall 57% increase in the number of lesions. Sixteen of the 17 patients receiving placebo were subsequently treated with isotretinoin.[14]

Sixteen patients received isotretinoin therapy beginning at 0.5mg/kg/day. Six patients had their dosage increased when no improvement in their acne was noted at the 1-month follow-up. Acne became worse in 2 patients treated with isotretinoin and they subsequently received treatment at a higher dose. The mean daily dose of isotretinoin at month 2 of the study was 0.65mg/kg/day. After one month, cystic lesions in patients treated with isotretinoin decreased by 17% from baseline. After 2 months, the lesions decreased by 32%. [14]

This study concluded that there was a 95% improvement in the 16 patients who were randomly selected to receive isotretinoin. Sixteen of the 17 patients receiving placebo were switched to isotretinoin, which resulted in a 98% improvement from baseline. Twenty-seven of the 32 patients treated with isotretinoin cleared completely. Eighteen patients received only one 4-month course of isotretinoin. Fifteen patients received 2 courses. Of these fifteen patients, twelve responded with the first course of treatment but had mild relapse after six months off treatment. All patients are now in remission averaging 38 months in duration. Continued healing and prolonged remission after discontinuation of therapy with isotretinoin was observed in these patients. [14].

A prospective trial was designed to assess the effect of early therapy on the outcome of acne scarring. This trial included 107 patients with facial acne, treated with isotretinoin 1mg/kg/day for 4 months (Table 3). At the end of treatment, the degree of acne scarring was scored. This study found that patients given treatment after 3 years of acne received a mean scar score of 4.34. Patients with acne for less than 3 years had a mean score of 1.11. The study concluded that less scaring resulted in patients who received isotretinoin early in their disease process.[5]

New Prescribing Guidelines

Effective April 10, 2002, all prescribers, pharmacists, and patients must comply with the conditions of the S.M.A.R.T. program.[13] Prescribers must sign and return to Roche the Letter of Understanding certifying their knowledge in minimizing fetal exposure to isotretinoin. Prescribers will receive Accutane® Qualification stickers that must be attached to all prescription forms. The stickers indicate to the pharmacist that the patient is qualified to receive isotretinoin. Females of childbearing potential must have 2 negative pregnancy tests prior to beginning isotretinoin and then monthly during treatment. Sexually active patients must use two forms of contraception for a least one-month prior to initiation of treatment, during treatment, and one month after discontinuing treatment. Patients must sign a consent form prior to beginning therapy.

Pharmacists may only dispense isotretinoin upon presentation of a prescription with a special Accutane® Qualification sticker, and will dispense a maximum of a 1-month supply. Prescriptions must be filled within 7 days from the date written on the yellow qualification sticker. Pharmacists must provide a Medication Guide for patients with each isotretinoin prescription. Requests for refills and phone-in prescriptions will not be filled.[2,13]

Summary

Acne is both psychologically and physically scarring. With proper training and knowledge, physicians can safely prescribe isotretinoin for patients with acne. Isotretinoin has severe adverse events but with the S.M.A.R.T. program in place, these adverse events can be prevented. The S.M.A.R.T. program requires patients, physicians and pharmacists to work as a team to reduce acne, the scarring from acne, and adverse events.

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