Estrogen Implants: Embodiments of Deeper Problems in the Marketing of Drugs

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J Gen Intern Med 25(9):893-5
DOI: 10.1007/s11606-010-1435-5
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Less than a decade ago estrogen was the number one drug prescribed to women in the U.S. Based on what in retrospect were flawed assumptions, inadequate or misleading data, failures of independent questioning of massive industry promotional efforts, and a faulty construct that menopause was a diagnosis requiring medical treatment, more than 60 million prescriptions were written annually for "hormone replacement" therapy.¹ The situation abruptly changed with the publication of the WHI study, demonstrating that for women taking estrogen/progesterone therapy, an excess of eight additional cases of breast cancer, seven of heart disease, eight strokes, and eight cases of pulmonary embolism occurred for each 10,000 women treated.² Following cessation of such widespread use of combined hormone therapy, the incidence of breast cancer fell sharply for the first time in decades, a decline most likely due to the decrease in estrogen use.³ This revelation that large numbers of breast cancers were likely related to hormonal therapy adds to an earlier iatro-demic of thousands of cases of endometrial cancer associated with estrogen-only therapy, and more recent evidence of possible increased lung cancer risk.⁴⁻⁷

Uncertainties and controversies over the optimal role and formulations for exogenous estrogen continue.⁸ And as reported in the current issue of *JGIM*, these controversies have been fueled by a small number of authors who wrote multiple pro-estrogen articles while often failing to disclose financial ties with estrogen manufacturers. Five frequent decriers of the WHI message stood out—authors who collectively wrote more than 100 editorials, guidelines, and reviews in leading menopause journals and for professional organizations.⁹ While 96% of these publications took a strong stance favoring estrogen use, in only 6 of 110 of these articles or guidelines was the author's conflict of interest disclosed. As detailed in the Tatsioni study, these authors regularly disputed the WHI findings and continued to editorialize benefits of estrogen for menopausal

symptoms as well as prevention of osteoporosis, heart disease and even breast cancer.⁹

The Tatsioni findings follow uncovering of documents by lawyers suing Wyeth and made public after a request by the New York Times and PLoS Medicine which describe how in 2003 Wyeth funded a MECC (Medical Education and Communication Company) called DesignWrite to draft a 14-page outline of an article on estrogen treatment with the author "TBD" (to be determined).^{10,11} The article was subsequently published in a peer-reviewed journal by Dr. Gloria Bachmann who (in her words) "only had one correction which I highlighted in red." Adriane Fugh-Berman has described how such "publication planning" by the industry represents an elaborate and ubiquitous practice, assisted by organizations such as The International Publication Planning Association (TIPPA), whose aim is "to foster excellence in medical publications and communications within the biopharmaceutical industry" and provide "practical strategies for developing, implementing and executing an effective publication and communication plan as a critical component of the clinical biopharmaceutical development process."^{5,12,13}

While these examples showcase scandalous abuses, focusing on such outliers can distract from probing the more widespread, pernicious, and subtle ways the medical literature and practice are distorted by the influence of the pharmaceutical industry. From conceptualization of problems, to design and conduct of the research, to continuing "education" of physicians and the public, industry is skillfully shaping our practices. Even the title of the Tatsioni article, which refers to the partisans' editorials on "estrogen replacement therapy," succumbs to a biased framework the industry has promoted.⁹ The terms HRT or ERT reinforce the erroneous view of menopause as an estrogen "deficiency" disease, rather than a natural part of a women's life cycle that may or may not pose disruptive symptoms or other problems amenable to hormone or other therapies.¹⁴ Authoritative organizations have urged abandonment of the term "HRT," yet many articles continue to reinforce this hormone "replacement" terminology that has shaped the mindset of a generation of women and their physicians.¹⁵ Another example of misleading thinking related to estrogen occurred in the 1980s when Premarin's manufacturer funded leading clinical epidemiologist Alvin Feinstein in publishing articles dismissing the alleged association with endometrial cancer as being due to "detection bias," (a claim later disproven).^{5,16,17} Recent articles from authors, also with financial conflicts, are now advancing the hypothesis that estrogen is protective against cardiac risks but needs to be given earlier to younger peri-menopausal women (based on post hoc analysis of the WHI trial).^{18,19}

Dr. Schiff was supported in part by grant U18HS016973 from the Agency for Healthcare Research and Quality University of Illinois at Chicago Center for Education and Research in Therapeutics (CERT). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Published online July 7, 2010

Medicine needs new ways of framing questions that go beyond simply weighing known risk and benefits—incorporating approaches such as the “precautionary principle.” This paradigm derives from the German word *Vorsorgeprinzip*. *Vorsorge* means “forecaring” carrying with it a sense of foresight and awareness of past and potential problems.^{20,21} Rather than waiting for iatrogenics such as estrogen related cancer or Vioxx-associated heart disease, more fundamentally conservative approaches need to be adopted.²² Before recommending estrogen therapy to all women for its “protective effects”—as was the norm a decade ago—we should demand a higher standard of efficacy and safety, higher than one might demand for a drug used solely for short term treatment of intolerable menopausal symptoms.

Thus we need to design mechanisms to counterbalance promotional messages to ensure a more balanced understanding of the role and use of pharmacotherapy—not just more reliable disclosure of biases and conflicts, but more robust measures that avoid and counteract them. Recently a historic gathering of 150 academics, regulators, students, educators, and consumers met in Chicago under the aegis of the Attorney Generals of the 50 U.S. states to grapple with ways to achieve such a better balance, particularly in medical and pharmacy school curricula.²³ Twenty-nine projects funded by an educational grant from the Neurontin settlement compared successes and failures to reach prescribers and consumers with alternate messages about drugs and drug promotion. Although a bit of a David and Goliath situation (industry promotion exceeds \$50 billion annually, while the Attorney General Consumer and Prescriber Education grant program was a one-time set-aside of \$21 million from the guilty plea of Warner-Lambert Pfizer for illegal off-label promotion of Neurontin), many creative ideas and efforts were presented. These included academic detailing, courses on promotion techniques at medical and pharmacy schools, role-playing exercises to arm practicing physicians with practical ways to address patients requesting drugs advertised on television, Consumer Reports’ rating systems for best-buy drugs, and use of more critical independent information resources such as Prescrire (the French Medical Letter), Cochrane Reviews, and Best Pills, Worst Pills. The conference also highlighted the role played by students themselves whose Pharm-Free activities (organized by the American Student Medical Association (AMSA) have helped shift medical school policies related to disclosure, drug reps, gifts, and educational curriculum.

One lesson repeatedly voiced at the meeting was the need for alliances between consumers and professionals to build a more effective counterweight to balance of patient vs. marketing interests. Imagine the power of women coming to their doctors’ offices, laden not with the latest product ads from magazines or TV commercials, but instead with informed hard questions about the evidence for the drugs they are being prescribed. This is of course exactly what happened after the WHI study, and such critical questioning needs to be replicated and expanded now for a host of drugs. For example, do we have adequate evidence of safety and efficacy for flibanserin, now being promoted for hypoactive sexual desire disorder (HSDD), a relatively new medical diagnosis the manufacturer claims is affecting 1 out of 10 women? What about the risks vs. benefits of statin drugs for primary prevention in women (advocated by studies such as the Jupiter trial), especially for younger women, who have lower coronary risks; thus their absolute (as opposed to the relative) benefits are considerably less?²⁴

More important than rethinking any particular drug is the need for a new construct for research, one that moves away from studies designed by pharmaceutical manufacturers to answer the question “does my drug work?” (to meet FDA approval and marketing needs) to studies that answer the question that matter most to consumers and professionals—“What is the best and safest treatment?” A new approach should go beyond the demonstration of a particular drug’s safety and efficacy to explore questions of which therapies (and not just drug therapies) ultimately work best and under what circumstances.²⁵ Such a paradigm would re-conceptualize research not as a means to a marketing end but a process under our control to continuously learn and improve care.

At the very least, we need more transparency in disclosing conflicts that may exist between these two aims, which as Tatsioni shows, needs improvement.⁹ And even when authors dutifully declare such conflicts, these are often not easily accessed, as they are missing from structured online abstracts, often not listed in print versions of leading journals (“to save space”), and inaccessible online unless one has a paid subscription. Instead when one tries to access, for example, conflicts in a New England Journal article online, one instead ends up with, an ad for Viagra.²⁶

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