Contents:

- Definitions – HRT vs. BHRT
- Review of Women’s Health Initiative Study
- Review of Literature in Favor of BHRT in Women
- Signs and Symptoms of Various Hormone Deficiencies in Women
- Diagnosis and Monitoring
- Common Dosing forms and Strengths and BHRT Terminology
- Fielding Common Complaints/Side Effects of Therapy
Traditional HRT

- Traditional HRT refers to the use of synthetic or semisynthetic hormones.
- Examples – Synthetic
  - Progestins (MPA - medroxyprogesterone acetate)
- Examples – Semisynthetic
  - Equine Estrogen - Premarin

BHRT

- Bioidentical hormone replacement therapy usually involves the use of steroid hormones including 17β-estradiol, estriol, progesterone, testosterone, and dehydroepiandrosterone (DHEA)
- Bioidentical hormones are derived from plant sources and are termed bioidentical because it is claimed that they are structurally identical to endogenous hormones, not just human hormone receptor binders

WHI Study

- Study published in 2002 in JAMA
- All women in the study had a uterus at baseline and received either 0.625 mg of CEEs (equine estrogen) and 2.5 mg of medroxyprogesterone acetate (MPA) or placebo. N = 16,608
- After a mean follow up of 5.2 years, the study was stopped early due to increase in breast cancer (26% increased risk of breast cancer in the HRT arm of the study, a 29% increase risk of MI or or death from CVD, a 200% increase risk of VTE, DVT and PE)
- On the plus side – there was a 33% decreased risk of hip fracture, 37% decreased risk of colorectal cancer, and symptom improvement
WHI Continued...

• Put another way
  – 7 extra cases per year per 10,000 women in the HRT group had heart disease
  – 8 extra cases per year per 10,000 women in the HRT group got breast cancer
  – 8 extra strokes per 10,000 women using HRT

Problems with the WHI study

• The study population of the HRT part of the WHI study was characterized by a high average age and a high frequency of obesity and hypertensive disorders
  - About two-thirds of the participants were enrolled in the study at age 60 years or older, and 21% were above the age of 70 years at randomization.
  - This does not reflect clinical practice in which women are usually prescribed HRT at the time they reach menopause and often due to climacteric complaints

• The frequency of obesity in the study population was above average. Only 30% of the participants were of normal weight [body mass index (BMI) < 25 kg/m²], and 30% of the participants had a BMI >30 kg/m², which would be described as obese

• Mean age was 63
• 49.9% were smokers
• Women with hot flashes were excluded

WHI Study – Problems synopsis

• The study basically took high risk patients who are generally not on hormones and pooled the data.
  - In 2011, The Journal of Clinical Endocrinology concluded that the risks discovered in the WHI study cannot be applied to women starting HRT shortly after menopause

• It is now well established that estrogen given <10 years after menopause protects women from heart disease and all cause mortality (JAMA 2007)

• Interestingly, JAMA WHI analysis in 2011 found that women with hysterectomy and therefore using Premarin only for 5.9 years had a lower risk of breast cancer than women using Premarin and progesterin because they were not taking progesterin

• The study used synthetic hormones.
  - Only Premarin and progesterin were studied.
• Bio-identical hormones were not studied
• Fixed, rather than individualized dosing was used
  - Older women are intrinsically at higher risk for cancer and heart disease, especially if they are overweight and smokers
Problems with Progestin

- Study after study correlates the use of synthetic progestins to negative outcomes
- Progesterone and synthetic progestins have similar effects on endometrial tissue but there is significant evidence that they have differing effects on breast tissue proliferation
- Synthetic progestins have clear association with increased risk for breast cancer
  - Women's Health Initiative: MPA significantly increased risk for breast cancer (RR=1.26; CI: 1.00-1.59)
  - Litinon et al: combination estrogen and progestogen increases risk of breast cancer after 2 years (P<0.02)
  - Nurses' Health Study: 58,000 postmenopausal women were followed for 16 years (725,000 women-years)
    - Unopposed estrogen use increased risk for breast cancer by 25% (CI: 1.25-1.18)
    - Estrogen and synthetic progestin: increased risk for breast cancer by 29% (CI: 1.02-1.18)
- Synthetic progestins have clear association with increased risk for breast cancer
  - Women's Health Initiative: MPA significantly increased risk for breast cancer (RR=1.26; CI: 1.00-1.59)
  - Lyytinen et al: combination estrogen and progestogen increases risk of breast cancer after 3 years (P<0.05)
  - Nurses' Health Study: 58,000 postmenopausal women were followed for 16 years (725,000 women-years)
    - Unopposed estrogen use increased risk for breast cancer by 25% (CI: 1.25-1.18)
    - Estrogen and synthetic progestin: increased risk for breast cancer by 29% (CI: 1.02-1.18)

Progesterone Literature Confusion

- "Progesterone abolishes estrogen and/or atorvastatin endothelium dependent vasodilatory effects". Atherosclerosis 2004
- This sounds like progesterone negates the beneficial effects of estrogen and/or atorvastatin
  - Look at the actual study....
  - And discover that they are talking about norethisterone

Fournier Study

- The most important study to date assessing risk using combinations of bioidentical estrogen and progesterone
  - 80,377 postmenopausal women
  - No increase or decrease in breast cancer in women on E2 and Progesterone. RR 1.0
  - E2 plus MPA (Provera) had RR of 1.69 or 69% increase in risk of breast cancer.
  - *Progestins are not Progesterone

Fournier A. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2007 Jan; 101(1)
Review Articles

  - ... indicating that the association of natural progesterone with estrogens confers less or even no risk of breast cancer as opposed to the use of other synthetic progestins

- JAOA Article 2011 - Bioidentical Hormones: An Evidence-Based Review for Primary Care Providers. Eileen Conaway, DO
  Conclusion: Bioidentical hormones that are approved by the FDA may be preferred over standard hormone replacement because of their physiologic benefits and safety profile

Progesterone

Progesterone and Norethisterone
Progesterone

- Decline begins 10 years before the onset of menopause
- Many women with symptoms of low progesterone get placed on antidepressant therapy during this time (age 30-50)

Functions of Progesterone in Women

- Regulation of blood sugar
- Builds bone
- Conversion of fat to energy
- Regulates thyroid activity
- Natural antidepressant
- Calming effect
- Important for fertility and is pro-gestational
- Promotes calming effect through GABA activation
- Fluid balance
- Promotes Th2 immunity
- Neuroprotective – promotes myelination
- Anti-inflammatory – relaxes smooth muscle
- Balances estrogen, counters proliferative effects of estrogen

Symptoms of Low Progesterone

- PMS
- Irritability
- Insomnia
- Anxiety
- Fluid Retention
- Bloating
- Breast Tenderness
- Anger
- Headaches
- Achy Joints
- Endometriosis, PCOS, Fibrocystic Breasts, Uterine Fibroids
- Menorrhagia
- Dysmenorrhea
- Many symptoms of low progesterone mimic those of estrogen dominance
Progesterone is beneficial to the cardiovascular system

• Coronary artery spasm, which increases the risk for heart attack and stroke, is reduced with the use of estrogen and/or progesterone.
  – Addition of MPA to estrogen has the opposite effect, resulting in vasoconstriction and increasing the risk for ischemic heart disease.

• Minshall et al. studied coronary hyperreactivity by infusing a thromboxane A2 mimetic in primates which were administered estrogen along with MPA or progesterone.
  – Estradiol given with progesterone protected coronary arteries against spasm but protective effect was lost when MPA was used instead.

• Miyagawa et al. compared reactivity of coronary arteries in primates pretreated with estradiol combined with either progesterone or MPA.
  – None of the animals treated with bioidentical progesterone experienced vasospasm while all of those treated with MPA showed significant vasospasms.


Progesterone Decreases Breast Cancer Risk

• Synthetic progestins increase BC risk.
• Progesterone decreases BC risk.
• Higher P4 in pregnancy 50% reduction in risk.
• Higher P4 during menstrual cycle premenopausal, 78% reduction in risk.


• Prospective study with 1083 women who were treated for fertility and follow for 13-33 years for breast cancer risk. Lowest progesterone levels were associated with 9.4 x the risk.

• Bioidentical progesterone decreased breast cell proliferation by 66%.

Progesterone is Neuroprotective

Progesterone Effects on Neurons

• Progesterone stimulates the release of dopamine in striatal tissue.
• Stimulates the release of GnRH from hypothalamic neurons after binding to specific sites on the cell membrane to affect movement and autonomic functions.
• Progesterone modulates oxytocin receptor binding in the hypothalamus.
• Progesterone inhibits opioid receptor binding.
• Progesterone effects the potentiation of GABA.
• Progesterone directs the incorporation of steroids into the cell membrane.

Progesterone dosing – pre-menopause

- Oral Progesterone 50-200mg QHS for two weeks in the luteal phase
  - Generally days 12-26
- May use 30-50mg days 1-13 if needed for mood stabilization
- Topical progesterone 20-100mg

*Note for conditions of more severe P/E imbalance (i.e. PCOS, endometriosis, menorrhagia) consider three weeks on and one week off

Progesterone lab work in pre-menopause

- Progesterone is best assessed between days 19-21 of the menstrual cycle using serum
  - Normal is somewhere between 2 and 30ng/ml
- Salivary baseline testing is interesting and may better capture peak progesterone if doing a 28 day salivary test

Progesterone dosing post-menopause

- Typically used to balance estrogen and for low progesterone symptoms such as insomnia, anxiety, irritability, and hot flashes
- Topical or oral with similar dosing to pre and peri-menopause
  - Oral 50-200mg
  - Topical 20-100mg
- Continued administration, no cycling. Some prescribers prefer to create “off days” to reset hormone receptors. Cycling with “off days” compared to continuous administration has not been studied
- “Off days” – may take weekends off, or take 3-5 days off at the end of each month (does not seem necessary with progesterone in my experience)
**Compounding Progesterone**

- **Oral progesterone Rx:**
  - 50-200mg Oral Micronized Progesterone capsules taken at bedtime
  - Alternative option: 100-200mg troche (SL lozenge) take ½ - 1 troche at bedtime (this option may save the patient money as the troches can be split in half)

- **Topical progesterone Rx:**
  - 10-50mg
  - Write as 200mg/ml for most cost savings to patient
  - Sig could then be something like 0.25 ml (50mg) topically as directed. Topical is less sedating so can use in AM or PM

**Progesterone Lab Work and Monitoring**

- Don’t chase numbers, but…
- P4 should be somewhere between 2-20 in serum follow up testing
- If taking progesterone at night as capsule or troche, AM draws are best. If using topical progesterone, test serum 2-12 hours after last administration
- Serum testing is especially useful if using oral progesterone and is generally predictable
- Salivary testing can be used if using topical progesterone, though is not standardized and different labs have different reference ranges
- In pre-menopause, it may be better to dose based on symptoms and titrate up until symptoms abate. Fatigue is generally the first sign that the dose may be too high. Some patients describe this as walking through sand in the morning. Lab work is less valuable here

**Estriol and Estradiol**

- Estriol
- Estradiol

---

9/26/2014
Estrogen function in the body

- Increases HDL and decreases LDL and triglycerides
- Maintains bone structure
- Increases serotonin
- Decreases fatigue
- Works as an antioxidant
- Maintains memory
- Helps absorption of calcium, magnesium and zinc
- Decreases arterial plaque
- Reduces cataracts
- Prevents Alzheimer’s disease
- Maintains skin collagen
- Maintains elasticity of the arteries
- Increases blood flow
- Improves sleep

Symptoms of Estrogen deficiency

- Hot flashes
- Osteopenia/osteoporosis
- Night sweats
- Fatigue
- Vaginal Dryness
- Dry, flat coarse hair
- Increased fine lines above the lip
- Poor memory and foggy thinking
- Low energy
- Depressed mood
- Decreased concentration
- Stress incontinence and Urinary tract infection

Advantages of using Estriol in combination with Estradiol in BHRT

- Estriol (E3) can bind preferentially to Estrogen Receptor (ER) beta and inhibit ER alpha
- Over-expression of ER alpha is associated with increased risk of breast cancer
- ER beta is protective of brain and cardiovascular function
- Low estriol levels associated with increased breast cancer
- Estriol inactivates cancer gene
Estrogen Administration – Problems with Oral Estradiol

- Topical, vaginal and pellet form of estrogen are superior to oral forms
- Oral estradiol can:
  - Increase blood pressure
  - Increase triglycerides
  - Increase estrone (E1) via CYP450 metabolism
  - Cause gallstones
  - Elevate liver enzymes
  - Increase SHBG (decreases testosterone)
  - Interrupt tryptophan metabolism and consequently serotonin metabolism
  - Lower Growth Hormone
  - Increase prothrombotic events
  - Increase CRP
  - Increase carbohydrate cravings

Topical Estradiol and Thromboembolism risk

- Transdermal estradiol with or without oral progesterone has no associated negative effect on coagulation or VTE.
  - This is a very different effect profile when compared to CEE and progestins.
- Canonico et al.: compared risk for VTE with different forms of HRT in 271 cases and 610 controls.
  - Transdermal estradiol and oral progesterone or pregnane derivatives were not associated with VTE risk (RR=0.7; CI:0.3-1.9 and RR =0.9; CI:0.4-2.3).

Benefits of Bio-Identical Estrogen

- E2 transdermal decreases IL-6 and TNF
- Estradiol improves vascular endothelial function
- Estradiol prevents bone loss
- E2 preserved tissue in mouse MI model
  - Estradiol preserves the integrity of ischemic tissue by augmenting the mobilization and incorporation of BM-derived EPCs into sites of neovascularization by eNOS-mediated augmentation of MMP-9 expression in the BM. Iwakura A, et al. Circulation. 2006 Mar 28;113(12):1605-14.
**Benefits of Bio-identical Estrogen**

- Estradiol prevents bone loss.

- Estradiol – natural antidepressant.

- Estradiol improves insulin sensitivity.

- E2 gel 0.0125mg daily reduced hot flashes and vaginal dryness.

- E2 lowers CRP.

**Estrogen Dosing - Vaginal**

- Vaginal administration has clear advantages.
  - Local and systemic effect
  - Less cream = cheaper
  - Better absorption
  - More predictable serum levels

- Vaginal dosing: 0.1mg of estradiol up to 0.5mg of estradiol total daily dose.
  - Example: Bi-est 80/20 15mg/ml. Sig 0.1ml PV daily = 1.2mg E3 and 0.3mg of E2 per 0.1ml.
  - 0.1ml is a small amount of cream and can be compounded in 1cc syringes. This is essentially 10x cheaper than using 1ml of cream.
  - My preference is for 50/50 bi-est which I typically write as E3/E2. An example is 2mg E3, 2mg E2 per ml. 0.1 ml PV OD. This creates little to no confusion for the pharmacist.
  - Half of the cream should be applied between the outer and inner labia and the other half should be applied intravaginally.
### Estrogen dosing - Troche

- Not my favorite due to issues with potentially swallowed oral estradiol (>50% is generally swallowed)
- Bi-est 80/20 or 50/50. Total estradiol dose should be between 0.25 and 2mg daily
  - Example: Biest 50/50 2mg per troche. Sig: ½ troche QD (1mg of estriol and 1mg of estradiol)
  - Another example: E3/E2 troche 1mg/1mg. ½ troche BID

### Estrogen dosing continued

- Can be used continuously or with “off days”
- Typical “off days” are weekends off or 3-5 days off at the end of the month
- E3 can be used by itself for vaginal dryness. Typically 1-3mg per ml. Use 1 ml vaginal cream.
  - Protocol is daily for two weeks then PRN
- Pellet – 12.5 – 25mg
- E3 is also wonderful in anti-aging skin creams for women. Typically 1mg per gram mixed with ALA, Vitamin C, DMAE, Co-Q10 etc.

### Estrogen Replacement – Lab work and Monitoring

- Serum estradiol should be between 15-150
  - I have noticed better results in the 30-100pg/ml
  - Some clinicians prefer ultrasensitive estradiol assays
- Get serum levels 2-12 hours after administration if using topical or vaginal creams
- Monitor estrone as well. Should be less than 100 pg/ml. High estrone may correlate to increased risk of breast cancer
- 2 4 16 OHE Estrone testing to check liver metabolism of estrogen.
  - 2-OHE1 “The good”
  - 4-OHE1 “The bad” – Causes DNA damage
  - 16-OHE1 “The ugly” – Strong estrogenic effect
  - 2:16 OHE1 ratio less than 2.0 indicate increased long term risk of breast, cervical, and other estrogen sensitive cancers
Testosterone

• Testosterone is needed for sense of well being
• Bone density
• Body composition
• Muscle mass and strength (especially upper body)
• Sex drive
• Maintains memory
• Helps prevent skin from sagging
• Decreases excess body fat
• Elevates nor-epinephrine in the brain (tricyclic effect)
• Sexual sensitivity (clitoral and nipple)
• Testosterone is lower in perimenopause and menopause

Testosterone Functions in the Body

Testosterone Deficiency in Women

• Muscle weakness
• Osteoporosis
• Low libido
• Poor recovery from exercise
• Declining sense of well being
• Low self esteem
• Thin lips
• Anxiety
• Sagging cheeks
• Droopy eyelids
• Dry, thin skin with poor elasticity
• Fatigue
Testosterone in Women - Studies

- Literature reviewing evaluation the safety of testosterone supplementation in women
  - "the predominant data shows that low dose T use is safe in regards to the breast and endometrium with experimental data suggesting a decrease in estrogen induced breast epithelial proliferation, and no adverse cardiovascular effects."


Testosterone in Women - Studies

- *Treat if low or low-normal and symptomatic
  - *Target range:
    - Total testosterone – 50-150 ng/dl
    - Free testosterone – 2-10 pg/ml
  - "many women feel better in the higher end of the range, though side effects may present themselves (acne, agitation, aggressiveness, facial hair growth, deepening voice)"

Testosterone Testing

- Serum testing:
  - Total testosterone - Reference range 10-80 ng/dl
  - Free Testosterone – Reference range 0.2 – 2.6 pg/ml
  - Treat if low or low-normal and symptomatic

- Target range:
  - Total testosterone – 50-150 ng/dl
  - Free testosterone – 2-10 pg/ml
Testosterone Dosing

- **Topical dosing** – 0.25-2mg total daily dose. Generally lipoderm base.
  - Example: Testosterone Lipoderm 2mg/ml. Sig ½ ml topicaly daily
- **Vaginal dosing** – 0.25-1mg total daily dose. Generally versa base
  - Example: 5mg/ml. Sig 0.1ml PV QD (0.5mg)
- **Troche** – 0.25-2mg total daily dose. Once daily or BID dosing. Troches have a shorter ½ life than creams
  - Example: Testosterone 2mg troche. Sig: ½ troche QAM
- **Pellet** – 50-200mg
- **Monitoring:** All levels can be checked 2-4 hours after administration

DHEA

**DHEA Functions in the Body**

- Decreases cholesterol
- Decreases formation of fatty deposits
- Prevents blood clots
- Increases bone growth
- Promotes weight loss
- Increases brain function
- Increases body mass
- Reduces oxidative stress and lipid peroxidation
- Reduces inflammation
- Activates immune system function
Low DHEA

- Low levels associated with
  - All cause mortality, Cardiovascular mortality
  - Obesity, Type 2 diabetes
  - Immune dysfunction
  - Autoimmune disease
  - Cancer
  - Hypertension
  - Cardiovascular disease
  - Depression and loss of well-being
  - Low libido, Erectile dysfunction
  - Osteoporosis


Physical Signs of DHEA deficiency

- Dry scalp/hair
- Loss of firmness of the cheeks
- Thinning under arm and pubic hair
- Abdominal obesity
- Other signs:
  - Decreased resilience to stress
  - Startled easily
  - Aversion to loud noises

DHEA supplementation

- Increase muscle strength and lean body mass
- Activate immune function
- Increase quality of life
- Improve sleep
- Increase feeling of well-being
- Decrease joint soreness
- Increase sensitivity of insulin
- Decrease triglycerides
- Stop the damaging effects of stress
- Elevate growth hormone levels
### DHEA and Osteoporosis

- DHEA 50 mg/d or placebo for 12 months
  - Improved hip BMD in older adults and spine BMD in older women.

  Jankowski CM, et al. Effects of DHEA Replacement Therapy on Bone Mineral Density in Older Adults: A Randomized, Controlled Trial. J Clin Endocrinol Metab. 2006 May 30

### DHEA – more studies


### DHEA – Lab work

- Serum DHEA-s reference range – very different ranges depending on the laboratory used. Some labs use age-specific ranges.
  - 15 - 19 years: 65 - 368
  - 20 - 24 years: 148 - 407
  - 25 - 34 years: 99 - 340
  - 35 - 44 years: 61 - 337
  - 45 - 54 years: 35 - 256
  - 55 - 64 years: 19 - 205
  - 65 - 74 years: 9 - 246
  - 75 years: 12 - 154

- Target level: 100-200
DHEA dosing

- Oral dosing for women 5mg – 25mg
- As DHEA converts to testosterone in women, higher doses may increase testosterone levels and could cause androgen related side effects (acne, facial hair growth, oily skin, hair loss etc)
- Typical dose is 5-10mg orally
- Topical dosing: 5-10mg daily dose
- Troche: 5-10mg daily dose
- Monitoring: Check serum DHEA-s

BHRT - Putting it all together

- E3/E2/T vaginal cream
  - Ex: 3/3.5 mg per .1ml PV M-F
- E3/E2/T topical cream
  - Ex: 1/1.2mg per ml. 0.5ml topical daily
- E3/E2/T troche
  - Ex: 1/1.2 mg per ml. ½ troche QAM
- Progesterone Capsule
  - Ex: 100mg QHS
- Progesterone Troche
  - Ex: 200mg troche. ½ troche QHS
- DHEA
  - Ex: 5mg oral DHEA QAM

Pellets

- Generally estradiol and testosterone pellets
- Use oral progesterone at bedtime to balance estradiol
- Two schools of thought – more testosterone less estradiol, or more estradiol less testosterone
- Dose ranges:
  - Testosterone 50mg-200mg
  - Estradiol 12.5mg – 25mg
- Pellets last 3-5 months
- Cost is sometimes similar to compounded hormone preparations
- Insurance does not cover procedure
- Extrusion happens 1-2% of the time
- If the dose is incorrect, you have problems
- Many women prefer how they feel with pellets over other HRT methods
### Common HRT issues

- **Yeast infection/UTI, vaginal irritation, skin irritation**
  - Change route, or base of cream
- **Complaint of fatigue – progesterone dose may be too high**
  - Decrease progesterone dose
- **Acne, agitation, deepening voice, more dark facial hair – likely too much testosterone**
  - Lower dose, or use Saw Palmetto, glucophage, or spironolactone
- **Breast tenderness, fluid retention or weight gain – E2 dose may be too high**
  - Balance E2/P. Decrease E2, or increase progesterone
- **Hot flashes**
  - Likely not enough estradiol
- **Persistant vaginal dryness**
  - Use E3 vaginal cream, or switch route of HRT to vaginal route
Topical Pain Management

Disclosure

- James Bui, RPh, has disclosed that he has financial interest or other relationship with the following:
  - Compounding pharmacist and Community Compounding Pharmacy

Overview

- Compounding & Pain Management
- Formulas & Indications
- Possible Formula Changes
- Managing Side Effects
- Pharmacist Counseling Points
- Other Topical Uses
- Cases
Pharmacy Compounding

“The art and science of preparing personalized medications for patients.”

(PCCA)

Pain Introduction

- Pain is unpleasant in sensory/emotional
- 1.5 billion people worldwide suffer from chronic pain
- 3-4.5% of global population suffer from neuropathic pain, increased with age
- Back pain is leading cause of American disability under 45 years of age


Categories of Pain

- Inflammatory: body response to tissue damage that potentiates pain
- Soft tissue: pressure ulcers, burns
- Intracranial pressure: brain tumor edema/hemorrhage
- Nociceptive: CNS/peripheral afferent pathways modulated via spinal cord
- Neuropathic: nerve destruction by disease
Pain Management

- Pain Assessment (local/systemic, acute/chronic)
- Choose pain control options appropriate for patient, family and setting
- Deliver interventions in timely, logical and coordinated fashion
- Empower and enable them to control their course to the greatest extent possible

Oral vs Topical Treatment in Pain

- Localized vs Systemic effect
  - “targeted” therapy, direct and concentrated
- Speed of effect
  - systemic bypass
- Systemic side effects
- Compounding
  - “individualized” therapy

Transdermal (Topical) Treatment

- Transdermal delivery allows solubilized drugs to penetrate tissue layers
- Gels form liposomes to carry the drug down between the cells of epidermis/dermis
- Direct drug delivery to site to minimize SE’s
- Confirmed research on peripheral site of action for many of these drugs
Common Topical Pain Agents

- **Absorption enhancers**: DMSO, menthol, camphor
- **Muscle relaxants**: cyclobenzaprine, baclofen, methocarbamol, orphenadrine
- **Anti-inflammatories**: diclofenac, ketoprofen, piroxicam, ibuprofen
- **Anesthetics**: lidocaine, tetracaine, benzocaine, bupivacaine
- **Neuromuscular**: ketamine, gabapentin, amantidine

Absorption Enhancers

DMSO (Dimethylsulfoxide) 5-10%
- Reversibly changes configuration of the protein structure of the stratum corneum
- Increasing thermodynamic activity of the drug
- Causes swelling in stratum corneum to induce formation of channels

Menthol 1%
- Disrupts stratum corneum lipid structure
- Fluidizes or perturbs integrity of barrier function of stratum corneum

Muscle Relaxants/Anti-Spasmodics

- **Baclofen** 2%
- **Cyclobenzaprine** 2%
- **Orphenadrine** 5%
- **Methocarbamol**

Can assist in the relief of:
- Low back pain and neck pain (BAC/CYC)
- Skeletal muscle spasms (BAC/CYC)
- Fibromyalgia (BAC)
- Myofascial Pain Syndrome (BAC/CYC)
- Acute painful musculoskeletal conditions (BAC/CYC)
- Whiplash (BAC/CYC)
**NSAID’s**

- Diclofenac 3%
- Ketoprofen 10%
- Piroxicam 3%

**Can assist in the relief of:**
- OA and RA
- Postoperative pain
- Mild pain due to inflammation and tissue injury
- Tendonitis
- Sprains and Strains
- Sports or overuse-type injuries

---

**Topical Diclofenac**

- Commercially available products:
  - Voltaren® 1% gel
  - Solaraze® 3% gel
  - Pennsaid® 1.5% in 45.5% DMSO solutions
  - Flector® 1.3% patch
- Approved for use in osteoarthritis as monotherapy
- Acute pain due to minor strains, sprains, and contusions
- Good absorption into hands and knees
- “Very low plasma levels—minimal adverse effects
- 33% of patients report dry skin with Pennsaid®
- Similar efficacy to oral diclofenac in 12 week trial.

---

**Oral NSAIDS: Concerns**

- Renal, GI and CV adverse events (blood pressure, ulcers, kidney disease)
- Drug interactions: warfarin, SSRI’s, anti-hypertensives
- Limited use in elderly patients: more sensitive to adverse events, increased risk of GI bleeds
**NSAID Research**

- Review of 3455 subjects showed good pain reduction results with few systemic adverse effects
  - Ibuprofen, ketoprofen, diclofenac, and piroxicam
- Review of 47 studies with 5512 subjects
  - Topical NSAID’s demonstrated good pain relief/reduction
  - Rate of systemic adverse effects same as placebo
- Topical ibuprofen 5% gel for chronic knee pain for 12 month was as beneficial vs. oral therapy with fewer adverse effects.


**American College of Rheumatology 2012 Recommendations regarding NSAIDS**

- Arthritis Care and Research
- Vol.64, No.4, April 2012, pp 465-474

Hand Osteoarthritis
- “We conditionally recommend that persons greater or equal to 75 years should use topical rather than oral NSAID’s. In persons less than 75 years, the therapeutic expert panel expressed no preference for using topical rather than oral NSAID’s.”
- Topical NSAID’s were listed as an option for knee and hip OA as well.

**LOCAL ANESTHETICS**

- **Lidocaine 5% / Tetracaine 2%**
  - Used to numb the site of pain
  - Present in all combinations of our creams
    - A local anesthetic causes reversible local anesthesia and a loss of nociception.
    - **MOA**
      - Alters signal conduction in neurons by blocking the sodium channels in the neuronal cell that are responsible for signal propagation.
NEUROPATHIC PAIN

- Ketamine 10% (NMDA-antag, peripheral mu)
- Gabapentin 6% (GABA-ag, Ca-channels)
- Amitriptyline 3% (presynaptic reuptake inhibitor)
- Imipramine 3% (presynaptic reuptake inhibitor)
- Orphenadrine 5% (Norflex) (NMDA-antag)

KETAMINE 5-10%

- Noncompetitive NMDA (N-methyl-D-aspartate) receptor antagonist
- Primary research and practice have proven it an effective medication in treating neuropathic pain
- No high or euphoria when used topically

KETAMINE

- General neuropathy
- Musculoskeletal pain & inflammation
- Postherpetic neuralgia
- Complex Regional Pain Syndrome
- Diabetic and chemo induced neuropathy
- Failed back syndrome
- Fibromyalgia
- Phantom limb pain
Ketamine Literature

- Analgesia is dose-dependent
- Double blind placebo controlled cross-over of 20 patients with complex regional pain syndrome.
  - ketamine plasma levels were below detectable limits
- Ketamine 10% cream inhibited allodynia and hyperalgesia.


Ketamine Literature

  - A total of 854 patient charts were reviewed. Twenty-one patients with symptoms, signs and/or a documented diagnosis of neuropathic pain were given a prescription of a transdermal preparation containing Lidocaine and Ketamine.
  - Transdermal cream containing Ketamine and Lidocaine was effective in 73% of patients with acute neuropathic pain and may be a good alternative to oral medications.

Formulas & Indications

ANTI-INFLAMMATORY: Osteoarthritis, Plantar Fasciitis, Bursitis, Tendonitis, Sports injuries/overuse...
- Diclofenac 3%, Baclofen 2%, Cysteobenzaprine 2%, Piroxicam 3%, Tetracaine 2% (7491)

NEUROPATHIC: general neuropathy
- Ketamine 5%, Baclofen 2%, Cysteobenzaprine 2%, Gabapentin 6%, Lidocaine 5% (9460)

Formulas & Indications cont.

COMBINATION NEUROPATHIC & ANTI-INFLAMMATORY: fibromyalgia, back pain, diabetic neuropathy, post-herpetic neuralgia etc

Basic
- Diclofenac 3%, Baclofen 2%, Cysteobenzaprine 2%, Gabapentin 6%, Tetracaine 2% (7494)

Advanced
- Ketoprofen 10%, Ketamine 10%, Gabapentin 6%, Cysteobenzaprine 2%, Lidocaine 5% (8701)
- Ketamine 10%, Cysteobenzaprine 2%, Diclofenac 3%, Gabapentin 6%, Orphenadrine 5%, Tetracaine 2% (7469)

Pregnancy/Breastfeeding

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>X, not established</td>
<td>Uncertain</td>
<td>Uncertain</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>X, limited</td>
<td>Y, usually</td>
<td>Y, usually</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>C, limited</td>
<td>Y, usually</td>
<td>Y, usually</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td>C</td>
<td>Y</td>
<td>Y</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cysteobenzaprine</td>
<td>C</td>
<td>Y</td>
<td>Y</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>C</td>
<td>Y</td>
<td>Y</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>C</td>
<td>Y</td>
<td>Y, usually</td>
<td>Maternal survival in breast feeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>C</td>
<td>Uncertain</td>
<td>Uncertain</td>
<td>Consider benefits vs risks?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case Study #1

AB is a 31y/o F with post-op C-section pain. She takes IBU 800mg TID and is having continued pain. She is breastfeeding and does not want to take controlled substances that may be passed on to her infant. She comes to your office today requesting alternative treatment options.

Case Study #1 (cont.)

AB - Post-Op C-section Pain
Which formula would you recommend?
- Ketamine 5%, Baclofen 2%, Cyclobenzaprine 2%, Gabapentin 6%, Lidocaine 5%
- Diclofenac 3%, Baclofen 2%, Cyclobenzaprine 2%, Piroxicam 3%, Tetracaine 2%
- Ketamine 10%, Cyclobenzaprine 2%, Diclofenac 3%, Gabapentin 6%, Orphenadrine 5%, Tetracaine 2%

Case Study #1 (cont.)

AB - Post C-section Op Pain
Which formula would you recommend?
- Ketamine 5%, Baclofen 2%, Cyclobenzaprine 2%, Gabapentin 6%, Lidocaine 5%
- Diclofenac 3%, Baclofen 2%, Cyclobenzaprine 2%, Piroxicam 3%, Tetracaine 2%
- Ketamine 10%, Cyclobenzaprine 2%, Diclofenac 3%, Gabapentin 6%, Orphenadrine 5%, Tetracaine 2%
Possible Formula Changes

*ANYTHING can be added in or removed

**Anti-inflammatories**
- Ketoprofen 5-15% (max 20%)
- Diclofenac 1-3% (max 5%)

**Neuroleptics**
- Ketamine 5-15% (max 15%)
- Gabapentin 6-8% (max 15%)
- Amitriptyline 1-3% (max 5%)

**Anesthetics**
- Lidocaine 2-5% (max 6%)
- Tetracaine 2% (max 4%)
- Bupivacaine 1-2% (max 3%)

**Muscle Relaxants**
- Baclofen 2-5% (max 5%)
- Cyclobenzaprine 2-5% (max 5%)

**Total powder volume should be < 40% for best results**

Case Study #1 (cont.)
AB has been using pain cream and presents with an exacerbated pain in surgical area and post-Op. She requests a stronger cream. What would you recommend?
- Current formula:
  - Ketamine 10%, Cyclobenzaprine 2%, Diclofenac 3%, Gabapentin 6%, Orphenadrine 5%, Tetracaine 2%

Case Study #2
BF is a 67 y/o female s/p LTKR presenting with L knee pain she reports swelling and intermittent numbness. She does not tolerate NSAIDS secondary to stomach ulcers.
- Which formula would be appropriate for BF?
  - Diclofenac 3%, Baclofen 2% Cyclobenzaprine 2%, Gabapentin 6%, Tetracaine 2%
  - Ketamine 5%, Baclofen 2%, Cyclobenzaprine 2%, Gabapentin 6%, Lidocaine 5%
  - Diclofenac 3%, Baclofen 2%, Cyclobenzaprine 2%, Piroxicam 3%, Tetracaine 2%
Case Study #2 (cont.)

BF is a 67 y/o female s/p LTKR presenting with L knee pain. She does not tolerate NSAIDS secondary to stomach ulcers.

- Current formula: Diclofenac 3%, Baclofen 2% Cyclobenzaprine 2%, Gabapentin 6%, Tetracaine 2% — possible changes?
- Alternative formula: Ketamine 10%, Cyclobenzaprine 2%, Diclofenac 3%, Gabapentin 6%, Orphenadrine 5%, Tetracaine 2% — possible changes?

Managing Side Effects

- The pain creams are generally well tolerated when used as directed.
- When a patient reports side effects (drowsiness, dizziness, etc) it is most often a result of overuse or enhanced absorption:
  - applied heat, reduced skin barrier, prolonged skin contact (DMSO)

Managing Side Effects (cont.)

Mild irritation and dryness of the skin
- Manage by wiping skin clean 1 hour after applying the cream followed by applying moisturizer.

Rash
- Occurs in about 1-3% of patients in our experience. Can be delayed reaction. May need treatment with topical steroid.
- If delayed rash, consider giving patient a trial without DMSO after initial rash has completely resolved.
Pharmacist Counseling Points

- Review: allergies, area of application
- Usual SIG: 1-2 pumps AA TID-QID
- Gloves recommended
- Rub cream in for 1-2 minutes, until dry
  - Piroxicam, Nifedipine - yellow color
- No bandages, heating pads, ice, other creams or lotions to treatment area
- Call if any concerns or questions.

Other Topical Uses

- Migraines
- Menstrual cramps
- Gynecological Pain (Gabapentin/lidocaine)
- Sexual enhancement (Oxytocin)
- Scar/Post-Surgical/Wound

Thank You!