The Compounded Hormone Therapy Fantasy

Concerns Regarding Purity, Dose, Poor FDA Oversight, and Media Irresponsibility

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What Is Bioidentical HT?
- Not a scientific term - no uniform definition in medical dictionary
- Molecularly very similar or identical to endogenous hormones; plant-derived from soybean or yam
- “Individualized exact doses” to replicate hormone levels of Estrogen, Progesterone, Testosterone
- Dosage adjusted according to salivary or blood hormone levels - unlike commercial HT which is adjusted based on symptom relief
- Purported anti-aging, sexual vibrancy and energizing effects are similar to structure/function claims made for dietary supplements rather than disease treatment/prevention claims made for drugs

“BIOIDENTICAL” REST IN PEACE
- The term ‘bioidentical’ is an anachronism and should be removed from our lexicon
- The correct terminology is ‘compounded’ (C-HT), or ‘government approved’ HT
DEFINITIONS:
FDA (government)-approved drugs

FDA-approved drugs include branded and generic products:
- **Branded drugs** reviewed for quality, safety and efficacy under New Drug Application (NDA)
- **Generic drugs** reviewed for quality and bioequivalence under Abbreviated NDA (ANDA)

Charts of government-approved hormone products available in the US and Canada are available online on NAMS website at www.menopause.org.

Terminology and Acronyms

- **Good Manufacturing Practices (GMPs)**: comprehensive, legally enforceable FDA regulations that oversee all aspects of the production of FDA-approved medications to ensure manufacturing quality (identity, potency, purity and sterility)
- **Active pharmaceutical ingredients (APIs)**: the drug moiety that exerts the intended pharmacological action; a medication is made up of API and inactive ingredients

DEFINITIONS: Good Manufacturing Practice (GMP)

Brand and generic drugs required by law to be produced under set regulations called Good Manufacturing Practice (GMP):
- Detailed and complex set of working standards to meet specific requirements for identity, quality, potency, and purity
- Pharmaceutical manufacturers periodically inspected by FDA for GMP-adherence
### What does GMP manufacturing quality encompass?

- The API is confirmed to be the specific chemical structure it is labeled to be.
- The medication contains the labeled strength of the active drug moiety that exerts a pharmacological effect.
- The medication does not exceed a defined, low threshold of degradation products, process impurities, residual solvents or residual amounts of other drugs made in the same facility.
- The absence of living, viable microorganisms or bacterial endotoxins.

### DEFINITIONS: Compounded drugs and traditional pharmacy compounding

**Traditional compounding:**
- *In response to a prescription*, pharmacists may combine, mix or alter ingredients to create unique medications.
- The product is a *compounded drug*.

### Source of active ingredient in compounded products

- Start with FDA-approved brand or generic drugs (*Advantage*: active ingredient and initial dose. *Disadvantage*: Inactive ingredients unsuitable for compounding requirement).
- Start with active pharmaceutical ingredients (API) and other inactive components (*Advantage*: avoidance of binders etc. *Disadvantage*: Uncertainty of identity, purity and potency; shipping, storage and repackaging problems).

### What does ‘FDA-registered’ mean?

- Compounding pharmacies may advertise that they are ‘registered with FDA’ or that they receive their API from an ‘FDA-registered’ supplier.
- Two types of registration are possible with the FDA:
  - Registered Manufacturer (e.g. pharmaceutical companies): Ensures adherence to all manufacturing GMPs.
  - Registered Re-packer (e.g. suppliers, re-packagers, some pharmacies): Ensures containers into which approved drugs are repackaged do not destroy quality or integrity of the product; Registrants are not held to manufacturing GMP standards.
- FDA-registered suppliers or re-packagers may or may not buy their active and/or inactive ingredients from FDA-registered manufacturers.
Some Basic Facts First

- Pharmacy compounding of C-HT is now a multi-billion dollar a year industry
- C-HT drugs are prescription drugs, not over-the-counter.
- Physicians are (or should be) always part of the triad.
- Without active medical profession participation, this industry could not prosper or function the way it has
- FDA has been questioning for decades its jurisdiction over pharmacy compounding

Key differences between US FDA-approved and compounded drugs

<table>
<thead>
<tr>
<th></th>
<th>FDA-Approved Drug</th>
<th>Compounded Drug</th>
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<tbody>
<tr>
<td>Made 'extemporaneously' after receipt of a RX</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>FDA review for quality, safety, efficacy before marketing or prescribing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Manufactured under GMP</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Labeling for safe use regulated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sterile products adhere to GMP</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Benefit-risk assessment</td>
<td>Conducted by FDA at population level</td>
<td>Conducted by prescriber at patient level</td>
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Risks Associated with Compounded Medications

- Substandard products
- Morbidity and mortality associated with compounded drugs – multiple examples of deaths due to infected products
- Medico-legal risks for physicians

Is there a link between C-HT use and uterine cancer?

The canary in the coal mine?

- 3 Cases on bioidentical HRT: Eden et al, MJA 2007;187:244-5
- 2 cases on bioidentical HRT: Jessel et al, Menopause 2009;16:1247
- 4 cases in NAMS survey: Menopause 2015;22:PAP
The Problems with C-HT

- Untested in good clinical trials (e.g. no endometrial safety data)
- "Natural" does not really equal "safer"
- No clinician or patient package inserts documenting safety/efficacy, and no black box warnings
- No uniform manufacturing standards. In one study 25% of compounded products tested failed quality control testing vs. 2% of commercially manufactured drug products
- No formal review of accuracy of advertised claims

There Would Be No Harm If the Following Were All True

- Patients fully informed of true risks/safety
- Physicians fully aware of limitations on safety/efficacy data
- All advertising of risks/benefits is completely truthful
- The pharmacies all produced a consistent, pure product and did not attempt to practice medicine
- All prescriptions were completely legitimate
- Salivary hormones levels actually meant something and were inexpensive to boot
- C-HT were proven as safe and effective as other HT

WHO IS BEING HARMED?

- Patients?
- Prescribing physicians?
- Medical societies and the medical profession?
- Commercial drug manufacturers?
- Compounding pharmacies and their industry?
- Regulatory agencies such as FDA and state pharmacy/medical boards?

POSSIBLE FACTS ABOUT C-HT

- May be just as effective as commercial HT, though never proven to be
- Never been shown to be safer or more effective
- Should be just as safe as commercial HT, but there’s no reason for it to be any safer
- If all this is true, why are some physicians favoring C-HT over traditional HT?
  *Because medicine is more than an art, it’s also a trade/business*
Potential C-HT Products

- Tablets/capsules
- Creams/gels
- Injectables
- Pellets

All of the above may be compounded as single or multiple molecules. Injectables and pellets have special infection risk.

How Do Some Compounding Pharmacies Hurt Patients?

- Practice medicine by adjusting doses of C-HT independent of physicians.
- Promote these products globally to any patient
- Make false claims regarding safety/efficacy
- Overcharge for these meds?
- Largest compounding pharmacies just drug manufacturers in disguise

How Do Physicians Hurt Patients?

- By taking patients off meds with known safety and efficacy profiles to place them on C-HT where these are unknown
- Waste scarce patient financial resources on meaningless hormone level testing and more expensive C-HT that offers no therapeutic advantage.
- Just because patients want it and are willing to pay for it does not mean you have to go along with it.

A final harm: Medical Information via the Internet

- It’s totally unregulated
- FDA has not even begun to really engage this issue, nor has the medical profession (or anyone else)
- Supreme Court takes the position that information is better than restriction of information
- Much of the information is false or misleading
- BUT, this is also an opportunity for professional medical societies to seize the initiative and provide good information
What Must the Pharmacy Profession Do to Help Itself?

- Better self-regulation
- Get rid of false and misleading advertising
- Identify and discipline the worst offenders

FDA has identified “red flags” of pharmacy compounding

- Compounding drugs that are essentially copies of commercially available products
- Compounding large volumes of drugs prior to and in anticipation of the receipt of a valid prescription
- Compounding drugs removed from the market for safety reasons

FDA may take enforcement action against pharmacies

- Compounding drugs prior to receipt of a valid RX
- Compounding drugs removed from the market for safety reasons
- Compounding drugs that are essentially copies of commercially available products

What Must Medicine Do To Correct Itself?

- Self-regulation - A license to practice medicine is not a license to practice bad medicine
- Undertake comparative trials to evaluate C-HT claims
- Full disclosure to patients of financial investments in labs and C-HT pharmacies
ORGANIZED MEDICINE IS NOT ON YOUR SIDE

If you get sued, the following position statements will be used against you

The HOD accepted a report by the AMA’s Council on Science and Public Health (CSAPH) entitled, “The Use of Hormones for Anti-Aging: A Review of Efficacy and Safety,” which was commissioned in June 2008. The report reviewed the scientific evidence on the benefits and risks of human growth hormone (HGH), dehydroepiandrosterone (DHEA), testosterone, and estrogens with or without progestins as supplements to prevent, slow, or reverse age-related changes in otherwise healthy adults. As part of its review, the CSAPH examined clinical guidelines and position statements by government agencies and medical specialty societies such as The Endocrine Society. The report states that “no credible scientific evidence exists on the value of so-called ‘bioidentical hormones,’ and there are concerns about their purity, potency and quality because they are not approved by the FDA.” This report further bolsters current AMA policy, which resulted from a Society-sponsored resolution based on the Society’s 2006 position statement on bioidentical hormones.

The International Menopause Society
MHT and Compounded Hormones

- The use of custom compounded bioidentical hormone therapy is not recommended.


The Women’s Health Practice and Research Network of the American College of Clinical Pharmacy recommends against the consistent use of compounded bioidentical hormones as a safer option compared with manufactured therapy and supports the statements of other key organizations, acknowledging the need for more robust clinical studies to evaluate the potential advantages and disadvantages of compounded bioidentical products compared with manufactured products.

ACOG PRACTICE BULLETIN
Number 14, January 2014
Recommendations and Conclusions

Following conclusions are based on limited or inconclusive scientific evidence (Level B)

- Data do not support use of progestin-only, testosterone, or compounded bioidentical hormones for treatment of VMS

How to lessen malpractice exposure

- Simplest – only prescribe FDA-approved products
- Ascertain an FDA-approved equivalent is not available
- Confirm compounding pharmacist is FDA registered
- Where is raw product (API) obtained?
- Is the API pharmaceutical grade for humans?
- How is the API stored?
- Has API been tested for purity?
- How is sterility ensured and tested during compounding?
- Is equipment free of contaminants of other drugs?
- Include all this information in the patient record

Using FDA-Approved HT Provides a Greater Assurance of Safety and Effectiveness Than Using C-HT

- Compounded drugs lack an FDA finding of:
  - Safety
  - Efficacy
  - Manufacturing quality (identity, potency, purity and sterility)
- Inappropriate compounding practices in the US can put the public at risk
  - Mass production
  - National distribution

CONCLUSIONS

- Compounded drugs lack an FDA finding of safety, efficacy, and GMP
- Compounded drugs are not interchangeable with FDA-approved brands or generics
- If an FDA-approved drug is available it must be prescribed and used by law
- If there is patient harm, liability concerns may arise due to prescribers role as learned intermediary