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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Tailoring Hormone Therapy to Patients' Needs



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INTRODUCTION

The menopause is a physiologic life event that all women experience. Yet, the associated symptoms vary from woman to woman, in both type and intensity. Further, the prevalence of estrogen-deficiency related disease such as cardiovascular disease, osteoporosis, and cognitive dysfunction differs among female populations and within each population group. Cultural, socioeconomic, and genetic factors impact postmenopausal health and well-being. However, it is generally accepted that the hormonal deprivation associated with the menopausal transition is responsible for much of the life quality, morbidity, and mortality of postmenopausal women.

Post-reproductive menopausal women have the same qualitative, but individualized quantitative, change in their sex hormone synthesis and secretion. This probably accounts for differences in their clinical presentation and response to the current practice of routine and traditional hormone therapy, regardless of the woman's actual needs. Arising from the latter, the concept of "adjustive low-dose hormone therapy" was developed.¹ This

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was based on clinical experience and three underlying principles: 1) emerging research documenting previously unrecognized hormonal function in non-reproductive aging women; 2) evolving technology that can cost-effectively differentiate healthy postmenopausal women from those who, in addition to being menopausal, have significant adverse risk factors and/or evidence of latent hormone-associated disease; and 3) a range of new hormone therapies that can be selectively used to meet an individual's specific health requirement.

HORMONAL INEQUALITY: CLINICAL CONSEQUENCES

The inferred objective of "hormone replacement therapy" (HRT) is the prescription of estrogen and progesterone to restore the pre-menopausal hormonal milieu. However, with regards to the route of administration and the available prescriptive sex-steroids, HRT cannot replicate the hormonal status of premenopausal women, as insulin therapy can for example in insulin-dependent diabetics. It is possible to pharmacologically induce a functional change that targets hormone-sensitive tissues. Therefore, the phrase "hormone therapy" (HT) is preferred as it indicates that all postmenopausal women are being treated pharmacologically.

The hormonal needs of women are

FROM THE EDITOR

David F. Archer, M.D.

In this issue, Dr. Morris Notelovitz describes the evaluation and need for individual prescribing of hormone therapy for postmenopausal women. His article identifies the risk factors for cardiovascular disease and bone loss, and addresses the changing replacement of hormonal medication. The differences in sex hormone binding globulin levels with oral versus transdermal preparations of estradiol are highlighted as one of the overlooked aspects of monitoring hormone therapy. All in all this article succinctly addresses common problems presented to the clinician with a rational approach for therapeutic interventions.

Dr. David Archer reviews the etiology of the menopausal hot flash, or night sweat. The sleep dysfunction attendant to these menopausal symptoms can result in daytime fatigue. Although hormonal therapy such as estrogen has been the mainstay of treatment, other non-hormonal approaches are reviewed. It should be noted that some alternative therapies do not have a significant advantage over placebo. Physicians should take into account when initiating therapy for hot flashes the time required for suppression of hot flashes (four to 12 weeks) and the concomitant placebo effect.

Menopausal Medicine

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varied. Oldenhave² quantified the prevalence and intensity of vasomotor symptoms in pre, peri and postmenopausal women and made three intriguing observations: 1) many regularly menstruating (and presumably hormonally intact) women reported typical vasomotor symptoms; 2) the majority of postmenopausal women in the survey were symptomatic, but the intensity varied considerably amongst them; and 3) a third group remained asymptomatic throughout their menopausal transition. The reason for this disparity is not known, but may be due to individual differences in the estrogen threshold of the vasomotor center,³ the constancy of plasma estrogen blood levels (symptoms can be induced by too much as well as by fluctuating estrogen levels), the amount of bio-available free estrogen, and the relative distribution (and function) of alpha and beta estrogen receptors. Cummings et al⁴ noted that relatively low levels of endogenous estrogen were associated with a reduced risk of vertebral and hip fractures in untreated elderly women, and that these fractures were inversely related to endogenous SHBG. The greater the SHBG value, the greater the relative risk for hip and vertebral fracture. Thus, it is self-evident that the hormone therapy of certain younger and older women varies according to the clinical presentation, hormonal status, and symptomatic response. The Cummings data were based on plasma assays of estrogen and SHBG, and obviously do not account for the target tissues' actual hormonal status. It is now established that significant aromatization of androgens to estrogens occurs in most tissues that are targets for HT.⁵ Aromatized estrogen cannot be measured in clinical practice, but can be compensated for in situations where aromatization is known to be accelerated – in the obese and in the elderly.

PHARMACOLOGIC DIFFERENCES: ALL HORMONAL PREPARATIONS ARE NOT EQUAL

The transcriptive processes that lead to a given organ's functional response to HT are governed by a variety of complex interactive factors including newly discovered repressors and co-repressors.⁶ There are three variables that can be pharmacologically manipulated: 1) the availability of free estrogen and testosterone (by the route and type of hormonal therapy); 2) the concentration of estrogen (by

adjusting the dose); and 3) the number of estrogen receptors (by down-regulation with progestins). Bioavailable free estradiol is determined largely by its binding to SHBG. In a recent study,⁷ transdermal estradiol 50 mcg stimulated less SHBG (12%) than the clinically equivalent dose of oral estrogen: 0.625 mg of conjugated equine estrogen (100%) and 1 mg of 17- β estradiol (45%). Adding androgens may also be helpful. The addition of 2.5 mg of methyltestosterone to 1.25 mg of esterified estrogen decreased SHBG (from \pm 46 to \pm 24 mcgDHT bound/dL), resulting in more free and therefore bioavailable estradiol and testosterone.⁸ The simple clinical message is this: for patients non-responsive to adequate traditional oral HT, the route of hormonal therapy, the type of oral estrogen, or the addition of an androgen should be considered before increasing the prescribed HT dose.

The dose of estrogen required to achieve a particular result varies both with the indication for treatment and the route of administration. For example, whereas 0.25 mg of oral 17- β estradiol is ineffective in treating hot flashes, it may be all that is needed to maintain an older women's bone mineral density. Alternatively, 25 μ g of transdermal estradiol has been found to maintain BMD in 70% of treated women and is also effective in hot flash control.⁹ All published ET studies have shown a dose-response improvement in BMD. Thus, the initial ET dose chosen should be based on the patient's clinical condition: a higher dose is required if she's osteoporotic and a lower dose to maintain bone mineral density if osteopenic. Annual reassessment will determine if the starting dose should be adjusted downward (for example once a BMD has been normalized) or increased if evidence of continuing bone loss is noted. Addition of testosterone to estrogen therapy, because of its SHBG-lowering effect or direct stimulation of the bone remodeling cycle, has been shown to be very effective in increasing BMD.¹⁰ This is especially true in women who appear to be "resistant" to standard dose HT. Androgenic progestins have an anabolic effect similar to that of testosterone.

Progestins vary in their potency to down-regulate estrogen receptors. Although this is not possible to quantify clinically, medroxyprogesterone acetate (MPA) but not progesterone, has been noted to significantly attenuate the

vasodilating properties of estrogen¹¹ and to impair the inhibition of atherogenic plaque formation by estrogen.¹² Norethindrone acetate (NETA) may enhance estrogen's protective effect.¹³ Two speculative reasons are suppression of SHBG and the limited bioconversion of NETA to ethinyl estradiol. A further difference between MPA and NETA is the half-life after oral administration. Whereas the half-life of MPA is 18 to 24 hours, blood levels of NETA (above baseline) are no longer detectable after four to six hours. Thus, the pharmacokinetic profile with combination NETA and estradiol is estrogen-dominant for most of the post-treatment day. This profile may be especially valuable in women known to have a compromised estrogen receptor reserve in vital target tissues, such as the coronary artery in women post-myocardial infarction.

THE PHARMACODYNAMICS OF HT MONITORING

Very few physicians monitor their patients' HT by measuring plasma estradiol levels. The reasons are varied and include concerns regarding the actual assay of estradiol, not incorporating other metabolites and constituents of the prescribed estrogen, and uncertainty regarding the clinical meaning and utility of this test.

There are, however, a number of clinical situations that, in the author's opinion, justify selective testing. These include ensuring adequate absorption and bioavailability of estradiol in women non-responsive to adequate HT, high-risk patients such as women with established coronary artery disease, and occasionally to monitor compliance with therapy.

To ensure the maximum clinical utility of this test, the prescription of 17- β estradiol either orally or parenterally is preferred. Thus, estradiol applied to the skin can also be measured as estradiol in the circulation. With oral therapy, the first-pass metabolism of estrogen converts most of the ingested estradiol to estrone and estrone sulphate. However, assay of estradiol alone is reflective of the dose actually prescribed and is remarkably consistent from study to study: 1 mg of oral 17- β estradiol results in a 10 to 12 hour post-ingestion blood value of 60 to 80 pg/ml.⁷ This is the "total" estradiol level assayed, and will vary with the individual's baseline estrogen metabolism. Values significantly above this level are indicative of excessive dosing; low values

could result from poor absorption or non-compliance with therapy.

Both animal¹¹ and clinical studies¹⁴ have confirmed 60 to 100 pg/dL levels of estradiol to be associated with vasodilation of acetylcholine infused atherosclerotic coronary arteries. The improved estrogen induced vasoreactivity of coronary arteries is said to account for \pm 70% of estrogen's cardiovascular protection. Simultaneous FSH assay is recommended to ensure that the measured estrogen is bioavailable. Dose-ranging estrogen studies have validated the progressive lowering of postmenopausal FSH levels in response to increasing the estrogen dose. However, FSH levels do not reach the premenopausal range due to the absence of inhibin-B in non-reproductive women. Inhibin-B is the peptide synthesized during the luteal phase of the menstrual cycle and serves as the primary negative feedback mechanism controlling FSH released in premenopausal women.¹⁵ Low premenopausal range FSH levels in menopausal women on HT are indicative of excessive estrogen dosing.

TECHNOLOGY AND CHOOSING WOMEN FOR HT

Although the majority of postmenopausal women may respond to generic and traditional hormone regimens, each woman's hormonal need is actually as individual to her as her own thumbprint. With the intelligent and judicious use of technology, added to comprehensive and thoughtful clinical evaluation, each woman's menopausal health status can be classified into one of the following categories that may or may not be hormone related: healthy with no risk factors; healthy with risk factors; healthy with latent disease; and evidence of overt disease. The presence or absence of menopausal symptoms will further determine the appropriate treatment.

Suggested investigations relevant to the above approach are based on the pathogenesis of some of the diseases attributable (at least in part) to hormone

deprivation and are readily available in clinical practice. These include vaginal pH as a bedside evaluation of adequate vaginal estrogenization (even in asymptomatic women or women on systemic hormone therapy);¹⁶ a 10- to 12-hour fasting

“Although the majority of postmenopausal women may respond to generic and traditional hormone regimens, each woman’s hormonal need is actually as individual to her as her own thumbprint.”

lipid profile to include total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides (hypertriglyceridemia is a reliable surrogate marker for insulin resistance and hypercoagulable states);¹⁷ DEXA bone mineral density (BMD) test (to preferably include hip and spine BMD since osteopenia/osteoporosis is a heterogeneous disease and can affect either region independently of the other); bone markers; urinary collagen cross-link excretion (to document high bone

turnover osteoporosis); and selectively bone-specific alkaline phosphatase (as a marker of low turnover osteopenia/osteoporosis).¹⁸ In addition, all women irrespective of whether they are considering HT should be offered a diagnostic quality mammogram and breast ultrasound if indicated.

Clinical judgment will determine the need for other tests such as thyroid profile, fasting glucose and insulin, hemostasis profile (PT, PTT, factor VII and VIII, fibrinogen, factor V Leiden, antithrombin III activity, PAI-1, etc.), liver function tests, and sex hormone profiling (as previously discussed). Monitoring of the endometrium should be based on standard gynecologic practice. Colonic screening is also recommended, but does not influence hormone prescription decisions.

TAILORING HORMONE THERAPY

Physicians now have a large pharmacopoeia of appropriately evaluated and approved hormonal products. These include new local vaginal therapies, a variety of oral estrogens, progestins, and progesterone (alone or in sequential/continuous combined combinations), parenteral HT, estrogen matrix patches with 2.5- and 7-day half-lives, continuous combined HT patches, estrogen gels, etc.

Many new non-hormonal drugs relevant to postmenopausal care are also available.

Although a number of helpful treatment algorithms have been published, the complex and variable needs of individual women in the real world of clinical practice precludes this approach from optimizing the actual benefit a woman can (and should) derive from her HT. Because of this, it is not possible, within the context of this review, to address all clinical scenarios other than to outline a few guiding principles.

Evaluate Before You Treat

A woman's menopausal symptoms (or their absence) do not determine other indications for long-term HT. The dose of HT will, for example, differ with the pre-treatment diagnosis of mild osteopenia (requiring low dose HT to maintain bone remodeling) versus osteoporosis. The route of ET could also be decided by a low HDL-cholesterol (favoring oral ET) or hypertriglyceridemia (transdermal or low-dose oral estrogen plus testosterone HT). Women with a previous non-hormone related venous thrombosis (after excluding thrombophilia) would be best treated with parenteral estrogen (to avoid stimulation of hepatic pro-coagulation factors) with an added androgenic progestin (to increase fibrinolysis).

Monitor While You Treat

Women who remain symptomatic on adequate HT may not be absorbing the amount prescribed or may have excess SHBG activity and therefore inadequate bioavailable sex steroids. Conversion to an alternate oral or transdermal estrogen preparation (with or without adding an androgen or androgenic progestin) usually resolves the issue, oftentimes with a lower dose of ET.

Symptomatic control of standard HT does not confirm adequate estrogenization of all target tissues or control of other hormone-related disorders. About 30% to 40% of women on systemic HT still have evidence of atrophic vaginitis (easily diagnosed by pH testing).¹⁶ An indeterminate number of women still lose or fail to improve the BMD while on HT. By measuring urinary collagen cross-link markers three months after initiating therapy, unresponsive high turnover bone losers can be readily identified and corrective treatment prescribed. Failure to improve bone mineral density (in the presence of normal

urinary collagen cross-link excretion) is indicative of suppressed bone modeling which can be confirmed by low levels of bone-specific alkaline phosphatase and indicates the need to include androgen therapy.

Differentiate Risk Factors From Target Tissue Response

The relevance of a "risk factor" response to HT varies with the presence and/or degree of established disease in the given target organ. For example, improving the lipid profile in younger women without significant CVD (primary prevention) is known to reduce the risk of myocardial infarction and other related cardiovascular disorders. In older women with established disease (for example as in the HERS study),¹⁹ HT may improve the lipid profile but can still be associated with an initial excess of CVD events. The disconnect may be explained by the presence and activity of the alpha ER, which is present and normally responsive in the livers of women with and without established cardiovascular disease and significantly reduced in the coronary arteries of women with atherogenic disease.²⁰ The latter would have been additionally compromised by the progestin-induced down-regulation of their already depleted coronary artery alpha ER content.

Two practical issues emerge from this example: 1) it is appropriate to rely on improvement of the lipid profile in primary prevention situations; and 2) in women post-CVD event however, ensuring an adequate level of bioavailable plasma estradiol is probably more meaningful. Where added progestin is needed, in my opinion, preference should be given to cyclic micronized progesterone (first 12 to 14 days of each month) or progestins with a short half-life, for example NETA. This type of regimen would ensure both estrogen-dominance for coronary artery function and adequate progestin for endometrial protection.

Always Ask Why

Although long-term HT may be associated with increased longevity, it is an improved quality of postmenopausal life that justifies the offering of HT to all menopausal women. The indication and need for HT varies across the individual's life-cycle. Annual review is advisable, at which time one of two questions should be asked: 1) if your patient is not taking

HT, ask why not; and 2) if she is on HT, ask why. This is the time to reassess the next year's health plan, to start HT if indicated, and to revise and adjust the regimen in those women continuing with HT. It is relatively simple to tailor hormone therapy to the patient's need. However, it takes time: time to educate your patient, time to listen to her needs, and time to think.

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Menopausal Hot Flashes: Incidence and Therapeutic Interventions



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The hot flash, when it occurs, is a signal event in the life of a woman, usually indicating the beginning of the menopause. Hot flashes occur in 40% of premenopausal women, but they also occur in 85% of postmenopausal women. The incidence is the same in both Caucasians and African Americans in the United States, although cross-cultural differences in the interpretation of the hot flash have been found in other populations.¹ Some populations do not appear to experience a hot flash at all; rather they use different terminology for what appears to be similar physiologic event. Males who have lost testicular function also experience a hot flash similar to that seen in postmenopausal women.

Night sweats are another term for the hot flash. A night sweat, by definition, only occurs during sleeping or at night and, although it is similar to the hot flash, the night sweat has been temporarily related to the episodic release of pituitary leutinizing hormone (hLH).¹

TYPICAL HOT FLASH/NIGHT SWEAT

For the individual female, the typical hot flash or night sweat is a well-defined entity. The beginning is a subjective feeling of intense heat. The perception that the ambient temperature has increased begins in the brain, specifically in the thermo-regulatory center located in the hypothalamus. Following the perception of increased heat, some substance or substances are released whose identity have not been clearly identified.² From a clinical standpoint, the next event is a reddening of the skin, first of the head, and neck, and then the anterior chest. This reddening of the skin represents a vasodilatory response that is the

body's mechanism of reducing core temperature.¹ Associated with the vasodilatory response is increase in perspiration and after this, as the perspiration evaporates from the skin, there is a cooling phase.

The average duration of a hot flash is approximately 2-3 minutes. The duration is variable. The average frequency of hot flashes, based on clinical trials, is somewhere on the order of one every 2-3 hours in a highly symptomatic individual, but less frequent in an individual who, for whatever reason, is not as symptomatic.

The intensity of the hot flash is also variable, but there have been attempts to grade the hot flash in the following manner. Severe hot flashes are those that actually interfere with what the individual is doing, whether it is working, reading, or some other activity. The severe hot flash is often associated with profuse sweating which can result in soaking the individual's clothing. A moderate hot flash is one that does not interfere with work, but it is certainly perceptible to the individual and often briefly interferes with their activity. The mild hot flash is nothing more than a transient redness of the skin without any associated perspiration or interruption of the activity.

Associated with the hot flash are several physiologic responses. There is a drop in skin resistance that reflects the perspiration. Skin temperature has been found to rise during the hot flash, but the core body temperature remains stable. There is an increase in the heart rate, with values as high as 120 beats per minute being reported. As mentioned earlier, there is a high concordance of approximately 80% with the pituitary release of hLH. This episodic release reflects central nervous system activation associated with the hot flash.¹

Night sweats are nothing more than a hot flash that occurs at night. The difference is that it is associated with light sleep, and often results in awakening. This alteration in sleep patterns has resulted in what appears to be an increased incidence of daytime fatigue. It has been difficult to sort out the whether the hot flash per se is the cause of the sleep disruption. It is possible that something other than the hot flash such as the hypoestrogenism causes the poor sleep pattern. Only replacement with estrogen has been studied as to the effect on improving the sleep pattern. It has been shown that sleep latency is reduced with conjugated equine

estrogen (CEE, Premarin®, Wyeth-Ayerst Laboratories, St. David's, PA).³ CEE decreases the sleep latency interval from 19 to 12 minutes. The same report found that the time spent in rapid eye movement sleep, which is deep, restful sleep, increased from 70 to 95 minutes with the administration of CEE. With the increase in time in REM sleep, the proportion of REM sleep was increased from 17 to 22 percent.

TREATMENT OF HOT FLASHES

Oral Estrogen and Progestogen

Estrogen therapy has been the standby for the treatment of the hot flash, and is the principal indication for hormone replacement therapy in postmenopausal women. Both 0.625-mg of CEE or 1 mg of estradiol 17 β (E₂) have been shown to be effective in reducing hot flashes.^{1,4} Estrogens have been shown to be effective in reducing the occurrence, incidence, and severity of the hot flashes. In a recent meta-analysis from Australia, placebo has been found to result in a 52% reduction in the frequency and intensity of the hot flash (Henry Burger, M.D., personal communication). Therefore, all trials of medications designed to treat a hot flash should have associated with them a placebo arm for comparison of the outcome.

The use of HRT, both CEE and medroxyprogesterone acetate (MPA) given either cyclically or continuously, or micronized progesterone given in a cyclic fashion, have shown a reduction in the odds ratio for hot flashes that is statistically significant.⁵ These data confirm that the addition of a progestational agent to the oral medication does not interfere with the efficacy of the estrogen. The use of 1mg of estradiol 17 β is as effective as CEE 0.625 mg in reducing the incidence of hot flashes.^{4,7} The addition of norethindrone acetate 0.5mg to estradiol 1 mg (E₂/NETA) has been reported to be even more effective in inhibiting the number of moderate to severe hot flashes over a 12-week period compared to estradiol alone [Notelovitz M, Abstract presented at the 1999 North American Menopause Society Meeting]. These authors found a significant increase in the percentage of women who achieved a 90% to 100% reduction in hot flashes over the 12 weeks of this clinical trial using the E₂/NETA. Approximately 80% of the women achieved this 90% to 100% reduction, compared to 20% on placebo.

Estrogen and Androgen – Oral

A combination of esterified estrogen with methyl testosterone has a FDA indication for the treatment of hot flashes that have not been resolved with estrogen alone. A comparison study between esterified estrogen and esterified estrogen and methyl testosterone combination has indicated that within one week the mean reduction in the intensity score was significantly different from baseline, but there were no differences between the two treatments.⁸

Transdermal Estradiol

Transdermal estradiol 17 β (TDS E₂) has been found to have a dose-related reduction in the number of hot flashes per hour.⁹ This reduction actually brings the number of hot flashes per hour to close to the level found in premenopausal women. In this study, a placebo had no effect on hot flash frequency. A recent publication has again shown that TDS E₂ delivery using a matrix patch rather than a reservoir system reduces hot flashes.¹⁰ There appears to be a dose response effect on hot flushes with delivery of 25, 50, and 100 μ g a day. Both 50 and 100 μ g per day of E₂ appeared to have a further reduction in the number of hot flashes compared to 25 mcg per day.

The delivery of estradiol via the transdermal route, whether it be in a matrix or a reservoir delivery system or administered as a gel, appears to have comparable effects on the inhibition of hot flashes. Suppression of hot flashes is an estradiol dose effect, and reflects the bioavailability and pharmacokinetics of the delivered estradiol.

Transdermal Estradiol With a Progestogen

A delivery system consisting of 50 μ g of E₂ and either 140 or 250 μ g per day of norethindrone acetate (NETA) in a transdermal system is available (Combi-Patch™, Hoechst Roussel, Colleagueville, PA). Published reports indicate a significant improvement in the mean number of hot flashes per day with either of the two doses of NETA.⁷ The reduction in hot flashes was significant compared to both baseline values and the placebo after 12 weeks. The reduction in the number of hot flashes per day fell from 11.15 to 2.13, and from 10.16 to 1.12 for the NETA 140 and 250 mcg per day TDS. It should be noted, and not as a reflection of the delivery system, that even with what would be considered a fully therapeutic

dose of estrogen that it is often difficult to achieve 100% inhibition of all hot flashes. Similar results have been found with oral estrogen and progestogen combinations.

The use of transdermal estradiol/norethindrone acetate reduced the mean daily intensity of the hot flashes over the three months of the study from a baseline value of approximately 5 on a scale of 0-9 with 9 being the worst to a mean of less than 1 for both the 50/140 and 50/250 E₂ NETA systems.⁷

Estradiol Delivered as a Vaginal Ring

Although vaginal preparations of estrogen are available, they have principally been used for local vulvar or vaginal atrophic changes. The estrogen ring, (Estring®, Pharmacia Corp., Peapack, NJ) as well as the recently introduced estradiol pellet (VagiFem™, Pharmacia Corp., Peapack, NJ), do not deliver sufficient estrogen into the systemic circulation to have any impact on hot flashes. These preparations are useful for the local treatment of vulvo-vaginal atrophy. One study has investigated an estradiol-releasing vaginal ring for treatment of menopausal symptoms.¹¹ This vaginal ring released either 80 or 160 μ g per day of E₂. In this study, both doses of E₂ delivered vaginally reduced the number of hot flashes per week compared to baseline. There did not appear to be any significant difference between the amount of reduction in hot flashes per week between the two medications.

PROGESTOGENS FOR HOT FLASHES

Medroxyprogesterone Acetate (MPA)

In a previous study reported in 1980, the use of medroxyprogesterone acetate (MPA) in doses of 20 to 40 mg per day in a crossover design showed a significant reduction in the occurrence of hot flashes versus placebo.¹² A subsequent study by the same authors indicated there was a reduction in the frequency of skin temperature elevations in these women.¹³

Megestrol Acetate

Megestrol acetate has been shown to significantly reduce the frequency and the hot flash score in both men and women compared to placebo.¹⁴ The frequency of hot flashes in men and women were similar at the beginning of the study with 73 hot flashes per week in the women and 81

in the men. After four weeks of treatment with megestrol acetate, the frequency of hot flashes was 26 in the women and 20 in the men with a p value of .0001. Megestrol acetate has also been found to have a dose response on the subjective and objective number of hot flashes per hour.¹⁵ With the use of 20, 40, and 80 mg per day of megestrol acetate there is a step-wise reduction in the number of hot flashes/hour.

Progesterone Alone

Despite the widespread advertisement for compounded progesterone cream, there is only one trial that investigates vasomotor symptoms with the use of a progesterone skin cream. In this trial, the participants filled out weekly symptom diaries rather than daily, and used 20 mg of progesterone per day in the cream.¹⁶ The data were self-reported, but vasomotor symptoms improved or resolved in 83% of the treated cases versus 19% in the placebo group. The differences in the treated versus placebo patients were statistically significant with a p<.001.

Tibolone

Tibolone is a unique compound that is not currently on the United States market. Tibolone is a pro-drug that has several different metabolites. These metabolites have been found to have tissue specific estrogen, androgen, and progestational activity in the human. A comparison study of tibolone versus E2/NETA (2.0 mg/1 mg, Kliogest, Novo Nordisk, Copenhagen, Denmark), tibolone (Organon, the Oss, Netherlands) had comparable efficacy in the reduction of hot flashes from baseline with no statistically significant difference between the use of tibolone or E2/NETA on the hot flash severity score at 12 weeks.¹⁷

Clonidine

This alpha 2 blocker has been found in controlled clinical trials to have a moderate degree of efficacy compared to placebo in the reduction of the number of hot flashes per week. This particular study used the transdermal delivery system in a dose of 100 µg per day.¹⁸ Over an eight-week trial, there was a significant reduction in the incidence of hot flashes from 40 per week to 12 per week in the clonidine group, and from 35 per week to 20 per week in the placebo group. Both oral and transdermal clonidine has been found to be better than placebo in the management of hot flashes.^{18,19}

Alternative Therapies

Black cohosh has been reported in controlled trials in Europe to have a degree of efficacy at reducing hot flashes compared to placebo. However, in published studies to date, vitamin E, Dong Quai, and the isoflavone found in Red Clover have not shown a significant difference compared to placebo.²⁰⁻²² A recently controlled trial with soy isoflavone has indicated an efficacy in the reduction of the incidence of hot flashes compared to placebo.²³ The published literature indicates a variable response of hot flashes to soy isoflavones.^{24,25}

Selective Serotonin Reuptake Inhibitors

Venlafaxine HCL (Effexor®, Wyeth-Ayerst Laboratories, St. David's, PA) has been shown to have a decrease of over 50% in hot flash scores in 58% of individuals treated.^{26,27}

Paroxetine HCL (Paxil®, Smithkline Beecham, Philadelphia, PA) was found to have a 67% reduction in frequency in a regimen of 10 mg daily for one week followed by 20 mg daily for four weeks.²⁸ This study was carried out in women who had previously been treated for breast cancer.

CONCLUSION

In conclusion, both estrogens and progestational steroids appear to reduce the number, frequency, and severity of hot flashes. A combination of both estrogen and a progestin, at least in recent clinical trials, appears to be better in reducing the frequency and severity of the hot flash compared to estrogen alone.

The route of administration, either oral or transdermal, does not appear to make a significant difference in improvement of hot flashes; rather it is a dose effect.

Selective serotonin reuptake inhibitors may have an effect both in men and women. Soy protein, specifically isoflavones, are possibly effective as is black cohosh. Vitamin E, Dong Quai, and Red Clover extract do not appear to be effective when compared to placebo. Clonidine, an alpha-adrenergic blocker, has been found to be effective when taken either orally or transdermally.

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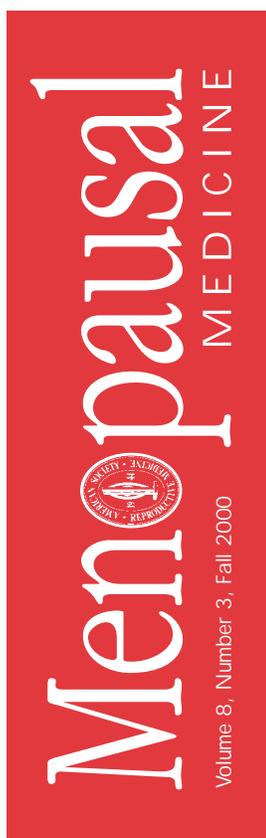
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