

ESA Submission to the TGA regarding Pharmacy Compounding

Introduction

Concerns regarding hormone replacement therapy (HRT) following publication of results from the Women's Health Initiative study created an environment for the propagation of the scientifically unproven idea that "bioidentical hormones" or "bioidentical HRT" are safer and more effective than traditional HRT

(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116832.htm>) The term "bio-identical hormones" ("BH") is a term used to describe formulations of hormones including oestrogens (oestradiol, oestrone, oestriol), progesterone, and androgens (DHEA, and testosterone). "BH", in the form of troches/lozenges or creams obtained from compounding pharmacies⁽¹⁾. These preparations may also be referred to as "natural" HRT. However, there is a lack of scientific data regarding efficacy and safety, in addition to concerns regarding inconsistency of dose and purity

Background

In a scientific sense, BH may be defined as compounds that have similar or exactly the same chemical and molecular structure as hormones that are produced in the human body⁽¹⁾. Thus Therapeutic Goods Administration (TGA) (and Federal Drug Administration (FDA)) approved BH formulations exist as HRT and include transdermal or oral oestradiol (available as tablets, gels or patches). The differences between these preparations and "BH" are summarised in the table below:

Characteristics	TGA approved HRT	"Bioidentical hormones"
Molecular structure	Similar or identical to human	Identical to human
TGA oversight	Yes	No
Dosage	Monitored, accurate and consistent	Not monitored; May be inaccurate or inconsistent
Purity	Monitored: pure	Not monitored: may be impure
Safety	Tested: risks known	Not TGA tested: risks unknown
Efficacy	Tested and proven	Not TGA tested: efficacy unknown
Scientific Evidence	Exists: conclusive	Insufficient
Tight marketing regulation	Yes	No

Adapted from (1)

Thus if dosage and purity were equal then all oestrogen containing hormone therapies, when controlled for route of administration and use with or without a progestin, whether HRT or "BH", would be expected to have similar risks including an increased risk of venous thromboembolism, stroke, endometrial cancer, and breast cancer. Case reports of pulmonary embolus, endometrial cancer and breast cancer associated with "BH" have been published⁽²⁾ and received by DAEN/ADRAC (page 12 of the TGA Reform of the Regulatory Framework for Pharmacy Compounding document) and are recognised adverse effects of HRT⁽¹⁾. There are no published studies in peer reviewed literature that show that (i) non-TGA approved compounded "BH" preparations are safer or more effective than TGA approved preparations that are standard of care and (ii) that "BH" carry less risk than TGA approved formulations.

“BH” produced by compounding pharmacies are not subject to the same oversight as traditional HRT with potential inconsistency for purity and dosage as has been reported by the FDA (www.fda.gov/cder/pharmcomp/survey.htm) with potential additional unknown risks associated with this.

BH are often prescribed on the basis of salivary hormone testing and there is no scientific evidence of a correlation between symptoms and measured salivary hormones or between salivary and tissues hormone levels⁽¹⁾.

The national and International endocrine and menopause societies including the Endocrine Society of Australia (www.endocrinesociety.org.au), Australasian Menopause Society (www.menopause.org.au), North American Menopause Society (www.menopause.org), International Menopause Society (http://www.imsociety.org/pdf_files/position_papers/global_consensus_statement_on_menopausal_hormone_therapy_2013.pdf), and the US Endocrine Society (https://www.endocrine.org/~media/endosociety/Files/Advocacy%20and%20Outreach/Position%20Statements/All/BH_Position_Statement_final_10_25_06_w_Header.pdf) do not support the use of “BH”.

Other hormonal preparations also offered in Australia in compounded form include thyroid hormones. The Endocrine Society of Australia has generated a position statement (appendix 2) which reinforces the same messages presented here around HRT and “BH”. Our recommendations included below are pertinent to all compounded hormonal products.

Response to Proposed Options

Option A: Not supported

Maintenance of the status quo would not address or correct the recognised problems with regard to

- constancy of dosage and purity in these preparations of “BH”
- promotion of products with misleading information regarding the relative safety and efficacy “BH”

Option B: Supported

We would support the proposed amendments to the regulations as outlined in Table 3A in Option B.

The benefits of Option B as outlined in Table 3A are:

- compulsory labelling of compounded medications to include “Compounded medicine. Not TGA approved”.
- Restriction of compounded hormones to where there is no registered medicine suitable which should provide some restriction to the use of “BH” as TGA registered bioidentical traditional HRT formulations are available (see Table 1 above). Regulatory authorities should consider limitation to prevent suppliers of compounded products from simply changing doses or combinations of hormones to ensure there is no identical registered preparation available. For example, there is no evidence to support the use of compounded preparations

containing a combination of oestrogens, progestins, DHEAS, melatonin and thyroid hormones; however, compounded preparations containing some/all of these hormones have been dispensed.

- Maintenance of records regarding manufacture and adverse drug events will help to address issues regarding lack of quantification of the public health risks as outlined on page 12 of the TGA Reform of the Regulatory Framework for Pharmacy Compounding document.

The risks associated with Option B are:

- That it does not address the problem of misleading claims regarding efficacy and safety that has been identified in the USA by the FDA <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116832.htm>) This issue could be addressed by the requirement for TGA approved Consumer Medicine Information (detailing formulation, safety and efficacy data) to be provided with the compounded medication as is required for TGA approved medication.
- Regulation excludes the jurisdictions of Queensland, Western Australia and Northern Territory with the potential problem of an unregulated supply of compounded pharmaceuticals bypassing states with regulation via the use of on-line or web-based pharmacies

Option C- Support Option C2

In addition to supporting Option B, we would support Option 2C as applied to the compounding of “BH”.

Additional proposal for consideration by the TGA

Although regulation of pharmacists involved in compounding pharmaceuticals is desirable, this does not address the problem of medical practitioners who prescribed these products and conduct salivary testing (for example; <http://www.menopausecentre.com.au>). We propose that the TGA consider that medical practitioners who wish to prescribe compounded “BH” must apply for and obtain authorised prescriber status according to Section 19(5) of the Therapeutic Goods Act. Medical practitioners are familiar with these processes and requirement as part of routine clinical practice. As part of their application, medical practitioners need to (i) provide indications for prescribing, (ii) provide evidence of efficacy and safety, (iii) obtain informed consent from patients and (iv) report to the thereby facilitating quantification of perceived need and adverse events. This proposal would enhance TGA oversight of the use of compounded pharmaceuticals and combined with improved regulation of compounding pharmacists, would assist in preventing the prescription of non-evidence based therapies and enable capturing and avoidance of adverse events.

References

1. Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010;95(7 Suppl 1):s1-s66.3.

2. Eden JA, NF H, M F. Three cases of endometrial cancer associated with "bioidentical" hormone replacement therapy. Medical Journal of Australia. 2007;187:244-5.

Appendix 1: US Endocrine Society Position Statement regarding Bioidentical hormones

Appendix 2: Australian Endocrine Society on thyroid hormone extracts

BIOIDENTICAL HORMONES

OCTOBER 2006

Introduction

“Bioidentical hormones,” particularly estrogen and progesterone, have been promoted as safer and more effective alternatives to more traditional hormone therapies, often by people outside of the medical community. In fact, little or no scientific and medical evidence exists to support such claims about “bioidentical hormones.” Additionally, many “bioidentical hormone” formulations are not subject to FDA oversight and can be inconsistent in dose and purity. As a result of unfounded but highly publicized claims, patients have received incomplete or incorrect information regarding the relative safety and efficacy of hormone preparations that are referred to as “bioidentical.”

“Bioidentical hormones” are defined as compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body. Though any hormone can be made to be “bioidentical,” the term is often used to describe formulations containing estrogens, progesterone, and androgens. Replacement of estrogen and progesterone is a common and effective treatment for symptoms associated with menopause, but may carry some risk of potentially serious side effects. As women seek safer treatments, they often request “bioidentical hormones” from their physicians.

Background

The Women’s Health Initiative (WHI), a long-term study of a large number of women taking traditional hormone therapy or placebo, has raised concerns about hormone therapy. This has created an environment for the propagation in the lay media of the scientifically unproven idea that “bioidentical hormones” are safer and more effective than traditional hormone therapy. No such comprehensive study has been done to examine the effects of “bioidentical hormones.” In fact, very few long-term scientific studies assessing clinical outcomes have been completed on “bioidentical hormones.”

The WHI measured a number of criteria, including the incidence of cardiovascular disease, cancers, and bone fractures. The study was cut short due to the observations of increased risks of cardiovascular disease and breast cancer in women taking combination hormone therapy. There were positive effects such as a decreased risk of colorectal cancer and bone fracture, but it was concluded that the adverse events outweighed the benefits of hormone therapy of the type and dosage used in the WHI. Nonetheless, many physicians felt that the results of the WHI did not warrant a total discontinuation of hormone therapy. Rather, the scientific and medical community currently recommends that a menopausal or post-menopausal woman discuss her individual risks and benefits of hormone therapy with her physician. If they decide that hormone therapy would be overall beneficial, then the physician should prescribe a regimen and closely monitor her.

Considerations

The hormones used in the WHI are commercially available, and their chemical and molecular structures closely resemble, but do not exactly replicate, those of hormones produced in the human body. The dosage of each hormone used in the WHI was constant among those women receiving hormone treatment.

No medical or scientific evidence exists to support the idea that the adverse and/or beneficial effects found in the WHI resulted from the molecular structure of the synthesized hormones, nor is there any sound scientific evidence to show that a different or “customized” dose of hormones would have changed the outcome. If dosage and purity were equal, then all estrogen-containing hormone therapies, “bioidentical” or “traditional,” would be expected to carry essentially the same risks and benefits. Therefore, regardless of the source or structure of the hormone administered therapeutically, all hormone therapy regimens—even those that are so-called “customized”—must be carefully controlled.

Hormone customization is very difficult to achieve, because blood hormone levels are difficult to measure and regulate accurately due to normal physiologic variations. Nonetheless, proponents of “bioidentical hormones” assert that simple tests of saliva can provide the information necessary to customize hormone doses. They also allege that customized “bioidentical hormones” are safer and more effective than modified hormones synthesized under close FDA supervision. These claims are not supported by scientific data.

Patients can obtain “bioidentical hormones” in two ways—as FDA-approved preparations that are formulated with strict oversight and dispensed by retail pharmacies; or from compounding pharmacies, where the hormones are changed from their original form into another form, purportedly for individual customization. Often these contain combinations of different forms of estrogen and/or progesterone with different potencies. Since the final hormone formulations of most compounding pharmacies are not subject to FDA monitoring for dose, purity, safety, or efficacy there may be additional and at this point unknown risks associated with them. Post-market surveys of such hormone preparations have uncovered inconsistencies in dose and quality.¹

¹ FDA Center for Drug Evaluation and Research. Report: Limited FDA Survey of Compounded Drug Products. January 2003. Available at <http://www.fda.gov/cder/pharmcomp/survey.htm>.

Table 1 compares traditional hormone therapy with “bioidentical hormone” therapy.

Table 1

	Traditional Hormones	Many “Bioidentical Hormones”
Molecular structure	Similar or identical ² to human	Identical to human
FDA oversight	Yes	No
Dosage	Monitored; accurate and consistent	Not monitored; may be inaccurate or inconsistent
Purity	Monitored; pure	Not monitored; may be impure
Safety	Tested; risks known	Not FDA tested; risks unknown
Efficacy	Tested and proven	Not FDA tested; unproven
Scientific evidence	Existent; conclusive	Insufficient

² A few “bioidentical hormones”—those available from retail pharmacies, such as estradiol and progesterone—are produced under FDA supervision and are monitored for dosage and purity as are preparations of traditional hormones. However, even FDA-monitored “bioidentical hormones” have not been examined in long-term studies such as the WHI and, therefore, have unproven safety and efficacy.

The controversies surrounding the safety and efficacy of “bioidentical hormones” illustrate the need for further scientific and medical scrutiny of these substances. Until such studies are completed, physicians should exercise caution when prescribing “bioidentical hormones” and counsel their patients about the controversy over the use of these preparations. Additionally, patients should educate themselves about hormone therapies and engage in candid discussions with their doctors. Much consideration should be given to the decision to undergo any hormone therapy, and “bioidentical hormones” present unique and additional concerns because of the process by which many of them are made.

Positions

The Endocrine Society is concerned that patients are receiving potentially misleading or false information about the benefits and risks of “bioidentical hormones.” Therefore, the Society supports FDA regulation and oversight of all hormones—“bioidentical” and traditional—regardless of chemical structure or method of manufacture. This should include, but not be limited to, the following:

- Surveys for purity and dosage accuracy
- Mandatory reporting by drug manufacturers of adverse events
- A registry of adverse events related to the use of hormone preparations
- Inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products

ESA Position Statement on Desiccated Thyroid or Thyroid Extract

Professor Peter R Ebeling MD FRACP, Chair, on behalf of ESA Medical Affairs Sub-Committee

Introduction

Desiccated thyroid or thyroid extract refers to either porcine (or mixed bovine and porcine) thyroid glands, dried and powdered for therapeutic use. All brands contain a mixture of thyroid hormones: T4 (thyroxine), T3 (triiodothyronine) in the proportions usually present in the thyroid gland (approximately 80% T4 and 20% T3). The following strengths are available: 1/8, 1/4, 1/2, 1, 2, and 3 grain tablets as well as 4 and 5 grain tablets. One grain (about 60 mg) of desiccated thyroid contains about 38 mcg of T4 and 9 mcg of T3. Because the preparation is whole thyroid gland, each 60 mg tablet also contains over 59 mg of all of the other constituents of thyroid glands, a small component of which may be biologically active.

As most doctors prescribe thyroxine rather than thyroid extract, the use of thyroid extract has become associated with alternative and complementary medicine practitioners (1,2). Desiccated thyroid or thyroid extract is not a pure product, not approved by the TGA, not available on the PBS, not produced by a pharmaceutical company, not subject to existing TGA regulations, has limited quality control, and is marketed as a “bioidentical hormone”, while “bioidentical” has been determined by the FDA in the USA as a marketing term.

Desiccated thyroid or thyroid extract is preferred by a minority of patients and doctors who claim better relief of some symptoms, such as fatigue and depression.

A number of specific claims are commonly made about thyroid extract:

1. Thyroid extract is better than thyroxine because it contains both T4 and T3.
2. Doses should be increased until symptoms are relieved regardless of laboratory tests, even if the TSH is decreased below the normal range, which can lead to adverse effects such as irregularity of the heart beat (atrial fibrillation) or thin bones (osteoporosis).
3. Other constituents of the dried thyroid glands besides the T4 and T3 (e.g. unmeasured amounts of diiodothyronine (T2), moniodothyronine (T1), calcitonin, other protein-bound iodine) may contribute to a perceived greater effectiveness or confer additional benefits.
4. Thyroid extract is "natural" and therefore preferable to synthesized thyroxine molecules.

The following areas of uncertainty do exist:

1. Is the reason some people fail to have complete relief of symptoms when tests show normal levels simply because there are other causes

of fatigue, depression, and weight gain that are mistakenly attributed to the thyroid? Could a placebo effect explain the better relief of these symptoms from thyroid extract?

2. Does a combination of T4 and T3 provide more effective symptom relief for some people than T4 alone? Multiple controlled trials have shown inconsistent benefits of various ratios of T4 and T3. However, there may be a subgroup who require T3 in addition to T4, because they cannot generate normal amounts from T4. However, if such a group exists the means to detect it have not.
3. Could the perceived benefit simply result from overtreatment? This is potentially deleterious to the patient in the long term, increasing the risk of both osteoporosis and atrial fibrillation.

Despite claims of proponents that desiccated thyroid or thyroid extract are superior to thyroxine or combinations of T4 and T3 for most people with hypothyroidism, no controlled clinical trials have been published, and most endocrinologists are concerned that superiority is due to a placebo effect or an effect of overtreatment.

Considerations

Thyroxine		Thyroid Extract
Molecular structure	Identical to human thyroxine	Porcine or bovine thyroxine and triiodothyronine; other components
TGA oversight	Yes	No
Dosage	Monitored; accurate and consistent	Monitored; may be inaccurate or inconsistent
Purity	Monitored; pure	Not monitored; impure
Safety	Tested; risks known	Not tested in trials; risks unknown
Efficacy	Tested and proven	Not tested; unproven
Scientific evidence	Existent; conclusive	Insufficient

The controversies surrounding the safety and efficacy of “bioidentical hormones” such as desiccated thyroid or thyroid extract illustrate the need for further scientific and medical scrutiny of these substances. Until such studies are completed, physicians should exercise caution when prescribing “bioidentical hormones” and counsel their patients about the controversy over the use of these preparations. Additionally, patients should educate themselves about hormone therapies and engage in candid discussions with their doctors. Much consideration should be given to the decision to undergo any hormone therapy, and “bioidentical hormones” present unique and additional concerns because of the process by which many of them are made and the lack of quality controls. In particular, purity and dose equivalence with thyroxine and between different preparations are not regulated.

ESA Position

In general, desiccated thyroid hormone or thyroid extract, combinations of thyroid hormones, or triiodothyronine should **not** be used as thyroid replacement therapy.

ESA advocates the use of a high-quality brand preparation of levothyroxine. Bioequivalence of levothyroxine preparations is based on total T4 measurement and not TSH levels; therefore, bioequivalence is not the same as therapeutic equivalence. However, the only two brands of levothyroxine (Oroxine, Eutroxig) available in Australia are identical.

Importantly, therapy should be titrated after an interval of at least 6 weeks following any change in levothyroxine dose. The serum TSH level is most important, and a free T4 estimate may also be included in the assessment.

There is a resurgence of interest in the possible benefits of treatment of hypothyroidism with combinations of T4 and T3 or with thyroid extract. The small-scale study that seems to have sparked this interest treated patients for only 5 weeks, focused on mood changes, used a T4 plus T3 combination that differs substantially from that found in natural thyroid products, may have found benefit in only a subset of patients, and has not been replicated (3,4). Insufficient evidence is available to know which patients with hypothyroidism, if any, would be better treated with a combination of T4 plus T3, rather than with T4 alone.

The ESA strongly recommends that all hormonal preparations that are intended to provide replacement therapy, whether prepared and classified according to standard pharmaceutical guidelines, or as compounded, natural or nutritional products, should be subject to similar quality assurance and potency criteria, including clear analytical definition of their composition.

The ESA is concerned that patients are receiving potentially misleading or false information about the benefits and risks of “bioidentical hormones” such as desiccated thyroid or thyroid extract. Therefore, ESA supports TGA regulation and oversight of all hormones—“bioidentical” and traditional—regardless of chemical structure or method of manufacture.

This should include, but not be limited to, the following:

- Surveys for purity and dosage accuracy of desiccated thyroid or thyroid extract.
- Mandatory reporting of adverse events.
- A registry of adverse events related to the use of bioidentical hormone preparations, including desiccated thyroid or thyroid extract, should be supported by the TGA and could be managed by an external organization, as the TGA does not regulate or monitor these compounds.
- Inclusion of uniform information for patients, such as warnings and precautions, in packaging of bioidentical hormone products, including desiccated thyroid or thyroid extract

References:

1. American Association Of Clinical Endocrinologists Medical Guidelines For Clinical Practice For The Evaluation And Treatment of Hyperthyroidism And Hypothyroidism. Updated version 2006.
2. The Endocrine Society (USA). Bioidentical Hormones Position Statement. October 2006.
3. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med.* 1999; 340:424-429.
4. Bunevicius R, Prange AJ. Mental improvement after replacement therapy with thyroxine plus triiodothyronine: relationship to cause of hypothyroidism. *Int J Neuropsychopharmacol.* 2000; 3:167-174.