Pharmacy Compounding: Benefits and Controversy
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What is Compounding?

Compounding is the preparation of customized medications by a pharmacist, according to a doctor’s specifications, to meet individual patient needs.

Agenda
- “Technical” Issues
- My spiritual journey
- Controversy associated with compounding
  - How do I stay out of trouble???

Technical Issues
- Definition of compounding
- What makes us different from “traditional” pharmacies
- Benefits of compounding
  - Literature documentation
- Specific patient populations
- Examples of what we can do because of our setup

What makes us different??
- We compound from raw pharmaceutical grade ingredients
- Scales
- Software:
  - Compounder Rx by PK Software
  - Script Assist by RS Software
- 795 Compliant
Benefits of Compounding

- Unavailable Commercial Products
  - Diary Hormones
- Alternate Dosage Forms
  - Rectal/vaginal Suppositories
  - Topical Gels
  - Topical Ointments/Creams
  - Suspensions
  - Capsules
  - Sublingual products
- Custom Dosing
  - Pediatrics
  - Bio-identical Hormone Replacement

Patient Populations

- Dermatology
  - “esthetics”
  - Pain
- Hospice/LTC Patients
- Veterinary Patients
- Pediatric Patients
- Bio-identical HRT


Topical Pain Gels
**Topical Ketoprofen**
- Large body of literature documentation
- Increased local absorption/actions
- Effective in a wide variety of soft tissue injuries
- Favorable side-effect profile compared to oral products


**Mason L et al.** 5 to 7 minute delay to onset of action

**Other options:**
- Lorazepam
- Haloperidol
- Prochlorperazine

**Compounded medication**
- Fentanyl lozenges
- Topical ketoprofen
- 17-hydroxyprogesterone
- Topical estradiol
- Topical testosterone
- Potassium bromide
- 4-amino pyridine

**Manufactured product**
- Actiq®
- Voltaren® Topical Gel
- Makena®
- Estrogel®
- Androgel®
- K-BroVet®
- Ampyra®

**ABHR gels/suppositories**
- Anti-seizure suppositories
- Topical ketoprofen
- Topical ketamine
- Wound care

**Topical Promethazine, et al**
- Applied topically to the palmar region of the wrist for those who can’t swallow
- 5 to 7 minute delay to onset of action
- Avoid trauma of injection

**Other options:**
- Lorazepam
- Haloperidol
- Prochlorperazine

**Veterinary Compounding**
- Products:
  - DES
- Dosage Forms:
  - Topical methimazole
- Flavoring:
  - Metronidazole
- Generalized problem solving
  - Where does an 800 pound gorilla sleep???
$40.00 !!!!!!
- All-trans retinoic acid
- Vesanoid® 10 mg capsules
- 6mg/day
  - $ 1605.93/100 capsules
  - Versus $289.07 + ????
- All-trans retinoic acid
  - Tretinoin

- Made from plants
- Chemically modified to be identical to human, female hormones
- Based on human body's hormone profile
- Not commercially manufactured; only available from compounding pharmacies
- Able to customize dose to meet specific needs

Female Hormone Hierarchy

- 17a-Hydroxyprogesterone
- 17a-Hydroxyprogesterone
- DHEA
- Androstenedione
- Testosterone
- DHT
- Estrone
- Estradiol
- Estriol
- 16a-Hydroxyestrone
Bio-Identical Tri-est (3 Hormones)
- Estrone 0.25mg (10%)
- Estradiol 0.25mg (10%)
- Estriol 2.0mg (80%)

or

Bi-Est (2 Hormones)
- Estradiol 0.5mg (20%)
- Estriol 2.0mg (80%)
- No Estrone

Let's Compare:

Human Estrogens
- Estrone (E1): 10-20%
- Estradiol (E2): 10-20%
- Estriol (E3): 60-80%

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Premarin®
- Estradiol/et al: 5-19%
- Estrone: 75-80%
- Estriol: 6-15%

Pregnant Mare Urine

Literature Review
- Is there a difference between the estrogens?
- Is there literature to document the benefit of Bio-Identical HRT?
Jozan, Kreitmann, and Bayard
- Studied effects of oestradiol, oestrone, oestriol and oestetrol on induction of progesterone receptors
- Dose response curves:
  - $E_2$ 10 X $> E_1$
  - $E_2$ 50 times greater than $E_4$
  - $E_2$ approximately equal to $E_1$


Melamed, et al.
- In vitro study using isocratic salt chromatography to study estrogen kinetics and elucidate $^3$H estradiol and estriol complexes
- Molecular study
  - Estrogen receptor complexes
- Animal study

Jozan, Kreitmann, and Bayard
- ...On the other hand, the low affinity of the estrogen receptor MCF-7 cells reported for OE3 does not explain the dose-response curve of PGR induction...Further studies will be necessary to clarify this point...

Jozan, Kreitmann, and Bayard
- ...when compared with untreated cells, OE2, OE3, and OE4 do not influence significantly the plating efficiency but all 3 hormones increase thymidine incorporation of cells in log phase growth...OE1 decreases plating efficiency, thymidine incorporation...
  - thus, OE3 and OE4 behave like complete OE2 agonists whereas OE1 has dissociated effects...

Melamed, et al.
- ...Estriol acts as a weak estrogen when administered as a single dose...produces full estrogenic responses upon chronic administration...when estriol is injected together with estradiol it acts as an antiestrogen...

Jozan, Kreitmann, and Bayard
- Hormonin # 1:
  - Oestriol: 0.135 mg (20%)
  - Oestrone: 0.7 mg (60%)
  - Oestradiol: 0.3 mg (20%)
  - Total dose: 1.135 versus 1.25 Tri-est
Three month trial of continuous therapy with oral unconjugated oestrogens.

Two groups: 10/8

Serum levels of E1, E2, E3, DHEA, FSH, and LH were measured.

Vaginal smears monitored

Once case of endometrial hyperplasia

Consistent relief of vasomotor symptoms


Clinical effectiveness was directly related to dosage (2 to 8 mg/day). 8mg/day failed to induce endometrial proliferation and proved a poor suppressor of FSH and LH. capacity to relieve vasomotor instability and improve vaginal maturation without notable side effects, sufficient reason to include this drug in the management of postmenopausal syndrome.


God is good!!!!
God’s timing is ALWAYS perfect
Nobody ever said it would be easy

Other studies

1998: Blue Ridge Apothecary Incorporated
Location
Insurance
3/13/2001: First prescription dispensed
9/11/2001: 911
4/2008: Sold to Kroger
4/2014: Bought from Kroger

Timeline

Questions?

Dumb questions are more easily handled than dumb mistakes.
Insurance Issues
- Do not submit claims on line for billing
- When necessary, will submit paper claims for reimbursement
- MOST OF THE TIME for private pay, our charges are less than brand copays

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Sample Prices

<table>
<thead>
<tr>
<th>Item</th>
<th>Quantity</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miracle Cream</td>
<td>30 grams</td>
<td>$24.00</td>
</tr>
<tr>
<td>Eucerin/Triamcinolone</td>
<td>454 grams</td>
<td>$29.00</td>
</tr>
<tr>
<td>Ketoprofen 10% gel</td>
<td>30 grams</td>
<td>$25.00</td>
</tr>
<tr>
<td>Retinoic Acid 0.025%</td>
<td>30 ml</td>
<td>$24.00</td>
</tr>
</tbody>
</table>

Food and Drug Administration

Women’s Health Initiative Trial
First Randomized Trial of its' kind
161,809 women between 50 and 79 years old
Estrogen/progestin versus placebo
Stopped early due to increased health risks
**No difference between subgroups**

7 more CHD
8 more strokes
8 more invasive breast cancers
6 fewer colorectal cancers
5 fewer hip fractures
23 Adverse Events - 11 Positive Outcomes = 12 more Adverse Events

2002: Publication of WHI Study
10/6/2005 through 4/4/06: Filing of citizen’s petition by Wyeth
FDA process
January 2008:
» Reply to petition
» “Education” campaign
» Warning letter to compounding pharmacies
» Import alert regarding estriol

Only one drug regimen used
Combination product with equine base estrogen/synthetic progestin
Over 42% of women in study stopped their medicine!!!
North Carolina coed’s death from an overdose of compounded lidocaine gel…under investigation by the state pharmacy, medical boards, and the Food and Drug Administration…

22…applied the compounded 10% lidocaine and 10% tetracaine…last December 28th…found in car having seizures…later slipped into a coma…died January 5th.

Employee of spa…had given…the compounded anesthetic…reportedly instructed her to apply the gel from her groin to her ankles and to wrap her legs in clear plastic before her appointment.

Autopsy pointed to elevated blood lidocaine levels as the cause of death…


Disciplinary Action

…made prescription medications…Lasergel and Lasergel Plus…

…employed “Pharmacy Services Representative”

From late 2003 through 2004, 252 x 30 gram tubes of Lasergel Plus were assigned various prescription numbers and were sold to Premier Body Laser and Skin Clinics

…labeling…did not contain any patient specific information, directions for use, or pharmacist identification…Some tubes contained the words “For Office Use Only”…

2004:
- Two advisory letters
- 2/10/06:
  - Consent agreement
- 10/4/12:
  - Product recall
HR 3204 DSQA

- Enacted 11/27/2013
- Three sections:
  - Reaffirmed FDCA 503A with changes
  - Added FDCA 503B which deals with outsourcing facilities
  - Established track and trace system for distributors and manufacturers
- Apparently this regulates ALL human compounders AND prescribers

MOU ( Surprise!!!! )

- Does not apply to physicians
- State board required to report:
  - Disciplinary actions against a pharmacy for compounding violations
  - Disciplinary actions taken against a compounding pharmacy for violations
- MAY precipitate an FDA inspection to determine 503A violations

The Curious Case of Makena®

- 17-hydroxyprogesterone

- Used weekly for 20 weeks for women at high risk of delivering prematurely
- Previously available only from compounding pharmacies:
  - $20.00 per dose
- K-V Pharmaceutical:
  - Restricted network
  - Sent warning letters to compounding pharmacies
  - $1,500.00 per dose (2/11)
- Results:
  - FDA
  - SEC
  - $690.00 per dose (4/11)
- State’s Board of Pharmacy

503B (This is new)

- Outsourcing Facility
  - Compounds and distributes sterile drugs but does not need a patient specific prescription
  - “Voluntarily” registers with FDA
  - Must comply with cGMPs
  - Compounding must be done by or supervised by a pharmacist
  - Does not have to be a pharmacy
- Can fill patient specific prescriptions
- 14 entities registered as of 1/1/14

How do I stay out of trouble

- JUST DON’T BE STUPID!!!!!
- Don’t manufacture:
  - Patient specific
  - Don’t make duplicates of existing products
- Read the appropriate USP chapters
- Be careful with your reps
  - Probably best not to have any
  - Beyond use dates

- 14 entities registered as of 1/1/14