JNDSS

Volume 3 • 2015

JOURNAL OF NURSING DOCTORAL STUDENTS SCHOLARSHIP

Penn Nursing Science
University of Pennsylvania School of Nursing

Prescribing menopausal hormone therapy outside of treatment guidelines: Considerations for nursing

Mary Hunter, RN, MN, WHNP-BC, ANP-BC
Doctoral student, University of California San Francisco

Abstract
Although guidelines limit menopausal hormone therapy (HT) to five years, over 25% of prescriptions are written for women over age 60. "Ghostwritten" articles and CE courses attributed to specialists with ties to manufacturers are intended to cast doubt on guidelines. Some providers prescribe HT beyond recommendations with the understanding that the patient has decided to continue using hormones despite the risks. As nurses, we can help patients differentiate marketing messages from scientific findings that inform evidence-based practice.
Key words: Hormone therapy, menopause, guidelines, prescription, marketing

Introduction

The evidence-based recommendations of UpToDate® represent a synthesis of the best science and the most recent medical information on a given topic. The organization accepts no funding from pharmaceutical companies, medical device manufacturers, or any other commercial entity, and its clinical guidelines are used by 90% of academic medical centers in the United States alone (UpToDate, 2015). Because of risks to health associated with menopausal hormone therapy (HT), the guidelines in this online database suggest that prescription of systemic estrogen is not recommended (with rare exceptions, such as for osteoporosis that cannot be treated with bisphosphonates) beyond three to five years after the last menstrual period (Martin & Barbieri, 2015). Only the minority of women who are unable to discontinue estrogen because of persistent and severe symptoms that cannot be treated by other means should consider using HT beyond five years. The authors emphasize this point by specifically providing data to guide decision making for a period of up to five years in women ages 50 to 59 years. The recommendations of Martin and Barbieri (2015) regarding the use of HT are subtly but substantially different from those of the North American Menopause Society (NAMS), an organization with acknowledged ties to the pharmaceutical industry (NAMS, 2012). For example, in the guidelines authored by Martin & Barbieri (2015) there is no suggestion that the risks of HT beyond five years (even when estrogen is used alone) can be counterbalanced by "quality of life" benefits, as is suggested in NAMS publications.

Regardless of prescribing guidelines, at least 25% of prescriptions for menopausal hormone therapy were written for patients over the age of 60, women who are more than five years past menopause (Hersh, 2004). In 2009, the last year for which these data were available, the prevalence of use ranged from 12.7% in women aged 61 to 65 to 3.9% in women over age 75 (Steinkellner, Denison, Eldridge, Lenzi, Chen, & Bowlin, 2012). Although there is a trend toward prescription of lower doses, Corbelli & Hess (2012) observed that there is no evidence to support the intuitive hypothesis that lower doses are associated with lower risk. Only 25% of hormone therapy prescriptions were written for low-dose therapy through 2009 (Ettinger et al., 2012). Standard or high dose oral formulations remained the most common regimens observed through 2009, and the average length of use had steadily increased from 2002 to 2009.

The reasons why long-term users may resist discontinuing menopausal hormone therapy vary. Understandably, many women fear the resumption of unpleasant symptoms such as hot flashes that prompted their initiation of estrogen use. Beliefs about menopause, aging, and hormone therapy also play a role in the long-term use of estrogen. Prior to 2002, "hormone *replacement* therapy" was promoted aggressively for relief of hot flashes and vaginal dryness, prevention of chronic diseases such as cardiovascular disease and osteoporosis, stabilization of mood, and cosmetic benefits. Some women believe that estrogen helps them keep a youthful appearance and healthy sex drive, avoid mood swings, maintain a healthy weight, and slow the aging process overall. These beliefs originated with the marketing of estrogen.

Marketing Pharmaceutical Estrogen

As detailed in *The Estrogen Elixir: A History of Hormone Replacement Therapy in America* (Watkins, 2007), estrogen formulations have been used to alleviate hot flashes since the early part of the 20th century. Synthetic estrogen was first marketed in pill form in 1938, an event that coincided with the use of the term "menopause" as a diagnosis. The estrogen compound diethylstilberstrol (DES) was developed to treat hot flashes, but the side effect of pronounced nausea prevented its widespread use. Premarin®, a better-tolerated preparation derived from the urine of pregnant mares, was developed at about the same time by Ayerst Laboratories, one of the first companies to emerge in the new and profitable business of drug manufacturing. DES and Premarin® were approved by the Food and Drug Administration (FDA) in 1941 and 1942, respectively. By 1947, there were 53 different menopausal hormone formulations sold by 23 different companies.

Menopausal hormone therapy was marketed to treat hot flashes, menopausal irritability, sexual disinterest, and aging. Ayerst, a company that spent a million dollars annually on advertising by the late 1960s, secretly paid Robert Wilson, MD, to write "Feminine Forever." This best-selling book published in 1966 helped cement the connection between estrogen supplementation and healthy aging in the American consciousness (Watkins, 2007). According to Wilson's writings, menopause is an estrogen deficiency

degenerative disease that requires treatment of all women who are otherwise "castrates." He claimed that estrogen prevented cancer, and he denied evidence to the contrary (Neel, 2002). The book helped create a discourse that: (a) promoted the idea and the product known as "hormone *replacement* therapy," (b) pathologized and medicalized menopause, (c) contributed to our culture's fear of aging and quest for eternal youth, and (d) conceptually related estrogen levels to the value (and self-esteem) of women.

In the 1950s and 1960s, full-page print ads in medical journals emphasized the value of Premarin® as a practice builder and a drug that could turn unattractive, irritable women into compliant, pleasant patients (Watkins, 2007). As a result of these advertising efforts, Premarin® maintained its position as the most popular brand of estrogen, placing it among the top five prescription medications by 1975. Premarin® was shown to cause endometrial cancer in the 1970s, a fact Ayerst denied for years in spite of evidence published in the New England Journal of Medicine (Smith et al.,1975; Ziel & Finkle, 1975; Watkins, 2007). The danger of unopposed estrogen to women with uteri was addressed clinically by the added prescription of a progestin, and in 1995, Prempro® (a combination pill) was added to the product line.

Starting in the 1980s, print and television advertisements used glamorous celebrities to market Premarin® and Prempro® directly to women. After Wyeth Laboratories, a division of American Home Products, acquired Ayerst in the late 1980s, it continued marketing aggressively to maintain the widely-held belief that estrogen could delay aging and promote health. In the late 1990s, Premarin® and Prempro® sales comprised almost 70% of the menopausal hormone therapy market in the US, and by 2001, the two products generated $2B in sales annually (Petersen, 2002). The prevalence of hormone therapy use among women 50-74 in the US was then over 30% (Ettinger et al., 2012), and despite increasing competition from other hormone manufacturers, Premarin® and Prempro® comprised 63% of total HT sales in the US (Hersh, 2004).

In 2012, Bloomberg.com reported that Wyeth had been sued by over 10,000 women for failing to warn them about the known risks of breast cancer associated with Premarin® and Prempro®, and the total amount estimated to be paid in settlements to plaintiffs exceeded $1.2B (Feely, 2012). Internal marketing materials in unsealed discovery documents associated with breast cancer litigation clearly show that Wyeth knew that Prempro® and Premarin® caused cancer (DIDA, 2014; Singer & Wilson, 2009). These documents describe how marketing efforts were directed toward dismissing conclusive evidence and distracting the public from the risk of breast cancer.

Promoting Hormone Therapy to Providers

The promotion of hormone therapy to providers (including nurses) includes direct contact by drug representatives, the provision of samples, orchestrating the authoring of continuing education materials and professional journal articles, and sponsoring

conferences and continuing education courses. According to internal marketing documents, these efforts are tailored to specific provider categories based on their status and ability to influence patients and other professionals (DIDA, 2014; Krueger v. Wyeth, Inc., 2008). Nurses and nurse practitioners are positioned at the bottom of the hierarchical provider model, and their usefulness as agents in HT promotion is based on the assumption that, as managed care increasingly limits the time physicians can devote to direct patient care, nurses will continue to have time to counsel patients.

Situated above nurses and physicians in this marketing hierarchy are leading women's health specialists with whom Wyeth has established collaborative relationships (DIDA, 2014; Fugh-Berman, 2010; Krueger v. Wyeth, Inc., 2008). Wyeth recruited these "thought leaders" to present talks, author continuing-education courses, and publish articles in professional journals about the advantages of menopausal hormone therapy. During 2009, the year it acquired Wyeth, Pfizer spent $2M to fund continuing-education courses for nurses and physicians on the importance of estrogen to women's health (Rosenberg, 2010). In 2010, the majority of trustees and advisory board members of the North American Menopause Society had ties to hormone manufacturers, primarily to Wyeth and the company that acquired it, Pfizer (NAMS, 2010; Rosenberg, 2010).

One method drug manufacturers have used to promote HT is the strategic placement of "ghostwritten" journal articles and continuing education course materials, such as those authored by Mark Brincat, MD, and Leon Speroff, MD, (DIDA, 2014; Fugh-Berman, 2010; Fugh-Berman, McDonald, Bell, Bethards, & Scialli, 2011). The term "ghostwriting" refers to the development by marketing companies of manuscripts with authorship attributed to leading specialty physicians. By agreeing to allow themselves to be identified as authors of articles specifically tailored to sales objectives, such physicians participate in a marketing strategy designed to persuade other providers to prescribe hormones. Some of these physicians have been paid to publish, while others have benefitted by being prolific publishers, thereby securing academic credit. It has been demonstrated that ghostwritten manuscripts show bias in tone, and in some cases scientific content is intentionally misleading (Fugh-Berman, 2010; Fugh-Berman et al., 2011).

Ayerst/Wyeth spent millions of dollars asserting that estrogen clinically improves the skin, and publications attributed to Mark Brincat, MD, have been part of these efforts (Brincat, 1983, 1985, 1987, 2000; DIDA, 2014). In the Drug Industry Database Archives (DIDA) at the University of California San Francisco, a repository of unsealed discovery documents associated with breast cancer lawsuits against Wyeth, at least 41 documents link Brincat to Ayerst/Wyeth and ghostwriting. Research attributed to Brincat has been cited hundreds of times since 1983 as the basis for claims that estrogen preserves or clinically improves the skin, and most articles on the topic reference these publications. Brincat's findings have not been replicated, and other investigators have concluded that estrogen has no clinical cosmetic benefit (FDA, 2014; Haapasaari, 1997; Phillips, 2008).

More recent HT internal marketing literature is unavailable, as these materials ordinarily become public only after a judge orders the unsealing of discovery documents. Ascertaining whether the practice of ghostwriting orchestrated by marketing firms hired by hormone manufacturers is ongoing is less straightforward without such evidence. After sales of Prempro® and Premarin® fell precipitously in 2002, Wyeth's marketing shifted to efforts to cast doubt on the Women's Health Initiative findings (Fugh-Berman et al., 2011; WHI, 2002, 2004). Fugh-Berman et al. (2011) examined journal articles that comprised reviews, editorials, comments, or letters on the topic of hormone therapy prescribing published between 2002 and 2006. The goals of the study were: (a) to determine whether promotional tone could be identified by readers blinded to the authors' identities, and (b) whether the articles exhibiting a promotional tone were more likely to have been authored by those with ties to hormone manufacturers. Their findings indicate that articles with a promotional tone were more than twice as likely to be authored by physicians with ties to hormone manufacturers.

The Fugh-Berman et al. (2011) study also compared the content of articles authored by individuals with known ties to hormone manufacturers with articles by authors with no such ties. Some of the themes found in the articles written by those with ties to manufacturers were: (a) the risks of hormone therapy have been exaggerated, (b) randomized clinical trials are not better than observational studies for determining the risks of hormone therapy, (c) the study populations used in the Women's Health Initiative were inappropriate for determining risks, (d) ongoing studies are expected to demonstrate protective effects from hormone therapy, and (e) different formulations and doses have different risk/benefit profiles (that is, hormone therapy tailored to individual women based on their unique attributes may be beneficial and have minimal risk). Fugh-Berman et al. (2011) reported that articles from three authors with ties to the hormone industry contained sections of the same text repeated word-for-word in different articles, suggesting ghostwriting.

A continued belief (on the part of both providers and patients) that HT is protective is partially responsible for prescription of HT. This is not surprising in that claims that HT prevents cardiovascular disease and memory loss appear in popular media and professional literature (Goldman, 2014; Speroff, 2010). An example of this phenomenon is media attention given to the Kronos Early Estrogen Prevention Study (KEEPS) trial, which was designed to determine whether estrogen, when taken early in menopause, could prevent cardiovascular disease (CVD) and/or cognitive decline (Kronos Longevity Research Institute, 2012). The KEEPS study, which began in 2005 and ended in 2012, was largely conducted to test the "timing" hypotheses, which suggests that WHI data showing more CVD and dementia after use of HT were associated with starting HT after menopause (not early in menopause). At the 2012 annual meeting of NAMS, the authors of the KEEPS study announced preliminary findings supporting claims that HT was protective against CVD and dementia when started early in menopause. Press releases and related articles appeared widely in popular media such as USA Today and WebMD, giving the public the impression that there was evidence to support

the claims. The 2012 assertions were not supported with study data, and it was not until 2014 that results on CVD outcomes showing no protection were published in a peer-reviewed journal (Harmon et al., 2014). (Results on cognition effects have yet to be published in a peer-reviewed journal.) A 2012 document claiming that KEEPS data showed that CVD and dementia had been prevented by HT remains on the NAMS website where it is prominently featured (NAMS, 2015).

Concluding Thoughts

Many providers are willing to continue prescribing hormone therapy beyond five years with the understanding that the patient has decided to continue using HT despite health risks. "It is a quality of life decision," are words used by providers and repeated by patients, phrasing that implies estrogen improves one's quality of life (Hunter, unpublished manuscript). Having warned patients of the risks, providers and hormone manufacturers are relieved of legal responsibility. Some women say that because the information they have received from the media and from their health care providers is inconsistent and conflicting, they do not find health warnings about hormone therapy persuasive (French, Smith, Holtrop, & Holmes-Rovner, 2006; Kolip, Hoefling-Engles, & Schmacke, 2009; Theroux, 2010). As nurses, we can help patients differentiate marketing messages from scientific findings that inform evidence-based practice. In that nurses have been targets for hormone marketing strategies, it is useful for us to examine our own knowledge and beliefs about menopause, aging, and the appropriate use of hormone therapy. Shared decision making that results in the prescription of menopausal HT outside of treatment guidelines demonstrates the effectiveness of seven decades of estrogen marketing. It also shows that the injunction to **do no harm** is often ignored by those who care for aging women.

References

Brincat, M., Moniz, D.F., Studd, J.W., Darby, A.J., Magos, A., & Cooper, D. (1983). Sex hormone and skin collagen content in postmenopausal women. *British Medical Journal, 287,* 1337-1338.

Brincat, M., Moniz, C, Studd, J., Darby, A., Magos, A., Emburly, G., Emburey, G., & Versi, E. (1985). Long-term effects of the menopause and sex hormones on skin thickness. *British Journal of Obstetrics and Gynaecology, 92,* 256-259.

Brincat, M., Versi, E., Moniz, C., Magos, A, de Trafford, J., & Studd, J. (1987). Skin collagen changes in postmenopausal women receiving different regimens of estrogen therapy. *Obstetrics and Gynecology, 70,* 123-127.

Brincat, M. (2000). Hormone replacement therapy and the skin. *Maturitas, 35,* 107-117.

Corbelli, J., & Hess, R. (2012). Hormone therapy prescribing trends in the decade after the Women's Health Initiative: How patients and providers have found a way to sleep better at night. *Menopause, 19,* 600-601.

Drug Industry Document Archive (DIDA). (2014). [Sample documents representing Wyeth Pharmaceutical correspondence with Brincat and Speroff related to ghostwriting.] Retrieved from http://dida.library.ucsf.edu/tid/hib37b10 and http://dida.library.ucsf.edu/tid/mqc37b10

Ettinger, B., Wang, S., Leslie, R., Patel, B., Boulware, M., Mann, M., & McBride, M. (2012). Evolution of postmenopausal hormone therapy between 2002 and 2009. *Menopause, 19,* 610-615.

Feely, J. (2012, June 19). Pfizer paid $896 million in Prempro settlements. Bloomberg.com. Retrieved from http://www.bloomberg.com/news/2012-06-19/pfizer-paid-896-million-in-prempro-accords-filing-shows-1-.html

Food and Drug Administration (FDA). (2013). Menopause and hormones. Retrieved from http://www.fda.gov/forconsumers/byaudience/forwomen/ucm118624.htm.

French, L, Smith, M, Holtrop, J, & Holmes-Rovner, M. (2006). Hormone therapy after the Women's Health Initiative: A qualitative study. *BMC Family Practice, 7*, 61.

Fugh-Berman, A. (2010). The haunting of medical journals: How ghostwriting sold "HRT." *PLoS Med, 7*, e1000335.

Fugh-Berman, A., McDonald, C., Bell, A., Bethards, E., & Scialli, A. (2011). Promotional tone in reviews of menopausal hormone therapy after the Women's Health Initiative: An analysis of published articles. PLoS Med, 8, e000425

Goldman, B. (2014, March 12) Estradiol – but not Premarin – prevents neurodegeneration in women at heightened dementia risk. Scope [blog] Retrieved from http://scopeblog.stanford.edu/2014/03/12/estradiol-but-not-premarin-prevents-neurodegeneration-in-women-at-heightened-dementia-risk/

Haapasaari, K., Raudaskoski., T, Kallioinen, M., Suvanto-Luukkonen, E., Kauppila, A., Laara, E., . . . Oikarinen,A. (1997). Systemic therapy with estrogen or estrogen with progestin has no effect on skin collagen in postmenopausal women. *Maturitas, 27*, 153-162.

Harmon S., Black D., Naftolin F., Brinton, E., Budoff, M., Cedars, M., . . . Hodis, H. (2014). Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women, *Annals of Internal Medicine,161*, 249-260. doi:10.7326/M14-0353.

Hunter, M. (2015). *Hormone therapy decision making in older women.* Manuscript in preparation.

Kolip, P., Hoefling-Engels, N., & Schmacke, N. (2009). Attitudes toward postmenopausal long-term hormone therapy. *Qualitative Health Research, 19,* 207-215

Krueger v. Wyeth, Inc. (2008). [Discovery documents.] April Krueger v. Wyeth, Inc. United States District Court, Southern District of California, Case number 03CV2496 – JAH (AJB).

Martin, K. & Barbieri, R. (2015). Treatment of menopausal symptoms with hormone therapy. UpToDate. Retrieved from http://www.uptodate.com

North American Menopause Society (NAMS). (2010). Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society, 17*, 242-255. DOI:10.1097/gme.0b013e3181d0f6b9

North American Menopause Society (NAMS). (2012). The 2012 hormone therapy position statement of The North American Menopause Society. *Menopause: The Journal of the North American Menopause Society, 19*, 257-271.

North American Menopause Society (NAMS). (2015). KEEPS results give new insight into hormone therapy. Retrieved from http://www.menopause.org/annual-meetings/2012-meeting/keeps-report

Neel, J. (2002, August 8). The marketing of menopause: Historically, hormone therapy heavy on promotion, light on science. National Public Radio. Retrieved from http://www.npr.org/news/specials/hrt/

Petersen, M. (2002, July 10). Wyeth stock falls 24% after report. The New York Times. Retrieved from http://www.nytimes.com/2002/07/10/us/wyeth-stock-falls-24-after-report.html

Phillips, T., Symons, J., & Menon, S. (2008). Does hormone therapy improve age-related skin changes in postmenopausal women?: A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women. *Journal of the American Academy of Dermatology, 59*, 397-404.

Rosenberg, M. (2010, November). Flash back: The troubling revival of hormone therapy. *Consumer's Digest.* Retrieved from http://www.consumersdigest.com/special-reports/flash-back

Singer, N. & Wilson, D. (2009, December 13). Menopause, as brought to you by big pharma. *The New York Times.* Retrieved from http://www.nytimes.com/2009/12/13/business/13drug.html

Smith, D. (1975). Association of exogenous estrogen and endometrial carcinoma. *New England Journal of Medicine, 293,* 1164-1167.

Speroff, L. (2010). Flash of insight or flush of confusion? *Menopause. 17*, 1108-10.

Steinkellner, A., Denison, S., Eldridge, S., Lenzi, L., Chen, W., & Bowlin, S. (2012). A decade of postmenopausal hormone therapy prescribing in the United States: Long-term effects of the Women's Health Initiative. Menopause: *The Journal of the North American Menopause Society, 19*, 616-621.

Theroux, R. (2010). Women's decision making during the menopausal transition. *Journal of the American Academy of Nurse Practitioners, 22*, 612-621.

UpToDate. (2015). About us. Retrieved from http://www.uptodate.com/home/about-us

Watkins, E. (2007). *The estrogen elixir.* Baltimore, MD: The Johns Hopkins University Press.

Wilson, R. (1966). *Feminine forever.* New York: Evans.

Women's Health Initiative Steering Committee (WHI). (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association, 291,* 1701-1712.

Writing Group for the Women's Health Initiative Investigators (WHI). (2002). Risk and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA, 288,* 321-333.

Ziel, H., & Finkle, W. (1975). Increased risk of endometrial carcinoma among users of conjugated estrogens. *New England Journal of Medicine, 193*, 1167-1170.