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Bioidentical, Natural, Semisynthetic, and Synthetic Hormone Replacement Therapy and Bioidentical Hormone Replacement Therapy

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Hormone replacement therapy (HRT) is a topic that has gained national and international prominence in recent years. More specifically, bioidentical hormone replacement therapy (BHRT) has been in the press and even the topic of senate hearings.¹ It has caused major pharmaceutical companies to expend millions of dollars addressing the topic and influencing political decision-making. It has resulted in letters to the U.S. Food and Drug Administration and a flood of letters from patients concerning their medications. Why has this erupted in recent years?

During the mid-1900s, there were a number of commercial products on the market containing bioidentical hormones (e.g., estradiol, estriol, estrone, progesterone, testosterone). All these hormones have had, or currently have, official monographs in the *United States Pharmacopeia (USP)*.

The conjugated estrogens product (Premarin) was approved in 1942. With the massive promotional campaign over the years, the non-human or non-bioidentical hormones assumed a major share in the marketplace for HRT patients. Even though the bioidentical hormones were still available, they could not compete with the highly marketed, patented, non-human hormones. Although the complete composition of Premarin and its active components remains undisclosed or unknown, Wyeth reports that it contains a mixture of 10 estrogens. Premarin's complex composition of conjugated equine estrogens has enabled Wyeth an extraordinary marketing exclusivity; there cannot be a generic product made if the actual composition of the brand product is undisclosed or not known. Additional hormones were brought to the market through patent protection mechanisms and such was the status during the 1970s and 1980s.

For those that are interested, the history of Premarin is entangled with a fascinating story of human intrigue involving ingenuity, influence, controversy, animal rights, competition, money, protection of stockholders, government regulatory power, patient rights, emotions, greed, power, personal and professional freedom, and, perhaps even ultimately, constitutional issues.²

Bioidentical human insulin is now used; previously insulin was extracted from pigs and cows and used in humans. **Bioidentical levothyroxine and triiodothyronine** (previously extracted thyroid from pigs) is now used; other hormones are considered as likely candidates to move from the use of animal-products to human-identical or bioidentical products. **Bioidentical estradiol, estriol, estrone, progesterone, and testosterone** have been on the market for years but to some degree were replaced by non-identical hormones a number of years ago. Today, many patients and physicians are requesting that bioidentical human hormones be compounded in dosage forms that are not commercially available.

Other bioidentical drugs that are used include water, electrolytes (e.g., sodium, potassium), dextrose, etc. Simplistically, we are simply replacing what the body has lost, even in BHRT (see Table 1).

TABLE 1. Bioidentical Drug Products Currently Used in Therapy.

- | | |
|--------------------|---|
| • Dextrose/Glucose | • Minerals (e.g., Ca, Na, K) |
| • Estradiol | • Progesterone |
| • Estriol | • Testosterone |
| • Estrone | • Triiodothyronine |
| • Insulin | • Vitamins (e.g., A, B complex, C, D, E, K) |
| • Levothyroxine | |

The word “bioidentical” is a contraction of the words “bios,” meaning “life,” and “identical,” meaning “the same as.” Therefore, “bioidentical” means “the same as life” or identical to what is in the living body. This is in contrast to those substances that are not the same as those that naturally occur in the human body, such as synthetic and semisynthetic conjugated hormones and others (see Table 2).

Definitions Therapies

BHRT is a treatment composed of bioidentical hormones with a structure identical to that of endogenous human hormones.

Estrogen replacement therapy (ERT) refers to the replacement of estrogen in patients.

Human hormone replacement therapy (HHRT) may be a better phrase than BHRT because health professionals refer to “human insulin” and “human thyroid”; it seems appropriate to use “human hormones” to describe the hormones used in HHRT, and it also may be less confusing than “bioidentical” or “natural.”¹

HRT is used for the treatment of postmenopausal symptoms such as hot flashes and vaginal dryness. HRT usually consists of either estrogen alone or estrogen with a progestin. This therapy also includes conjugated estrogens and progestins that do not occur naturally in the body but may have some similar effects. However, they may also have additional unintended side effects. HRT also refers to treatment of postandropausal symptoms such as decreased libido and sexual dysfunction; HRT for men usually consists of testosterone or dehydroepiandrosterone (DHEA) replacement.

Natural hormone replacement therapy (NHRT) is often considered synonymous with BHRT. It is widely used in the popular press but is frowned upon by health professionals because of possible confusion created by the use of the word “natural.” The term “natural” can refer to the source of the hormone as well as to the actual hormone that is bioidentical or endogenous.

Testosterone replacement therapy (TRT) refers to the replacement of testosterone. As men undergo andropause, a slow decline in the level of testosterone occurs, resulting in symptoms of depression, loss of libido, and sexual dysfunction.

Drug Source-Preparation

Natural means to be in accordance with or determined by nature. The drug may be extracted from a natural resource (plant, animal, mineral).

Semisynthetic means that it is related to or is produced by synthesis from natural-starting materials (many antibiotics, hormones, other drugs).

Synthetic means that it was produced artificially; devised, arranged, or fabricated; relating to or involving synthesis (production of a substance by the union of elements or simpler chemical compounds or by the degradation of a complex compound [most drugs are produced by chemical synthesis]).

Drugs

Conjugated estrogens (Premarin) are a mixture of substances and are NOT pure chemically defined estrogens as are used in BHRT. Equine estrogens are largely mixtures of estrone sodium sulfate and equilin sodium sulfate. They have been produced semisynthetically from estrogen intermediates synthesized from diosgenin, extraction from pregnant mares urine, and other natural precursors. Little or no equilin and equilinenin are produced in humans.

Estradiol is the most potent estrogen naturally produced in the body, and it is the most commonly used bioidentical estrogen.

Estriol is an estrogenic metabolite of estradiol, usually the predominant estrogenic metabolite found in the urine (especially during pregnancy).

Estrogen is a generic term for any substance, natural or synthetic, that exerts biological effects characteristic of estrogenic hormones such as estradiol.

Estrone is one of the natural estrogens produced in the body. It is the primary postmenopausal estrogen and accounts for 10% to 20% of circulating estrogen.

Progesterone is the hormone that is a precursor of estrogen, testosterone, and cortisone. It also protects against certain types of cancer, aids the effect of thyroid hormones, maintains sex drive, promotes thermogenesis and bone building, serves as an antidepressant to diuretics and plays a role in normalizing blood clotting, blood glucose, zinc, and copper levels. Progesterone is often used with estrogen replacement in women to decrease the risk of endometrial hyperplasia, adenocarcinoma, and many other adverse effects associated with unopposed estrogen replacement.

Progestins (i.e., medroxyprogesterone) are compounds that have biologic activities similar to progesterone. A large number of synthetic or semisynthetic steroids having

biologic activities similar to those of progesterone have been made and these are commonly called progestins. They can also have undesirable side effects.

Testosterone is an androgen that is abundant in the body. It is primarily responsible for increased libido and energy, along with many other aspects associated with well-being. As men experience andropause, the level of testosterone tends to decline very slowly, which causes unwanted effects.

Talking Points About Bioidentical Hormone Replacement Therapy

- BHRT differs from HRT, as only hormones that occur naturally in the body are used for therapy.
- Bioidentical hormones are hormone supplements whose biochemical structures are identical to those produced by the human body.
- An important advantage of utilizing compounded bioidentical hormones is that dosages and dosage forms (see Table 3) can be tailored to the individual's unique hormonal requirements.
- Bioidentical hormones are pure USP drug substances that can be uniquely formulated in the dosage needed by a patient in a dosage form that is selected and designed to enhance compliance.
- BHRT hormones include estradiol, estriol, estrone, progesterone, testosterone, and others.
- The term “natural” may have two different meanings when applied to BHRT. First, they **DO** occur naturally in the body. Second, many of them are derived from plant (soy and yam) materials initially and then synthesized into the pure chemical USP drug substance. They are semisynthetic hormones but can still be bioidentical. This can be a source of confusion with the terms.
- Some BHRT hormones are commercially manufactured by drug companies and are available on prescription; all are commercially available by major drug companies in countries throughout the world.
- All BHRT hormones are available for compounding for your patients so you can individualize the therapy of each patient to meet their needs.
- All BHRT hormones have USP monographs and purity standards.
- BHRT hormones may be synthesized from natural or chemical precursors but are still human identical.
- Products like Premarin are extracted, chemically modified (semisynthetic), and manufactured but are **NOT** bioidentical.
- Natural hormones is a term sometimes used to refer to phytoestrogens, isoflavones, diosgenin, and other substances that occur in natural products and may have estrogen-like activities. However, these examples are not bioidentical hormones.
- An approximate dosage comparison is that conjugated estrogens 0.625 mg compares to about Bi-Est/Tri-Est 2.5 mg, estradiol 0.5 to 1 mg orally, and about 0.05 mg/24 hours of estradiol transdermal.
- An approximate dosage comparison is medroxyprogesterone 2.5 to 5 mg which is about equal to progesterone 100 mg.

TABLE 2. List of Bioidentical and Non-bioidentical Hormones Currently Used.

Drug	Bioidentical	Non-bioidentical
Conjugated Estrogens		X
Estradiol	X	
Estriol	X	
Estrone	X	
Premarin		X
Progesterone	X	
Progestins		X
Testosterone	X	

TABLE 3. Example Dosage Forms That Can Be Compounded for Patients.

- Capsules
- Creams, Topical
- Gels, Topical
- Injections
- Lotions, Topical
- Mini-Troches/Mini-Lozenges
- Ointments
- Oral Drops
- Pluronic Lecithin Organogel Topical Gels
- Solutions, Clear Topical-Nonaqueous
- Sublingual drops
- Troches/Lozenges
- Vaginal Creams and Gels

Example Compounded Prescriptions

Rx
Estradiol and Progesterone Topical Cream

Rx
Estradiol and Progesterone in Pluronic Lecithin Organogel

Rx
Estradiol, Progesterone, and Testosterone Capsules

Rx
Progesterone Clear Topical Solution

Rx
Progesterone Sublingual Drops

Rx
Progesterone Topical Cream

Rx
Progesterone Topical Gel

Rx
Progesterone Troches

Rx
Progesterone Vaginal Cream Gel

Rx
Testosterone Sublingual Drops

Rx
Testosterone Topical Gel

Rx
Testosterone Troches

Summary

Bioidentical hormones are available in commercially manufactured (e.g., Prometrium, Estragel, Androgel) and compounded forms. Since these hormones are the same as what the body has been producing for years, they should be safe, effective, and without adverse problems provided the dosing is done properly, which is worked out between the physician, patient, and the pharmacist. So, **YES**, BHRT hormones are safe and effective when properly used.

References

1. Allen LV Jr. Supplemental hearing questions posed to Loyd V. Allen, Jr. by BA Kupchella, Investigative Counsel, U.S. Senate Special Committee on Aging, May 30, 2007.
2. Vance D. Premarin: The intriguing history of a controversial drug. *IJPC* 2007; 11(4): 282–286.