

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members and guest commentators,* experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

Question: If the decision has been made to discontinue hormone therapy (HT), what is the best way to do so? Would you recommend tapering or going "cold turkey," and how would you take into account the patient's subsequent risk factors for osteoporosis, and related bladder and sexual problems?

Participants

* Veronica A. Ravnikar, MD
Chair, Department of Obstetrics-Gynecology
South Shore Hospital
South Weymouth, MA

* Michel E. Rivlin, MD
Associate Professor
Department of Obstetrics and Gynecology
University of Mississippi Medical Center
Jackson, MS

* Lee P. Shulman, MD
Professor of Obstetrics and Gynecology
Feinberg School of Medicine
Northwestern University
Chicago, IL

Cynthia A. Stuenkel, MD
Clinical Professor of Medicine
Division of Endocrine and Metabolism
University of California, San Diego
La Jolla, CA

Answers:

The 2002 discontinuation of the HT arm of the Women's Health Initiative (WHI) study provides the largest profile to date of women's symptoms after the pharmacologic discontinuation of HT. The most frequently reported symptoms were (in decreasing order) joint pain or stiffness, feeling tired, vasomotor symptoms, difficulty sleeping, and bloating or gas.¹ The musculoskeletal symptoms were a surprise in terms of frequency, but were not a surprise to the patients and providers, who have always been perplexed by new or increased joint stiffness with estrogen deficiency. Women who had severe hot flashes during the entry phase washout were excluded from entering the study, and the average age of women studied post-HT was 69 (yet they still had withdrawal symptoms!). Finally, the younger cohort of women in the withdrawal study had more emotional symptoms, neurologic symptoms (headaches), breast tenderness, and vaginal and vasomotor symptoms. In general, up to 25% of women who stop HT restart because of these "menopausal symptoms."¹ Therefore, finding a way to taper HT therapy is important.

Tapering by Day or Dose

There are two tapering modalities; namely, the "day" and the "dose" taper.² The dose taper works best in women who have started HT perimenopausally, since they may be on low-dose oral contraceptives, and are best treated after age 50-54 with postmenopausal HT at standard doses, followed by an appropriate decrease in dose (for example, 0.625 mg to 0.3 mg). Once on the lowest dose possible, continuing at such a dose for an additional 6 months with a "day" taper may be effective; that is, taking HT for 5 out of 7 days, and then for 3 out of 7 days. Despite a lack of study data that such tapering works, it makes sense to use such a regimen in women who had severe vasomotor symptoms before starting HT; these are the individuals who experience symptom rebound once therapy is discontinued.

Along with this tapering, it might be beneficial

to modify or limit the use of progestins to every 3 months, with a final progestin withdrawal and/or endometrial stripe analysis. Progestins themselves cause undesirable symptoms such as irritability and depression. All women should be encouraged to lose weight and to exercise, since these lifestyle modalities have been shown to decrease vasomotor symptoms.^{2,3} Ad-

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– *Veronica A. Ravnikar, MD*

ditionally, in women who remain symptomatic during the taper, or who want—or need—to discontinue HT abruptly, use of selective serotonin reuptake inhibitors (SSRIs) or selective serotonin and norepinephrine reuptake inhibitors is beneficial.⁴

Recommended Timeline

De novo hormone administration, in distinction, should always be started at the lowest dose possible and, at this point, should not be continued for more than 5 years, although this timeline is still arbitrary. Patients who have no uterus can be put back on estrogen therapy (ET), but not if they have had a stroke or transient ischemic attack (TIA). Patients who have a uterus can be placed back on HT, but not if they have had a stroke or TIA and a history of breast cancer.⁵ Patients who still require ET or HT beyond 5 years may do best with transcutaneous forms or with vaginal administration of low-dose estrogen (for symptoms of vaginal thinning).

Postmenopausal HT is FDA-approved for the treatment of vasomotor symptoms and vaginal atrophy. HT is not a first-line therapy for osteoporosis prevention, as bisphosphonate therapy is the preferred treatment. Certainly, if a patient stops HT, bone loss ensues. Depend-

ing on the patient's bone density baseline prior to the use of hormones or after their discontinuation, bisphosphonates may be added. However, if a patient has absolute contraindications or intolerance to bisphosphonates, then long-term use of HT for osteoporosis prevention may be indicated. Although HT is not approved for the treatment of osteoporosis, it may still be useful in rare and select cases when there is an intolerance to bisphosphonates and no major contraindications to ET or HT.

Compliance Matters

Finally, women starting or restarting HT should be advised that discontinuation of HT is associated with withdrawal symptoms in a large percentage of patients.¹ Therefore, not adhering to therapy or taking it improperly can cause physical sequelae. We have all heard patients complain that HT is not effective for their symptoms, only to determine upon further questioning that the patients are not taking their HT as prescribed. The therapy is discontinued periodically and may cause symptoms that patients do not relate to estrogen withdrawal, such as joint stiffness, depression and headaches. Prior to prescribing HT, preparing patients for these withdrawal symptoms and stressing the need for staying on a consistent HT schedule will definitely lessen confusion for the patient, even if she is symptomatic during this time period.

– *Veronica A. Ravnikar, MD*

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It is my opinion that gradually decreasing the dosage of hormone is preferable to abrupt cessation of therapy. This view is based on the observation that sudden withdrawal of ovarian function, as typically seen in the surgical removal of ovaries in premenopausal women, is associated with severe vasomotor symptomatology. Furthermore, natural menopause is typically a slow process extending over several years, with a gradual diminution in ovarian hormone production, and it is this process that

With regard to osteoporosis, I advise women at high risk to either reconsider HT or to consider prophylaxis with a bisphosphonate or a selective estrogen-receptor modulator (SERM), preferring the former in patients with vasomotor symptoms and the latter in women with gastric symptomatology.

– Michel E. Rivlin, MD

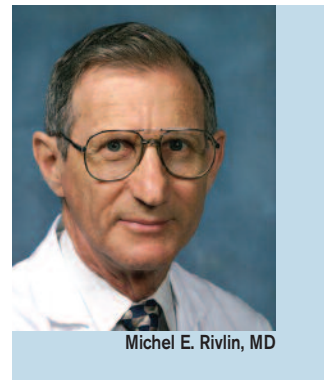
I feel should be imitated as best one can by gradually diminishing the exogenous hormone dosage. Exceptions to this preferred approach occur when HT is contraindicated as, for instance, when breast cancer or a deep venous thrombosis occurs in a woman on therapy, in which case abrupt cessation cannot be avoided.

Addressing the Problems

In my own practice, I seldom stop HT in women who are doing well. However, in many instances, women are persuaded to stop HT by other practitioners (in particular, internists and family physicians), or by family, friends and/or the media. Unfortunately, this well-meaning advice usually ends there,

and the problems associated with hormone deprivation are left unaddressed. Then, by default, it becomes my obligation to advise these women that since their replacement hormones have been withdrawn, they are now at risk for osteoporosis and urogenital atrophy, with the former's fracture risk and the latter's risk of bladder symptomatology and sexual dysfunction.

With regard to osteoporosis, I advise women at high risk to either reconsider HT or to consider prophylaxis with a bisphosphonate or a selective estrogen-receptor modulator (SERM), preferring the former in patients with vasomotor symptoms and the latter in women with gastric symptomatology. For women at low risk, observation with spaced bone density studies is probably adequate. Urogenital atrophy usually



Michel E. Rivlin, MD

manifests with urinary symptoms, including nocturia and urgency, and sexual dysfunction with vaginal dryness resulting in dyspareunia. For women with these problems who do not wish to resume HT, I explain that while vaginal lubricants are useful, estrogen is the only medication that can restore atrophic vaginal mucosa to its functional state. I then inform them of the excellent results that can be obtained with local ET, but point out that at least some hormone absorption occurs with local treatment (although generally much less than would occur with systemic therapy).

In conclusion, I cannot emphasize enough that each woman is approached as an individual, and her own special circumstances and opinion play vital roles in reaching a joint therapeutic decision.

– Michel E. Rivlin, MD

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The use of HT for the relief of menopausal symptoms continues to be a controversial topic among women and clinicians. Despite a burgeoning literature that presents evidence supporting the use of HT by either most or very few menopausal women, decisions regarding the use, or lack thereof, of HT by menopausal women is guided by health status, a complex array of symptoms, and an equally complex range of concerns about potential short- and long-term adverse events.

Reasons for Discontinuing HT

In this regard, many women who choose to use systemic HT to relieve menopausal symptoms may elect to discontinue for a variety of personal and medical reasons. Ettinger and colleagues¹ evaluated menopausal women in the United States, and found that the presence of vasomotor symptoms was the most common reason for using systemic HT. The authors also found that older women were more likely to discontinue HT than younger women, and for different reasons. Specifically, treatment-related side effects, such as vaginal bleeding, were the reasons for discontinuing HT that were cited most often by older women. Ringa and colleagues² evaluated a French cohort and, similarly, found that the presence of vasomotor symptoms was the most common reason for initiating systemic HT, and that younger women were less likely to discontinue HT than older menopausal women.

Regardless of the reasons for discontinuing HT, clinicians are frequently requested to provide advice concerning the optimal approach for discontinuing the hormonal regimen so as to minimize the reemergence of menopausal symptoms. Unfortunately, there is essentially no evidence to support a particular approach for discontinuing HT without exacting a se-

vere return of menopausal symptoms.³ Regardless, certain clinical circumstances can guide the discontinuation of HT. Obviously, the detection of medical conditions that preclude the continuing use of HT should prompt its immediate discontinuation. Such conditions include thromboembolic events such as pulmonary embolus, cardiovascular events such as myocardial infarction, and malignancies such as breast cancer. In such cases, the reemergence of menopausal symptoms should best be managed by nonhormonal regimens such as the use of SSRIs, even if such regimens are less effective than the previously used hormone regimen.

The Best Way to Discontinue

Women who choose to discontinue HT for reasons other than health promotion or disease prevention thus face a clinical dilemma regarding the optimal approach to discontinuing HT. Such reasons can include the intolerance of side effects (including, but not

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— Lee P. Shulman, MD

limited to, breast tenderness, vaginal bleeding, nausea and headache), concerns about the safety of HT, peer pressure and economic issues. Grady and colleagues⁴ reported that approximately one-fourth of women who choose to discontinue HT are unable to do so because of the recurrence of severe vasomotor symptomatology. For the majority of women who choose to discontinue HT and have mild or no menopause-related symptoms, there is no evidence that tapering HT provides any short- or long-term clinical benefit. Accordingly, I encourage such

women to stop using HT “cold turkey.”

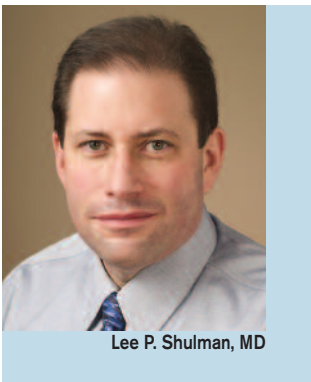
However, for women who try to discontinue HT but find themselves with a return of debilitating menopausal symptoms, consideration of tapering the regimen is warranted, and is an approach that I use. Many HT regimens now include a variety of doses, including lower doses of estrogens and progestins in oral and non-oral delivery systems. This can allow for the facile tapering of medication for women who experience severe symptoms when a less gradual approach is attempted.

Regardless of whether an immediate or long-term approach to discontinuation is elected, clinicians and patients need to consider certain health issues, such as osteoporosis, vaginal atrophy and other estrogen-related conditions that may be likely to occur after the discontinuation of HT, and warrant

close monitoring and intervention with preventive and therapeutic regimens that do not include systemic hormone therapies. It is important “not to lose the forest for the trees.” Although our patients may believe that the use of systemic HT is primarily or solely for the treatment of

vasomotor symptoms, the use of such systemic hormone therapies provides considerable positive health benefits that, if ignored, will surely lead to a markedly increased likelihood of a constellation of adverse clinical outcomes that can impact quality of life and longevity.

– Lee P. Shulman, MD



Lee P. Shulman, MD

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At this time, I would advise a patient who is considering discontinuation of HT that there is no proven “best way” to do so. As is my approach with many decisions without clear-cut guidelines, I would first clarify the patient's position on the matter. Why does she want to stop? Her level of motivation might temper her degree of willingness to deal with withdrawal symptoms. How does she feel about tapering or going “cold turkey?” She might have very clear ideas about how she wishes to proceed.

I would then review what personal characteristics have been shown to bode well (or ill) for a successful discontinuation, and see how the patient compares. Grady et al¹ found that three characteristics were associated with difficulty quitting HT: (1) having a hysterectomy, (2) using HT for 10 or more years, and (3) citing reasons other than health promotion (ie, symptom relief) for being on HT. In a telephone survey of 377 women enrolled in the Kaiser Foundation Health Plan,¹ women with all three characteristics were more likely to be unsuccessful in quitting HT (44%), compared with those with two (25%) or none (9%) of these three characteristics.

Symptom Recurrence

The WHI study selected participants who did *not* have debilitating vasomotor symptoms at baseline. Eight to 12 months after the WHI ended, Ockene et al surveyed 90% of the study participants who were still taking their study HT pills or placebo when the intervention was stopped.² Overall, discontinuing study pills was associated with moderate or severe vasomotor symptoms in approximately 21% of those assigned combined hormones versus approximately 5% of women in the placebo group. However, among women who reported vasomotor symptoms at baseline, recurrence of symptoms upon discontinuation of the study pills was reported by 21% of those assigned to placebo, versus more than half (55%) of the women assigned to HT.² This suggests that women who take hormones to relieve menopausal symptoms can anticipate a 50/50 chance of symptom recurrence when they stop taking hormones!

Timing of symptom recurrence. In one randomized, controlled trial,³ women who had been taking HT were randomly assigned to 12 weeks of treatment with either placebo or continuation of HT. Hot flashes and night sweats peaked at 8 weeks and started to decline by 12 weeks in the group assigned to placebo. In another recent trial,⁴ symptoms peaked at 12 weeks after abruptly discontinuing HT.

Likelihood of success. In the survey by Grady et al,¹ 74% of women were successful in stopping HT (no hormone therapy for 6 months); 26% resumed treatment because of troublesome withdrawal symptoms. In a trial by Haimov-Kochman et al, 40% of women resumed HT because of vasomotor symptoms.⁴

Tapering or “Cold Turkey?”

If a woman is amenable, I would recommend going “cold turkey.” If symptoms are unbearable (as defined by the patient), I would recommend resuming HT until her symptoms have resolved, and then switching to a tapered approach. Whether tapering by “days” or by “dose,” a gradual reduction gives women the opportunity to determine their lowest effective dose of HT.^{5,6} The taper need not follow a rigid regimen, and could include dosing “plateaus” when bothersome symptoms resume.

If they elect to taper (and many women do), what is the most effective technique? Again, we really don’t have data to answer this question. In one trial, taper by “days” included taking the usual dose for one less day per week for a month. So, instead of 7 days per week, the taper would begin with 6 days per week for the first month, 5 days per week for the second month, etc.⁴ If they elect a taper by “dose,” many women find that cutting the estrogen patch by slivers is of benefit. This allows them to reduce their dose much more gradually than would be possible with a complete reduction in patch size, or a lowering of the oral estrogen dose by the increments currently available.

I would not routinely recommend starting another intervention (such as black cohosh, isoflavones, etc.) upon discontinuation of HT; it is important for women to get a sense of their

baseline symptoms, which could erroneously be attributed to a new medication. In my view, it is especially important not to initiate treatment with a SERM (such as raloxifene) during this transition because women may blame their increase in hot flashes (even with evidence to the contrary)³ on the new medication, and will likely stop taking it.

Subsequent Risk Factors

At this point in their lives, most women qualify for a bone mineral density (BMD) test if they haven’t already had one. The BMD test will establish a current BMD baseline. If they have a BMD < -2.5 SD or they’ve already had an osteoporotic frac-

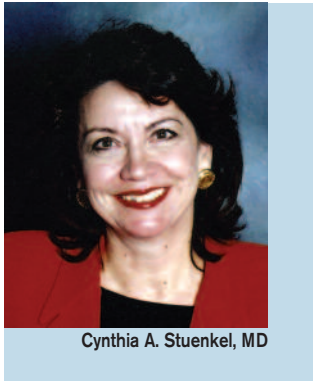
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ture, they qualify for pharmacologic treatment. If they fall into the low range (BMD -1 to -2.4 SD), it’s important to evaluate their risks for fracture and falls, and make an individual decision regarding therapy. The new World Health Organization paradigms for calculating individual absolute fracture risk will help us decide more accurately who needs treatment. If you elect not to treat or if the patient’s BMD is in the normal range when HT is stopped, reassess (including a repeat BMD) in 2 years. It’s also important to review recommendations and reinforce the importance of calcium and vitamin D supplementation, weight-bearing exercise and fall prevention with all

women regardless of their BMD values.

Our knowledge about urogenital health has greatly expanded in recent years. While we used to think that HT improved incontinence, we know now that hormones aggravate the condition. Recurrent urinary tract infections,



Cynthia A. Stuenkel, MD

however, do respond favorably to ET. I'd recommend a vaginal estrogen preparation; choices include estrogen creams, tablets and rings. Patient preference and cost both enter into the decision about what to recommend. If creams are used, it's important to remember that women often use more than is necessary.

I advise women to try to reduce the amount and frequency of application to the minimum amount that provides symptom relief.

"Sexuality problems" cover a lot of territory, so it would be important to take a very careful history to understand exactly what is troubling the patient. The primary sexual problem relieved with ET is vaginal dryness. If over-the-counter vaginal lubricants and moisturizers were not effective, I would prescribe vaginal estrogen.

– Cynthia A. Stuenkel, MD

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From the Editor (continued from page 9)

An Excellent Objective

Our objective is excellent—to deliver the best and most current care to all patients. The solution remains problematic, but not insurmountable, provided we do the best we can with the most pertinent current knowledge. But if we are going to change practice and implement evidence, the hard work is to involve the best people, summarize the state of the science, recognize difficulties in achieving change, develop strategies and tactics for achieving change and, most essentially, create markers for measuring the efficacy of the outcome.

In getting to that point we certainly need to avoid *total* reliance on "data" or use of outdated methods. It is hoped that in this effort we can also narrow the gap between medical students' knowledge at the time of graduation and the best currently available information.

Where does this leave us with respect to pharmacotherapy for menopausal women post-WHI? I will attempt to address that issue in the near future. And what about my original question: Is evidence-based medicine a pipe dream? It's your call!

Wulf H. Utian, MD, PhD

Executive Director, NAMS
Consultant in Women's Health
The Cleveland Clinic Foundation

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