International Journal of Impotence Research (2008) 20, 45–52

0955-9930/08 $30.00
www.nature.com/ijir

REVIEW

Ethical problems with bioidentical hormone therapy

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The term 'bioidentical' hormone replacement therapy (BHRT) is widely misunderstood by the patient population and misrepresented in patient literature. Within the clinical community, BHRT is currently being prescribed by some as an 'innovative therapy' with no published evidence in peer-reviewed journals that it is better than the current standard of care; in at least one case, BHRT is being used as a study agent in unregulated and unethical research involving very high doses of estrogen and progesterone. Additionally, professional ethics problems abound within the prescribing population, since those claiming expertise and training in BHRT vary widely in competencies, may cross practice boundaries, and may have overt conflicts of interest if they are selling or promoting their own for-profit recipes of BHRT on commercial forums. Ultimately, BHRT presents clinical, research and professional ethics problems that are discussed in depth.
International Journal of Impotence Research (2008) **20,** 45–52; doi:10.1038/sj.ijir.3901622; published online 13 December 2007

Keywords: ethics; menopause; perimenopause; hormone therapy; BHRT; CAM

Introduction

Bioidentical hormone replacement therapy (BHRT) is defined by Boothby *et al.*[1] as 'hormone treatment with individually compounded recipes of certain steroids in various dosage forms, including dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol … the use of the term 'natural' refers to steroid hormones occurring naturally in women and does not refer to phytoestrogens or similar substances.' Fugh-Berman and Bythrow[2] state that bioidentical hormones, a 'pseudoscientific neologism … refer to endogenous hormones, including estriol, estrone, estradiol, progesterone, testosterone, DHEA, thyroxine, and cortisol [which are] synthesized or semisynthesized.' This paper focuses on what patients understand and appreciate about 'bioidentical' estrogen and progesterone hormones, but looks at how BHRT is framed in other areas of endocrinology to point out contradictions.

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Received 22 July 2007; revised 22 October 2007; accepted 22 October 2007; published online 13 December 2007

Historical nomenclature

The origin of the term 'bioidentical' hormones appears to be traced to Wright,[3,4] to describe the physiologic distinction he noted between 'patentable' and unpatentable hormones, viewing the latter as more natural because of assertions that the molecular structures from plant-derived, or unpatented, hormones were more 'identical' to human hormones. Wright's assertion remains unsubstantiated because to this author's knowledge, no one has put forth structural crystallographic data demonstrating structural identity with circulating human hormones.

Wright was critical of the term 'hormone replacement therapy'[5] when it comprised conjugated equine estrogen and progestin, and through his popular book,[3] heavily influenced current BHRT prescribers and advocates.

Dalton, noted for identifying premenstrual syndrome in 1953,[6] was the first advocate of natural progesterone for treating premenstrual syndrome,[7–9] and also promoted saliva testing as a reliable indicator of hormone levels. Her observations were later challenged,[10] but she influenced Lee who promoted the notion that 'estrogen dominance' was caused by progesterone deficiency.[2,11,12]

Lee and Wright are most frequently cited by BHRT prescribers as pioneers of bioidentical, or compounded, hormone therapy; Wright became known for his 'triple estrogen' recipe.[4,13]

Throughout the 1990s, the term used to describe compounded hormones from botanical sources was 'natural hormone therapy'. When the results of the Women's Health Initiative (WHI) trial were published,[14] women were cautioned against the use of hormone therapy, and the Food and Drug Administration (FDA)'s Guidance for Industry stated that in the absence of data on other formulations of estrogens, progestins and progesterones, 'risks should be assumed to be similar.'[15] Wright's 'bioidentical' phrasing was used by the BHRT prescribing community as a way to promote to patients presumed differences between conjugated equine estrogen and progestin—the hormones used in the WHI study—from BHRT formulations of estrogen and progesterone, which were promoted as safer than FDA-regulated preparations, despite no evidence for this claim in the peer-reviewed literature.[1,2,13,16] When celebrity author Suzanne Somers published a popular book,[17] she introduced the term 'bioidentical' into the popular press and patient population; it has thus become a poorly understood new adjective in the field.

Current issues with the 'bioidentical' nomenclature

Although FDA-approved formulations of estrogen and progesterone are available,[1,2,13] the term 'bioidentical' has become inappropriately synonymous with 'natural' or 'not synthetic' and should be redefined to correct patient misconceptions.[2] BHRT is often prescribed to individuals based on the analysis of a person's salivary hormone levels, however these tests are criticized for being unreliable because there is no correlation between symptoms and hormone levels.[1,2,18] For these reasons, dosing of FDA-regulated female hormone preparations is typically based on providing symptom relief. Clinical ethical problems could result when salivary tests persuade asymptomatic women into taking hormones they may not need, and symptomatic women into taking higher doses that could pose greater risks.[2]

There is a disconnect between what the peer-reviewed literature reports on BHRT and what patients may read about BHRT in popular books or on the Internet.[3,17,19–29] Although explanations of BHRT from these kind of sources are not representative of the entire field, or what is available online from more credible sources, such as The Endocrine Society, information about BHRT in the popular press is frequently based on statements made in popular books or on the Internet by physicians in private practice. For example, patients read on privately run physician websites that BHRT refers to 'bio-identical, molecularly identical, naturally derived hormones';[20] or 'plant-derived hormones, estradiol and micronized progesterone, made of concentrated soy and/or yam, that are bioidentical to the hormones naturally created by the human body';[21] and that it is 'superior to the patented pharmaceutical or synthetic HRT [because] it has the same molecular structure as the progesterone produced in the human body and the body recognizes it.'[19] The emphasis on 'natural' remains widespread, even though all bioidentical hormones are synthesized from precursor compounds. The physician-authored foreword to Somers' book states that 'bioidentical estrogen and progesterone are bioengineered from natural plant products that contain the same chemical structure as natural female sex hormones. They do not mimic female hormones but instead augment a woman's natural hormone production.'[17] This statement is physiologically untenable.

At this point in time, there is no published evidence in the peer-reviewed literature[1,2,18,30] that (1) compounded BHRT preparations are safer or more effective than FDA-approved formulations of HRT (the standard of care) for which dosing and duration of therapy is already highly individualized; (2) compounded BHRT preparations carry less risks than FDA-approved formulations and (3) saliva testing is a reliable measure on which to base hormonal dosing. Recent data actually suggest that as a result of stopping HRT, a significant reduction in breast cancers and heart disease occurred,[16] punctuating concern over the risks of BHRT. The key question this analysis seeks to address is whether BHRT is accurately represented to the patient population in terms of benefits, risks and standard of care, which fall under the ethical principles of respect for persons and beneficence. Since most patients first seek out information on hormone therapy through self-education,[25,31,32] what appears in the popular press, popular books and on popular websites run by physicians in private practice directly affects informed decision-making. Most patients only hear of BHRT through the popular press, which is why presentation of BHRT in this forum is particularly critical when looking at ethical issues.

BHRT: is it complimentary and alternative therapy?

Because there is ultimately a 'paucity of studies' in the peer-reviewed literature that have properly evaluated BHRT,[30] it meets the criteria for an unproven offering within the field of complimentary and alternative medicine (CAM) rather than a therapy of conventional medicine, meaning it is not standard of care practice. Despite this, much of the literature available to the patient community on BHRT does not openly present it as a CAM therapy, but as a state-of-the-art therapy offered by 'cutting edge, Western-trained physicians.'[17]

When patients seek out information about BHRT on the Internet, they may find some reputable sources of information that warn them about false claims, such as The Endocrine Society's position statement,[18] but they will also find several prominent BHRT websites maintained by physicians in private practice, who may appear to be credible as well.[19–21] Studies surveying Internet health-seeking behaviors support the hypothesis that most patients do not have the background to decipher credible sources from noncredible sources,[28,32–36] and when they are looking for solutions to menopausal discomfort, the sites making false claims have convincing arguments for laypersons.[27,28,31]

Representative websites of this nature are run by prescribers who are conventionally trained physicians who self-identify as pioneers or experts in the field of bioidentical hormones;[21] or state that they have clinical evidence to support the safety and efficacy of BHRT.[19] In one typical example, a BHRT prescriber's credentials (whose opening website slogan reads: '… no hidden agenda') are described as 'physician and patient advocate with 31 years of clinical experience.'[21] The website has a disclaimer that states it receives no sponsorship from pharmaceutical companies, and therefore has no 'agenda'. Despite this, the website contains a wealth of products for sale, including her own branded 'natural progesterone cream' and other 'hormone support' products. Although the prescriber's biography states that she is an 'internationally recognized physician [and] expert in conventional and integrative medicine,' a search for more substantive information revealed that the prescriber has no academic affiliations, no published work in peer-reviewed journals (based on a search of PubMed), and no specialized training in endocrinology, even though she claims expertise in hormones. Most patients seeking BHRT would conclude from such website wording that the prescriber is offering state-of-the-art care, prompting consultation.

Cirigliano[13] suggests a more ironic problem among those women who may understand and appreciate BHRT as a CAM option. Given that BHRT is still a product that contains estrogen and progesterone, is it really an alternative to HRT, since it is presumed to carry the same risks and same benefits, thereby hiding within the CAM classification when it does not belong there? Thus, Cirigliano suggests that even when clearly presented as a CAM product, BHRT is really a drug, as defined by the FDA, as it is 'intended for treatment, mitigation, and/or prevention of disease and/or to affect the structure or any function of the body.' If BHRT meets the FDA definition of a drug, Cirigliano[13] suggests the FDA should have regulatory authority over BHRT.

The reality is that BHRT, even though a CAM therapy, meets the definition of 'experimental' or innovative therapy as defined by ethicists.[37] When BHRT is sold by the practitioner who prescribes it, this constitutes a serious conflict of interest and violates professional ethical conduct. In addition, there are established ethical dilemmas present in the field of CAM, such as failure to produce CAM study designs that meet institutional review board (IRB) scrutiny and approval; suitably and consistently trained practitioners; informed consent in the patient population and just allocation of CAM therapies since they are expensive and not covered by health insurance plans (even in Canada or the United Kingdom).[38] Patient/consumers with greater disposable income may be unduly burdened with coercive or misrepresented statements about BHRT.

What patients are reading about BHRT: perceptions and reality

Patients who self-educate about BHRT frequently start with nontechnical books describing anecdotal examples of BHRT use that validate their experiences of estrogen loss. Somers' book is one example of a text that does this; under 'Advice' it remained on the *New York Times* Bestseller's list fall 2006 throughout much of the spring of 2007, receiving wide coverage by CNN;[39] it continues to be one of the best-selling books on Amazon under 'Menopause' (according to October, 2007 Amazon sales statistics, posted on www.amazon.com). What is most problematic is that this book makes unsubstantiated claims that BHRT has fewer risks than conventional HRT, and prevents breast cancer and heart disease. Many patients do not question these statements, even though they are wary of increased risks of breast cancer and cardiovascular disease with conventional HRT. Regardless of formulations, hormone therapies using estrogen and progesterone are presumed to carry similar risks.[1,2,13,16,18,40]

'Big pharma' conspiracies

Patients read in popular books and on the Internet that information about the benefits of BHRT is being kept from the public by pharmaceutical companies to protect their market.[19,21,41] The disturbing history surrounding HRT marketing and unpublicized safety concerns[16,42] are misused by some BHRT advocates as evidence to back up this conspiracy theory, even though such statements are made on commercial websites that sell BHRT-related products or books. While some BHRT promoters claim that conventional HRT had a history of being prescribed without concern for safety issues; in fact, it is now apparent that it is BHRT promoters who are guilty of this practice.

To excuse the absence of evidence for hyperbolic claims about BHRT, some advocates assert that because bioidentical hormones cannot be patented,

pharmaceutical companies have no incentive to underwrite such research. The fact that investigator expertise is absent in most CAM practices,[38] and that the National Institutes of Health (NIH) research portfolio is severely underfunded,[43] is much more central to the problem. There are a few BHRT prescribers/investigators who are doing IRB-approved research, such as Leonetti,[44–46] but many such studies are not considered reliable by rigorous peers.[1,2,13] Moskowitz[47] references several studies using bioidentical hormones in an attempt to demonstrate that BHRT has a good safety profile, but the data presented only serve to demonstrate similar risks to conventional HRT.

The National Center for Complementary and Alternative Medicine (http://nccam.nih.gov) is the center that would typically fund research that some BHRT promoters claim is being prevented by the pharmaceutical lobby. This agency has the authority to launch studies of BHRT through experienced investigators. This agency also reviews research grant proposals based on scientific merit. Criteria for successfully funded projects include novel research ideas, investigator expertise, ethical study design and sound methodology. Since BHRT prescribers are mostly physicians in private practice or in the CAM community, few have the training or academic support to craft an NIH-styled research proposal that would achieve a fundable score. Investigators with no publications in recognized peer-reviewed literature, and no academic affiliations, would also have difficulty being funded by the NIH or private foundations using the NIH model for reviewing grant proposals.

How BHRT is framed in other endocrine areas

Patient literature regarding female reproductive BHRT is contradictory when one explores how BHRT is framed within other areas of endocrinology. In the diabetes community, synthesized products are embraced by patients; 'natural' animal insulins from beef and pork have long been abandoned in favor of 'human' insulins manufactured using recombinant DNA technology. Modifications of insulin to enhance pharmacokinetic attributes are likewise seen as a benefit.

Thyroid patients are misinformed that dessicated porcine thyroid hormone is superior to levothyroxine (which is 'bioidentical' thyroid hormone),[48] and that it is being denied to them by doctors who are persuaded by pharmaceutical companies. Self-described patient advocates claim that bioidentical thyroid hormone does not 'convert' properly in the body because it is 'synthetic' arguing that porcine thyroid hormone is more suitable for humans because it is 'natural'.[49]

In stark contrast, BHRT patient advocates claim that conjugated equine estrogen does not convert properly in the body because it is 'synthetic', arguing that compounded estrogen and progesterone synthesized from plants are more suitable for humans because it is 'natural'. Of note, one thyroid patient website that strongly advocates porcine thyroid hormone, also urges patients to reject conjugated equine estrogen.[50] Similarly, Somers,[17] who touts BHRT for ovarian hormone replacement, advises that porcine thyroid hormone is superior to bioidentical thyroid hormone (levothyroxine) because it is 'natural.'

Patients and lay authors who lack the necessary scientific literacy or appropriate training in critical thinking may not have the capacity to decipher pseudoscientific rhetoric from valid science. Given the confusing patient literature available on BHRT, also observed by other authors,[1,2,13] genuine informed consent regarding BHRT is unachievable.

Natural versus 'synthesized' hormones

The terminology that appears to attract patients to all CAM therapies, including BHRT, is the word 'natural'—which may be invoked to describe a completely synthesized product (for example, plant-derived BHRT), or a completely impure, untested and potentially dangerous product. A common claim that patients read is that 'synthetic' hormones have more side effects—solely because they are synthetic.[3,17,19–21,29,51] One physician website indicates that it is actually toxic: 'Commonly prescribed synthetic hormones, such as Premarin or Prempro, are a potential poison to [menopausal women] … Bio-identical progesterone has the same molecular structure as the progesterone produced in the human body and the body recognizes it. Progestin is a synthetic drug whose molecular structure is different, thus triggering dangerous side effects in the body.'[19] The fact that 'synthetic' HRT is derived from an animal, but 'natural' HRT is derived from plants, defies logic, evidenced from this statement: ''Bioidentical' means biologically identical to human hormones—exact replicas of we make in our own bodies. Made from soy, wild yam, and other plant extracts, bioidentical hormones are synthesized in a lab to exactly replicate human hormones. Bioidentical hormones are not drugs, however. They are completely different from synthetic hormones, which are made from the urine of pregnant mares …'[17]

Patients do not seem to be concerned that 'natural' products cost more, are usually not covered by drug plans and that prescribers of such products in private practice charge much more for a consultation than a conventional practitioner who is covered by insurance plans.[38,52,53] Even in countries with universal health care, CAM is private medicine, and patients pay large sums of money out of pocket for services and products.[38]

Is BHRT an 'innovative therapy'?

Within the framework of research ethics, there are distinctions between innovative therapy, standard of care therapy and research. The lines between experimental and innovative therapy frequently blur, and the field of reproductive medicine is rich with examples of innovative therapy that has led to harms.[54] Any notable departure from the standard of care is defined as experimental, or innovative therapy. When the innovation is designed to provide therapy for one, particular individual, it indeed meets the criteria for innovative therapy. Research, on the other hand, is designed to test a hypothesis, permit conclusions to be drawn and contribute to generalizable knowledge.[37] Thus, once data collection and publishing of results is involved, the activity is research and not simply an 'innovative therapy'. When clinicians report on their innovations on their websites or in books, it is unclear whether this can be called 'research' but it is clear that radically new procedures should be made the object of formal research at an early stage to determine safety and efficacy.[55] Furthermore, when innovative procedures are aimed at the socially and medically vulnerable population of peri- and postmenopausal women, the clinical innovator (the BHRT prescriber) must ensure that the risks of the innovative therapy are reasonable and that the anticipated benefit is represented truthfully. Thus, if there is no published evidence that there is any benefit of BHRT over the standard therapy, this raises questions about whether the innovative therapy is being honestly represented to patients, and whether there are ethical problems in offering it at all. Based on the patient literature available on BHRT, the potential risks of BHRT are not being disclosed, and patients are not aware that they are receiving a therapy that is not standard of care.

Unregulated research involving BHRT

A glaring example of unregulated and unethical research in BHRT is The Wiley Protocol, which became more widely known to the public through Somers' promotion of it as legitimate research.[39,56] The Wiley Protocol has involved over 1000 participants in the administration of 'a trademarked, patent-pending delivery system consisting of bioidentical estradiol and progesterone in a topical cream preparation dosed to mimic the natural hormones produced by [a 20-year old woman].'[41] This protocol emphasizes a 'rhythmic' dosing schedule using potentially unsafe high dosages of hormones.[39,57,58] Somers' book misrepresents TS Wiley, its lay investigator, as a respected and published scientist. Somers' book also serves as a recruitment tool for unwitting human subjects. This is a multicenter Phase II trial (with no record of Phase I testing) involving 129 study sites in 29 US states, and 2 study sites in British Columbia, Canada.[59,60] Since data is being collected and presented on women enrolled in this trial,[59–62] but has not been IRB approved (interviews: TS Wiley, and D Turner, 13 March 2007; J Taguchi, 15 March 2007), or monitored by an investigator with experience in scientific methodology or clinical research,[41] it does not meet criteria for regulated or ethical research.[37,63] There are no formal exclusion or inclusion criteria for patient enrollment (interview: J Taguchi, 15 March 2007), and the study population spans women aged 19 through 90, who may not understand that they are enrolled in unethical research.[64] Serious safety concerns about this protocol have been raised.[61,65] Co-investigators appear to be prescribers of this protocol who widely vary in training, ranging from physicians to massage therapists; and pharmacists who are contractually obligated to Wiley as a source of the compounded pharmaceuticals sold to participants of the protocol.[66] The study is funded by participants, who are paying for the protocol with their prescriptions. Typically, study agents should not be sold.[67]

This may be the tip of the iceberg. Several other BHRT prescribers make reference to having conducted 'clinical trials' in BHRT. Even if they are collecting data and publishing their results involving their trial experiences to contribute to generalizable knowledge, they are still doing research that may not have gone through IRB approval. Despite this, IRB-approved studies based on (1) unethically collected preliminary data or (2) new data collected from enrolled participants in an unethical trial, would still be ethically unsound. Unclear FDA governance of botanical sources of hormones under The Dietary Supplement Health and Education Act of 1994, and legal recognition for compounding pharmacies under The FDA Modernization Act of 1997, creates confusion regarding the ethical use of compounded pharmaceutical agents in research.

Professional ethics and BHRT

Professional ethics issues related to conflict of interest are frequently entangled with some prescribers of BHRT, who may be marketing their own line of BHRT and related supplements. The line of professional ethics is crossed when a practitioner promotes and prescribes his or her own innovative therapy as a 'product' when it is not standard of care. Deeper problems surround the crossing of practice boundaries in those who prescribe BHRT. Several of the CAM providers who prescribe BHRT self-identify as experts in BHRT and women's health, claiming they are well known internationally. These are misleading statements when the

expertise is not recognized by academic peers, but only by name recognition in the popular press. For example, when prescribers are inviting consultation in a particular specialty, there are professional ethical duties to have 'standards of awareness and proficiency'[68] and a duty to be competent and licensed when charging fees to patients. In the Wiley case, it appears consultation fees may be charged by a layperson with no training.[41] In another case, a physician prescribes therapies based on telephone consults.[2] It seems possible that some BHRT practitioners are exploiting the confusion amidst the WHI guidelines to make a profit and market BHRT products and related services.

Discussion

One of the central ethical problems with BHRT surrounds the principle of respect for persons and the doctrine of informed consent. The doctrine of informed consent demands that patients have the genuine capacity to understand and appreciate the potential risks and benefits of their therapies, and other available options.[69] Barriers to informed consent include literacy and numeracy, language and mental health problems that may include depression and anxiety—problems that are not infrequent in the peri- and postmenopausal community. In the context of health information, medical literacy and scientific literacy are particularly problematic as few patients can claim it. A substantial number of women seek out BHRT to restore sexual well-being and functioning, in particular, who may be psychologically more vulnerable. This creates a particularly vulnerable population that may require special protections.[54,70] Restoration of libido is a central promise made by several BHRT prescribers who self-promote on the Internet or in popular books. Informed consent further demands full disclosure of all risks and benefits by the practitioner, while voluntariness must be present.[71–73] When statements about BHRT are inaccurate or misleading, informed consent cannot take place. Moreover, when statements are made about BHRT that overpromise results, this is considered coercion. Finally, it remains problematic that the majority of BHRT patients likely do not understand and appreciate the differences between standard of care and innovative therapies; in the case of research, disturbing issues remain regarding whether patients understand they are human subjects.

The principle of beneficence demands that risks and benefits of BHRT be carefully weighed, but when safety claims about BHRT are made in the absence of any evidence, this is a clear breach of beneficence. The principle of nonmaleficence provides a duty for practitioners to specifically do no harm, as well as a duty to warn. The principle of justice refers to the equal distribution of benefits and harms within a population of patients who may stand to benefit. BHRT is primarily a therapy offered to patients who pay out of pocket for it, and who are economically advantaged. As such, it remains an unequal alternative, and any data collected would not be representative of the overall menopausal community.

Conclusions

Disturbing clinical ethics, professional ethics and research ethics problems loom as BHRT continues to be prescribed without any regulation or oversight. Although misleading advertising can apply to other health products, particularly around diet and nutrition, hormone therapy is not a 'supplement' but a necessary therapy that burdens all women in menopause. Menopausal women are thus vulnerable patients seeking relief from debilitating symptoms and interested in preventing diseases associated with estrogen loss. They are unduly burdened, and even coerced, with misinformation and inaccurate patient literature that is meant to guide them in decision-making. This creates special obligations for health care providers who treat menopausal patients. Special education sessions about the risks and benefits of various treatments, along with time for correcting misinformation, may become the new standard of care for in-office visits at the 'chairside' until further oversight and regulation of BHRT occurs.

Conflict of interest
None.

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