Correspondence: Hormone Therapy for Postmenopausal Women

TO THE EDITOR:

In an assessment of therapies to treat the symptoms of menopause, Pinkerton (Jan. 30 issue)[1] dismisses compounded therapies (except for those used in patients with allergies or when there is a medical need for unusual dosing regimens), and she notes safety concerns. This blanket generalization overlooks the substantial Food and Drug Administration (FDA) oversight established by the 2013 Drug Quality and Security Act (DQSA).

Contrary to Pinkerton's assertion of "minimal government regulation and monitoring," the drug outsourcing facilities supervised under the DQSA must register with the FDA, be subject to regular unannounced inspections, comply with Current Good Manufacturing Practices, and use FDA regulated ingredients. Patients have depended on compounders and outsourcing facilities for decades to provide the customized formulations that work well for them, along with counseling on use of the compounded medication. I am extremely concerned about the potential consequences for women who use these therapies of disregarding this sector in its entirety owing to unfounded safety concerns.

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No potential conflict of interest relevant to this letter was reported.

1. Pinkerton JV. Hormone therapy for postmenopausal women. N Engl J Med 2020; 382: 446-55.

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TO THE EDITOR:

In her article on hormone therapy, Pinkerton focused on data from the Women's Health Initiative and did not mention the Danish Osteoporosis Prevention Study, which randomly assigned 1006 recently postmenopausal or perimenopausal women to estradiol or no estradiol for 11 years and followed them for 16 years. Women who received estradiol had significantly lower mortality (among 15 women vs. 26 women) and a significantly lower incidence of myocardial infarction (5 vs. 11) than women who did not receive estradiol, without an increase in the incidence of cancer (36 and 39, respectively), venous thromboembolism (2 and 1), or stroke (11 and 14).[1]

The article by Pinkerton also did not address sexual dysfunction[2] or menopause-related cognitive impairment,[3] which has been reported to be present in 60% of perimenopausal and postmenopausal women.[2-4] Subjective reports of symptoms are confirmed by objective evidence of decreases in measures of verbal memory, episodic memory, list learning, verbal fluency, or executive functioning.[2-4] Lack of awareness among physicians of this association between memory loss and menopause may have disastrous consequences for menopausal women, including the misdiagnosis of dementia in women with these symptoms.[3]

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No potential conflict of interest relevant to this letter was reported.

1. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012; 345: e6409.

2. Davis SR, Lambrinoudaki I, Lumsden M, et al. Menopause. Nat Rev Dis Primers 2015; 1: 15004.

3. Devi G. Menopause-related cognitive impairment. Obstet Gynecol 2018; 132: 1325-7.

4. Greendale GA, Derby CA, Maki PM. Perimenopause and cognition. Obstet Gynecol Clin North Am 2011; 38: 519-35..

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THE AUTHOR REPLIES::

Schwartz notes concerns about the recommendation to avoid the use of compounded therapies except in special circumstances. The 2013 DQSA provides national licensure standards and FDA inspections for outsourcing wholesale distributors and third-party logistics providers who ship across state lines.[1] Compounding pharmacies that are not outsourcing providers are monitored by states, with wide variability in oversight.[1] The Pharmacy Compounding Accreditation Board assesses voluntary compliance with sterile and nonsterile pharmacy compounding processes. Major medical societies, including the American Medical Association, the American College of Obstetricians and Gynecologists, and the North American Menopause Society, recommend against compounded

hormone therapies owing to safety concerns regarding overdosing or underdosing, impurities, the lack of sterility, insufficient scientific efficacy and safety data, and the lack of labels providing information on dosing, ingredients, and risks.

FDA-approved bioidentical therapies include systemic and vaginal estrogen and progesterone and vaginal dehydroepiandrosterone. Medical indications for compounded hormone therapies should be documented.[1,2] For example, oral progesterone should not be used in patients with peanut allergy, preservative-free vaginal estrogen may be warranted, pellets with supraphysiologic levels of testosterone for sexual disorders are not recommended, and special dosing or formulations may be required. Federal and state oversight is needed for increased transparency about compounded product ingredients, financial conflicts of interest, and monitoring of adverse events.

With respect to the comments by Devi and colleagues: since the Danish Osteoporosis Prevention Study was open label, did not involve a placebo, and was much smaller than the Women's Health Initiative, the data are less robust. Devi et al. also call attention to the effects of menopause on sexual function and memory. Systemic and vaginal estrogen improve lubrication and blood flow and decrease the symptoms of genitourinary syndrome of menopause and painful sex, without effects on sexual interest, arousal, or orgasm beyond reduced vasomotor symptoms.[2] For women with low libido, transdermal estrogen is recommended because it has less effect on testosterone bioavailability than oral hormone therapy.

Memory problems during menopause (e.g., forgetfulness, losing keys, and difficulty concentrating or retrieving names) are usually not associated with clinically significant impairment. Treatment of depression, anxiety, and sleep disturbances, increased concentration to focus attention, and increased exercise may decrease memory problems.[3] Neuropsychological testing is recommended if cognitive symptoms interfere with daily life.3 Estrogen has been associated with improved cognition after early surgical menopause,[3] has neutral effects if used early in postmenopausal women,[4,5] and may worsen memory if initiated in patients older than 65 years of age.[2] Hormone therapy is not recommended to prevent or treat cognitive dysfunction or decline.

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Since publication of her article, the author reports no further potential conflict of interest.

1. 1. Pinkerton JV, Pickar JH. Update on medical and regulatory issues pertaining to compounded and FDA-approved drugs, including hormone therapy. Menopause 2016; 23: 215-23.
2. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017; 24: 728-53.
3. Greendale GA, Karlamangla AS, Maki PM. The menopause transition and cognition. JAMA 2020; 323: 1495-6.
4. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective Study. PLoS Med 2015;12(6): e1001833.
5. Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized

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