

Point/Counterpoint: The Case Against Bioidentical Hormones

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“There is always an easy solution to every human problem—neat, plausible, and wrong.”

H.L. Mencken

The most essential canon of clinical practice can be formulated as follows: *In the practice of medicine physicians have to strictly follow: scientific principles, legal rules, and ethical guidelines.* However, those guiding directives are not static, but evolve with time. This evolution recently became more rapid than ever. U.S. health care law has evolved over the last 20 years into one of the most regulated and complicated areas of the legal system.¹ Medical ethics has undergone many unprecedented changes as well.^{2,3} The pace of scientific advancement is astonishing. The theories that were considered to be “conclusively valid” just a few years ago are being proven false today. Hormonal replacement therapy (HRT) in women is a good example.⁴

Recently, term “bioidentical” sex hormones started to gain visibility in the media and in the medical community. There is a wide spectrum of opinions about the subject in the popular press, ranging from enthusiastic endorsements^{5,6} to very harsh criticism.⁷ Several major medical societies have recently published statements reflecting their opinions of “bioidentical hormone replacement therapy.”⁸⁻¹⁴ Moreover, some governmental agencies also became interested in this subject.¹⁵⁻¹⁷ There is no question that the concept of bioidentical hormones is the subject of a heated controversy.

Practicing clinicians should remain objective in the face of controversy. Today, this task is not easy. For numerous reasons the medical profession has been losing its traditional power, including the essential power to protect the best interest of patients. Sociologists have demonstrated that even while physicians were increasing their power to control diseases, the medical profession was losing both its autonomy and its time-honored clout.^{18,19}

Currently, inept bureaucrats, unscrupulous trial lawyers, and profit-oriented third-party payers control the medical field. Under such circumstances the burden imposed on ethical physicians is enormous. Contrary to conventional wisdom, there are medical situations in which there is no single right answer. Physicians should not deny beneficial treatment to patients. But neither should they enthusiastically promote scientifically unproven therapies. That said, physicians should remember that science is not a static collection of unquestionable dogmas. On the contrary, science proceeds when earlier hypotheses are refuted by new data. This was elegantly summarized by J.H. Baron:

Science involves the conception and construction of refutable hypotheses, and their testing by repeatable experiments, followed by publication of the results. Thus, science is uncertain, tentative, probabilistic and universal. Every scientific statement remains tentative forever.²⁰

The classic statement by C. Glymour and D. Stalker is still valid today: The practice of scientific medicine is similar to consultant engineering. The subjects are people rather than a construction, but similarly to engineers, physicians must apply in their work both explicit scientific principles and a great deal of tacit knowledge.²¹

Pitfalls in Endocrine Terminology

To understand the bioidentical hormone controversy, one has to be aware of serious limitations of current endocrine terminology. K. Becker used the colorful term “tyranny of hormone terminology” to denote that hormonal nomenclature is often confounding, and even misleading.²² Those semantic problems cause substantial confusion among the general public. For simplicity’s sake, various exogenous substances that can act as agonists of known hormonal receptors are being called “hormones.” Such oversimplification contributes greatly to the public’s inability to differentiate between the terms “hormones” and “drugs.”

The quandary of terminology does not, however, change the following objective facts: A drug is a substance intended for use in the diagnosis, treatment, or prevention of disease.²³ In such a context, both xenobiotics (chemicals not produced in the organisms) and various endogenous substances, including hormones, may be used as drugs. Physiological concentration of a hormone in the healthy organism exerts its proper biological function. However, chronic administration of the supra-physiological amounts of a hormone will ultimately lead to pathology. Xenobiotics are not universally noxious, and endogenous hormones are not universally salubrious. Even the hormones produced by the body itself can be very toxic under certain circumstances. Hyperandrogenism and hyperthyroidism are classic examples of harmful actions of endogenously produced hormones. Clearly, hormonal preparations should be treated as potentially dangerous substances. In fact, testosterone is classified as a Schedule III drug by the Controlled Substance Act—and rightly so.²⁴

Endocrine Therapy and the Molecular Structure of Hormones

In clinical practice hormones are used in replacement or suppression therapy,²⁵ as well as in the performance of diagnostic evocative or suppressive tests.²² Underproduction of the hormone due to malfunction of the endocrine gland can be remedied by hormone replacement. Theoretically, the goal of such therapy is a full restoration of physiological hormone secretory patterns. In practice only the approximation of the physiological state is usually attainable. Yet, such approximation is usually therapeutically satisfactory and results in an acceptable outcome.

Hormones can be defined as chemical signals secreted into the bloodstream that act on distant tissues. Hormonal signaling represents a special case of the more general process of signaling between

cells (signal transduction).²⁵ Classically, signal transduction involves the binding of extracellular signaling molecules (or ligands) to cell surfaces or nuclear receptors that triggers events inside the cell.

As stated above, the aim of HRT is to closely mimic physiological processes. Therefore, it is obvious that generally it should employ hormonal ligands that are identical to those occurring in nature. There are, however, exceptions to this rule. Modification of the hormone's molecular structure may create a drug that is more useful in therapy than the natural substance. Insulin lispro is a classic example. Novel formulations of receptor-specific hormone ligands are being developed (e.g., estrogen agonists/antagonists, somatostatin receptor subtype ligands), resulting in more selective therapeutic targeting.²⁵

Endocrine Changes with Aging

“*Mors certa, hora incerta*” (death certain, its hour uncertain) is the Latin proverb that reminds us of the very upsetting but unavoidable fact that we have to age and ultimately die. It would be very alluring to be able to explain the aging process by some coherent underlying mechanism that could be stopped. For a long time there have been many hypotheses attempting to attribute the changes of aging to slow hormonal changes. It has been postulated that such changes may be reversed by appropriately selected “hormonal supplementation.” This fruitless search for a hormonal “fountain of youth” continues today. Various hormonal compounds including testosterone are touted as “rejuvenating tonics.”

Unfortunately, the complexity of the aging process precludes simplistic formulations that equate aging with hormone deficiency.²⁶ Biological aging is characterized by a progressive and predictable loss of coordinated cell and tissue function, and as a result the organism becomes less fit to reproduce and survive. This steady process manifests across multiple organs and systems. Deterioration of function is heterogeneous among systems and individuals. The basic mechanism underlying aging is unknown, and so far does not appear to be endocrine related. Hormones are biologically powerful molecules that may exert therapeutic benefits and effectively replace pathologic deficits. However, their excessive use will by definition result in hormonal excess and associated pathologies. Therefore, hormones should not be prescribed without clear-cut indications and appropriate monitoring.

Steroid Hormones and General Health

Steroid hormones, especially testosterone and estradiol, affect numerous organ systems in addition to regulating reproductive functions. It is therefore not surprising that clinicians directed their interests toward very complex physiology and pathophysiology of sex steroid hormones. The use of sex hormones in medical practice has steadily increased over the last three decades. Female HRT was enthusiastically promoted, and in 2000 Premarin (the commercial estrogenic preparation containing conjugated equine estrogens) became the second most frequently prescribed drug in the United States.²⁷ This initial enthusiasm decreased after the Women's Health Initiative (WHI) and Heart and Estrogen/Progestin Replacement Study (HERS).⁴ Paradoxically, those studies further increased public interest in the use of sex steroid hormones—mainly due to pervasive but not always objective portrayal of the results of those investigations in the mass media.

Public Attitude Towards Endocrine Disorders, Health, and Science

There is a growing chasm between public expectations and the reality of what even the most advanced medical science can now deliver. Despite increased reliance on technology, much of the general public has very little understanding of basic tenets of science—the phenomenon described as scientific illiteracy and innumeracy.²⁰ Consequently, there is an unfortunate tendency among the general public to automatically attribute an endocrine basis to various nonspecific symptoms, even when the objective evidence is lacking. For example, hypogonadism is automatically evoked to explain tiredness, weight gain, loss of sex drive, or mood swings. Some of these symptoms may be in fact caused or aggravated by endocrinopathies. However, diagnosis in endocrinology should rest not on the nature of the symptoms, but on the external validation by rigorous clinical and laboratory evaluation.²⁸ To avoid unnecessary disappointments, physicians practicing scientific medicine should educate their patients not only about what they can expect from scientific medicine, but also about what they should not expect. The physician's duty is not to please or satisfy every patient's desire, but to treat the disease and do no harm in the process.

The Conundrum of Nonspecific Somatic Symptoms

According to Greenberg, in about 50% of clinical encounters physicians are unable to identify any obvious organic disease responsible for patients' complaints.²⁹ Physicians have an ethical duty to diligently establish the true reason for which a patient seeks medical care, rather than assume that all patients must have an underlying serious organic disease. Possible somatic disorders have to be ruled out by all available means. However, the astute clinician should remember that there are three possible reasons for subjective symptoms perceived by the patient:

- **Organic causes.** There is a distinct organic endocrine (or nonendocrine) pathological process that is severe enough to influence a patient's health. Such a process can be validated by various objective testing methods.
- **Somatization disorder.** Patients tend to convert their psychological problems into symptoms perceived as somatic. In this frequent scenario, patients genuinely believe they are gravely ill, despite all the evidence to contrary.
- **Factitious disorder and malingering.** Patients present with symptoms, and even signs they produce themselves, to obtain external or internal gain. A proper diagnostic method proceeds from the most likely (or common) diagnoses to the least likely, and does not skip over factitious disorders.³⁰

Allopathic medicine's traditional remedies will only work in the first scenario. In the other two, a psychiatrist and/or psychotherapist may be needed.

Reproductive Endocrinopathies and Psychopathology

It is not uncommon to encounter patients who believe very strongly that “sex hormone imbalance” is responsible for a wide array of their psychological problems. Such patients come to see endocrinology consultants with certain preconceived notions. They believe that a properly chosen “hormonal pill” is all they need to solve their existential problems. They expect that unhappiness, anxiety, uncontrollable anger, or mysterious “brain fog” will be

lifted with the properly “fine-tuned” hormonal treatment. Many of these patients do not even verbalize those unrealistic expectations since they consider them to be obvious and true. They were told to anticipate this treatment outcome by friends, and they read about it on the Internet.

Unfortunately, there is no scientific evidence to support the popular belief that mild-to-moderate endocrine abnormality can result in profound psychopathology.³¹ Only extremely severe and uncontrolled endocrine conditions such as thyroid storm, or severe hyperadrenalism, can cause acute mental status changes.³² Such situations, however, are rare in the 21st century. The most common cause of depressed mood is depression (a psychiatric disorder) and not a mysterious endocrine disease. Sadly, psychiatry referrals still have a stigma, and some patients insist on being referred to an endocrinologist instead. It is beneficial to correct existing hormonal problems in a patient affected by psychiatric problems, but hormonal treatment will not replace psychotherapy and treatment with psychotropic medications, if needed, administered by a competent mental health professional. Psychiatry is an extremely complex clinical science that relies on diagnostic and therapeutic paradigms that are distinctly different from those of somatic medicine. Endocrinologists who do not consider that they are qualified to serve as surrogate psychiatrists should resist the temptation to offer “a simple solution” by prescribing currently fashionable antidepressants.

Bioidentical Hormones Defined

Despite its outwardly scientific appearance, the term “bioidentical hormones” is quite vague, and is used in various contexts. Most commonly, it denotes plant-derived hormones claimed to be “identical in structure” to those produced by the human body, and therefore supposed to be “safer and more effective” than commercial FDA-approved preparations. Preparations of bioidentical hormones are compounded by pharmacists.^{8,13} The “compounding process” refers to creation of a drug by mixing various components by a qualified pharmacist. The need for compounding dramatically decreased after the mass pharmaceutical manufacturing process was developed. However, in certain communities the concept of compounding appears to be in revival. Disturbingly, in some instances treatment with compounded preparations is initiated and directed by a compounding pharmacist, with minimal (if any) involvement of a physician.

The list of hormones used in these preparations includes: estradiol, estrone, estriol, progesterone, testosterone, dehydroepiandrosterone (DHEA), and others. Some of those hormones, such as testosterone, estradiol, and progesterone, have well established roles in human physiology. The biological function and clinical utility of some other hormones (e.g. estriol and DHEA) is, however, much less clear.^{11,33} Unlike in the past, hormones that are indeed identical to those produced in the human body, including estrogen and progesterone, are now commercially manufactured. Those commercial preparations are under the purview of the FDA and do not need to be compounded.

Clinical Concerns about Bioidentical Hormones

As the primary concern of any clinician is patient safety, the objective and unbiased examination of risks and benefits associated with bioidentical HRT is of utmost importance.

Exaggerated Claims about Efficacy and Safety

The public is being persuaded that treatment with bioidentical hormones has to be safer, more effective, and free of side effects, since those preparations are “natural.” There are statements in popular publications on the Internet to the effect that certain preparations can prevent and/or treat Alzheimer’s disease, stroke, and even various forms of cancer. These assertions have not been peer-reviewed or subjected to any type of formal scientific scrutiny. A systematic review of the current scientific literature does not appear to support these notions.^{5,11} Until well-designed scientific studies are available, the existence of meaningful differences between bioidentical and conventional hormones remains to be established.

Concerns regarding Bi-Est and Tri-Est

The name Bi-Est or biestrogen is commonly used to describe a preparation consisting of 20% estradiol and 80% estriol on a milligram per milligram basis. Tri-Est or triestrogen contains a ratio of 10% estradiol, 10% estrone, and 80% estriol. Some compounding pharmacies claim that these mixtures are designed to mimic natural estrogenic activity occurring in young females with intact ovaries. However, hormonal ratios found in Bi-Est and Tri-Est are not based on each agent’s estrogenic potency or individual bioavailability when given orally, but simply on the milligram quantity of the different agents added together.¹⁴

Estriol is the peripheral metabolite of estrone and estradiol, not a secretory product of the ovary.³⁴ Estriol is produced in significant amounts during pregnancy by the placenta. It can also be produced by some tumors. Therefore, concentrations of this hormone are very low in healthy non-pregnant females. In non-pregnant females, the formation of estriol is considered to be an example of metabolic detoxification, i.e. conversion of biologically active material to less active form.³⁴ Each woman uniquely produces estriol based on individual tissue estrogen metabolism. The enthusiasm about the potential role of estriol in menopausal HRT may be traced back to reports that this estrogen limited the growth of breast tumors in the rat model.³⁵ However, subsequent research did not confirm those initial observations.^{14,36}

Estrone is minimally produced by ovarian secretion. Most of it is produced by peripheral conversion from adrenal and ovarian androstenedione, mainly in adipose tissue.³⁷ Moreover, estrone, as estrone sulfate, a commercially available product, can be used in therapy without a need for compounding.

In summary, there is no scientific evidence that specific combinations of oral estrogens provide improved safety or efficacy compared to FDA-approved pharmaceutical products in treatment of menopausal women. Additional clinical and basic research of this subject is needed.

Variable Potency

In some instances patients have received compounded preparations containing much larger or much smaller amounts of an active ingredient than the label indicated.³⁸ Limited FDA surveys revealed disturbing inconsistencies in the strength and purity of compounded preparations.³⁹ Inappropriately high levels of hormonal components in a compounded formulation can cause serious patient injury.^{38,40} This is especially true for compounded injectable depot-testosterone preparations. On the other hand, inappropriately low hormonal content in compounded formulations can mean that the patient, unbeknownst to the physician,

receives suboptimal doses of a prescribed medication. In addition, the stability of compounded medication is not known, as each drug is individually formulated. Expiration dates given by compounding pharmacists are often based on educated guesses.

Impurity and Contamination

The possibility of cross-contamination of compounded preparations with various medications is a valid concern. This is particularly likely to occur in smaller pharmacies, where the same compounding equipment is used for preparation of various drugs.^{38,40,41} In addition, assuring the sterility of compounded formulations may be difficult. Most compounded medications are not clinically tested to determine their sterility. Professional Compounding Centers of America and similar organizations have protocols advising stringent sterilization procedures for injectable preparations. However, it is unknown how strictly these voluntary protocols are followed and with what success. Certain compounding pharmacies prepare purportedly “aseptic” preparations without the use of an autoclave.³⁸

Individualized Dosing and Salivary Hormone Testing

Salivary hormone-level testing is recommended by many proponents of bioidentical hormones as a way of providing patients with “individualized” therapy. Such tests are available to consumers over the Internet. Some websites include elaborate questionnaires supposedly designed to establish the type of saliva testing needed.⁴² Results of these tests are subsequently used to determine the type and dosage of compounded formulations. Only a few types of salivary hormone testing methods are FDA approved.⁴³ In fact, the vast majority of salivary hormone tests results contain a disclaimer that those tests are not FDA approved and should be used only for research purposes. Yet such tests are still utilized to support clinical decisions by some promoters of bioidentical hormones.

Endorsers of salivary assays quote their positive empirical experience as well as some recent research studies in support of this methodology.⁴⁴⁻⁴⁶ There are many troubling aspects of such an approach. First, when talking about the empirical experience, those practitioners simply report anecdotal information such as positive testimonies from their patients, or their own subjective impressions. Therefore, they base their conclusions on nonscientific information, which is neither randomized, nor placebo controlled, nor peer reviewed.⁴⁷ Second, the limited research, although interesting, does not prove that salivary testing can be used as reliable ancillary tests for *clinical* purposes. AACE Protocol for Standardized Production of Clinical Practice Guidelines points out that a physician must frequently act on the basis of incomplete information.⁴⁸ In order to help the physician sort through such information, several strength-of-evidence scales have been proposed.^{49,50} The evidence usually quoted by salivary test promoters simply does not pass the muster of level 1 or even level 2 evidence.⁴⁸ The only exception here is cortisol measurement.^{44,51} In contrast to cortisol salivary level, large intra-subject variability has been shown in salivary sex hormone concentrations.^{8,51} Salivary sex hormone levels fluctuated depending on numerous variables such as diet, hydration status, and circadian rhythm. These conditions are difficult to standardize.⁸ Finally, standard blood tests for sex steroids are well established, with the exception of free testosterone measurement.⁵² Free testosterone direct analog methods are unreliable for free testosterone. Dialysis methods and calculation methods that have accurate and sensitive

assays for blood testosterone, such as mass spectroscopy, are reliable.⁵³⁻⁵⁵ Also, venipuncture is a straightforward and minimally invasive procedure. Hence, there is little need to resort to salivary sex hormone testing in the medical practice setting.

Individualized Dosing

Sex hormones do not belong to a pharmacological class of drugs with clear indications for individualized dosing. From the perspective of clinical pharmacology, individualized dosing is indicated for drugs characterized by a narrow therapeutic window. Drugs with nonlinear pharmacokinetics (those with renal elimination) are good examples. Drugs that are not metabolized during the first pass through the liver, and those with clearly defined (in large population pharmacokinetic studies) therapeutic and toxic concentrations meet the requirements for individualized dosing as well. In contrast, sex hormones do not meet these criteria.⁸

Cost Effectiveness

The direct costs of compounded drugs and dubious salivary tests are usually greater than those of traditional preparations and tests.^{5,44} The budget of an average American family is already tight. Many women influenced by the mixture of unsubstantiated promises are making choices they probably would not make if presented with scientifically based information.

Conclusions

All the information presented here should be carefully explained to patients who request bioidentical hormones. Their misconceptions about bioidentical hormones should be tactfully and thoroughly discussed. A decision to prescribe any type of menopausal hormone therapy should be based on careful clinical evaluation of risks and benefits of such therapy in a specific patient.¹²

Additional objective research is needed to help protect the health and safety of the public. This should be approached with utmost diligence and objectivity. Both positive and negative biases have no place in endeavors addressing public safety. Issues of public safety should be always balanced with the individual freedom to make *informed* personal choices.¹⁶ Obviously, such informed personal decisions should be based on objective information that is not tainted by any commercial or doctrinal bias.

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