Multidisciplinary Evaluation and Treatment of Vulvar Disorders

The Role of Compounding Pharmacy

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Disclosures

• Innovation Compounding Pharmacy – Kennesaw, GA
Objectives

• To understand the purpose of a compounding pharmacy
• To familiarize the benefits & drawbacks of compounding
• To delineate compounding options for the vulvar region
• To determine appropriate formulations for commonly prescribed vulvar preparations
What is Compounding?

• Compounding pharmacists work directly with prescribers including physicians, NP/PAs, physical/sex therapists, and other clinicians to create customized medication solutions for patients whose healthcare needs cannot be met by manufactured medications.

• 5000 year old profession, the oldest form of pharmacy

• Regulated by State Boards of Pharmacy and Accreditation Boards

• “Thinking outside of the box”

• Manipulating the dosage form!

• Customized, individualized medicine tailored to the patient’s specific need
How Do I Choose a Compounding Pharmacy?

• Licensed in your State
• Pharmacist Knowledge and Access
• Adherence to USP Guidelines, Testing
  • USP <795> - Non-Sterile Compounding
  • USP <797> - Sterile Compounding
• Diversity of Portfolio to your Practice Needs
  • Pelvic Health/FSD/IC
• Pricing and Patient Care/Access
• Reputation
• Compounding Ability and Dosage Form Assortment
• Most Important – Accreditation and Inspection!!
PCAB – Pharmacy Compounding Accreditation Board

- A service of the Accreditation Commission for Healthcare (ACHC)
- Offers the most comprehensive compliance solution in the industry, with standards based on U.S. Pharmacopeial Convention (USP) guidelines
- Accredits pharmacies that compound medications whether in the retail, hospital, mail order, or closed door setting
- A pharmacy’s commitment to continuous compliance significantly reduces the risk associated with compounding medications and demonstrates a commitment to meeting the highest industry standards for quality and safety
- http://www.achc.org/accreditation-locations.html
Benefits of Compounding

• Alternate Options to Commercially Available
  • Vaginal diazepam, vulvar/vestibular gabapentin, etc.
  • Bladder instillations for interstitial cystitis (IC)

• ↑ Patient Compliance
  • Patient Sensitivities
    • Allergies
    • Preservatives, gluten, dyes, lactose, glucose, and sugar
    • Base sensitivity
  • GI Upset Avoidance/Bypass Liver (with Transdermal Preps)
  • Flavoring
  • Affordable – combo products, etc.
More Benefits of Compounding

• Ability to Adjust Risk Management Profile and Dosing

• Dosage Form—Let the med go where you want it to go!
  • Vaginal/Rectal: cream, ointment, capsule, suppository, mini-insert, tampon, douche, oil
  • Topical: cream, lotion, ointment, oil, gel
  • Oral: capsule, solution, suspension, lozenge, troche, gel
  • Sublingual: troche, rapid-dissolving tablet (RDT), drop
  • Intramuscular/Subcutaneous/Intravenous injection, infusion, implant

• Combination Therapy
  • Gaba/Keto/Cyclo/Lido vulvovestibular foam
  • Diazepam/baclofen/lidocaine vaginal suppository
  • To name a few!
Drawbacks of Compounding

• Typically not covered on patient insurance plans
• Cannot duplicate commercially-available products (products with a patent)
• Not FDA-approved
• Healthcare community’s general lack of understanding regarding the role of compounding
• Double-blind placebo-controlled studies (lack of)
Compounding for the Vulvar Region

- Local Therapy
  - Low/No systemic absorption
  - Topical agents recommended by expert consensus statement
- pH balanced, preservative/alcohol-free preps
- Therapies that are supported by literature/clinical data
- Increasing patient comfort and compliance
- Therapy directed at diagnosis

Dosage Forms

Vaginal Cream
Vulvovestibular Foam
Vulvovestibular Cream
Rectal/Vaginal Suppository Capsule
Rectal/Vaginal Mini Insert
Urethral Suppository
Vulvodynia and Vestibulodynia – 2015 Consensus Terminology

• A. Vulvar pain caused by a specific disorder
  • a. Infectious (e.g., recurrent candidiasis, herpes)
  • b. Inflammatory (e.g., lichen sclerosis, lichen planus, immunobullous disorders)
  • c. Neoplastic (e.g., Paget disease, squamous cell carcinoma)
  • d. Neurologic (e.g., postherpetic neuralgia, nerve compression or nerve injury, neuroma)
  • e. Trauma (e.g., female genital cutting, obstetric)
  • f. Iatrogenic (e.g., postoperative, chemotherapy, radiation)
  • g. Hormonal deficiencies (e.g., genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)

• B. Vulvodynia: vulvar pain of at least 3 months’ duration, without a clear identifiable cause, which may have potential associated factors; The following are the descriptors:
  • a. Localized (e.g., vestibulodynia, clitorodynia) or generalized or mixed (localized and generalized)
  • b. Provoked (e.g., insertional, contact) or spontaneous or mixed (provoked and spontaneous)
  • c. Onset (primary or secondary)
  • d. Temporal pattern (intermittent, persistent, constant, immediate, delayed)

a Women may have both a specific disorder (e.g., lichen sclerosis) and vulvodynia.
Neurologic Conditions

- **Rationale:** women with vestibulodynia have a congenital disorder with a significant increase in the number of intraepithelial nerve endings within the vulvar vestibule.

- **Higher numbers of nerve fibers reported in the vestibule of women with vestibulodynia compared with controls.**

- **Neuroproliferative Topical Agents**
  - **Gabapentin 2-6%**
    - Well-tolerated topically, very effective in generalized vulvodynia, unprovoked.
    - Centrally acting, target areas of nerves/brain that control the concept of pain, complex synergy between increased GABA synthesis.
    - 80% of women in study demonstrated at least 50% improvement in pain scores. Sexual function improves in 17/20 with evaluable results.
  - **Ketamine 0.5-5%**
    - Centrally acting, inhibit NMDA receptors, and NO synthase which decreases pain perception. Blocks Ca channels, depresses Na channels, and alters cholinergic neurotransmission.
    - Proctodynia?
Neurologic, cont.

- **Amitriptyline 2%** 7-8
  - Reduces peripheral nerve desensitization, affects adenosine A receptors and sodium channels
  - Oral amitriptyline: 60% effective but high side effect profile (drowsiness, dry mouth, stigmata) 9
  - First-line recommendation 10-11

- **Baclofen 2-3%** 12
  - GABA receptor agonist

- **Cyclobenzaprine 2-4%** 13-14
  - Centrally acting muscle relaxant and anti-spasmodic, inhibits sodium channels, thus reducing muscular hyperactivity

- **Lidocaine 2.5-7.5%** 15-17, EMLA (Lidocaine2.5%-Prilocaine 2.5%)
  - Local anesthetic – blockade of sodium channels on peripheral nociceptors and block transmission of discharges from peripheral sensory nerves
  - Not recommended as long term treatment option
  - Overnight cottonball application
Neurologic Combos - Examples

- Lidocaine 2-5%/ Gabapentin 2-6%/ Ketamine 5%
- Amitriptyline 2%/ Baclofen 2%/ Gabapentin 2% (ABG)
- Gabapentin 5%/ Ketamine 5%/ Cyclobenzaprine 3%/ Lidocaine 5%
- Amitriptyline 2%/ Baclofen 2% cream (ABC)

- Cream, Ointment, Suppository, Foam
- Synergistic action
- Targets several mechanisms of actions
Hormonal Conditions

- Place in vulvar atrophy/atrophic vestibulitis \(^{10,19-23}\)
  - Estradiol 0.01-0.03%/Testosterone 0.1% cream BID
  - Estradiol 0.01%/vitamin E 200IU/gram cream
  - ± Lidocaine
  - DHEA 2.5-10mg

- E/T levels altered and decreased receptor saturation in women on OCP, hysterectomy/oophorectomy, chemotherapy, endometriosis tx, menopause.

- Hormones act in their original forms to target the specific receptors present in the vestibule or vulva in order to restore the natural presence of hormones in the female.

- Increased SHBG and decreased free testosterone and estradiol are frequently found in women with PVD who are on hormonal contraceptives. \(^{18,20}\)
Inflammatory, Allergic Vulvitis, and Lichens Conditions

- **Rationale:** procytokines have been identified in vulvodynia patient, suggesting inflammation may be playing a role despite the lack of inflammation histologically. 27
- Women with lichen sclerosus have a 4 - 6% risk of developing vulvar carcinoma. LS has been found in greater than 60% of cases of squamous carcinoma of the vulva.
- **Anti-Inflammatories**
  - **Clobetasol propionate 0.05% cream** 28-29
    - Topical Ultrapotent Corticosteroid
    - Act by the induction of phospholipase A2 inhibitory proteins, called lipocortins, which control biosynthesis of potent inflammatory mediators such as prostaglandins and leukotrienes by inhibiting release of their common precursor arachidonic acid.
    - First line for vulvar lichen sclerosis
    - Superior to pimecrolimus 30, tacrolimus 31, and testosterone 32
    - Superior to hydrocortisone in vulval vestibulitis 33
Inflammatory, cont.

- **Triamcinolone acetonide 0.1% cream** \(^{34}\)
  - Intermediate-acting synthetic glucocorticoid
  - Contact dermatitis
- **Cromolyn 4% cream** \(^{35-36}\)
  - *Rationale: Increased mast-cell in patient with chronic idiopathic vulvar vestibulitis*
  - inhibits the release of histamine and inflammation mediations from mast cells in vulvar tissue, “mast cell stabilizer”
Infectious Conditions

- Chronic Candidal Vulvovaginitis/Bacterial Vaginosis
- **Boric Acid 600mg vaginal capsules/suppositories**
  - When used as a vaginal capsule, boric acid has been effective in the treatment of vulvovaginal candidiasis (VVC), recurrent vulvovaginal candidiasis, and bacterial vaginosis (BV).
  - Decreases pH in the vagina, difficult for yeast to grow because of cell wall destruction (hole-puncher). Bacteriostatic and fungistatic.
  - Safe, alternative, economic option for women with recurrent and chronic symptoms of vaginitis when conventional treatment fails because of the involvement of non-albicans Candida spp. or azole-resistant strains.
Infectious Conditions, cont.

- Recurrent/Resistant Bacterial Vaginosis
- **Lactobacillus Acidophilus 300 MU /gram Vaginal Cream** (probiotic vaginal cream)
  - **Rationale:** absent or low concentrations of lactobacilli associated with BV, often leading to pain as symptom
  - Vaginal lactobacilli were isolated from 73.7% of 825 women **without** BV, and from 29.8% of 131 women **with** BV ($p < 0.001$)
  - Normal vaginal, digestive, urinary, microbiota dominated by lactobacilli. Most known for its probiotic effect, but has been shown useful in the treatment of vaginal infections caused by bacteria (BV and recurrent BV) and yeast. $\text{H}_2\text{O}_2$-producing *L. acidophilus*
  - Production of lactic acid by lactobacilli, which is mainly responsible for the low vaginal pH, contributes, probably even more than production of $\text{H}_2\text{O}_2$, to the inhibition of growth of *G. vaginalis*. 
Secondary to Hypertonic Pelvic Floor

- **Diazepam 5-20 mg vaginal suppositories**\(^{24-26}\)
  - + Baclofen, Lidocaine, Ketamine, Amitriptyline

- **Levator Ani Syndrome, Vaginismus**

- Antispasmodic. Enhances the action of GABA by tightly binding to A-type GABA receptors, thus opening the membrane channels and allowing the entry of chloride ions.

- *Pelvic floor muscle dysfunction* is almost universally present in women with vulvodynia. High resting tension, muscle irritability, tenderness to palpation, and overall weakness are extremely common. The role of these abnormalities in the occurrence of pain is confirmed by improvement with normalization of pelvic floor function through physical therapy or biofeedback.

- Rectal Data: peak [conc]: 1.5 hours; bioavailability: (rectal, gel), 90% relative to diazepam injectable. Elimination: (rectal, gel), about 46 hours
Targeting Vanilloid Receptors

- **Capsaicin 0.025-0.5% cream or ointment** ³⁷, ⁴⁰
  - Rationale: increased vanilloid receptor (VR1) innervation found in women with vulvodynia. ³⁸ Agonist effects on vanilloid receptors located in the peripheral terminals of nociceptors. After hyperesthesia to the initial exposure, capsaicin produces a long-lasting desensitization to burning and pain. ³⁹
  - Preceded by Lidocaine/Prilocaine
  - Derived from hot peppers - severe burning on application.
  - After initial use, long –lasting desensitization
  - Two uncontrolled studies
  - Not recommended as first-line treatment but as a last-effort or alternative to surgery.
Thank you!

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References


7. Lehman JS, Sciallis GF. Effective use of topical amitriptyline hydrochloride 2.5% and ketamine hydrochloride 0.5% for analgesia in refractory proctodynia. J Drugs Dermatol. 2008. Sep;7(9):887–9


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