



*"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."*



# Neuropathic Pain – What Can a Compounding Pharmacy Offer?

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# Disclosure

- Scott Groen has no financial relationships with the WRHA to disclose
- Scott Groen does not receive any compensation from any pharmaceutical or medical device company
- Scott Groen is an employee of Tache Pharmacy, a privately owned independent pharmacy in Winnipeg

# Goals and Objectives

- Acquire a basic understanding of transdermal drug delivery
- Determine the potential advantages of utilizing the transdermal route
- Identify medications that may be used transdermally for neuropathic pain treatment, and some specific examples for some specific situations
- Identify some other alternate dosages forms for neuropathic pain treatment available from a compounding pharmacy

# Cost of Chronic Pain

- Quality of Life
  - Physical functioning
  - Ability to perform activities of daily living
  - Work
  - Recreation
- Social Consequences
  - Marital/family relations
  - Intimacy/sexual activity
  - Social isolation
- Psychological Morbidity
  - Depression
  - Anxiety, anger
  - Sleep disturbances
  - Loss of self-esteem
- Socioeconomic Consequences
  - Healthcare costs
  - Disability
  - Lost workdays

# Neuropathic Pain: Issues and Challenges

- Neuropathic pain is often under assessed and under treated
- Complex pathophysiology
  - Multiple mechanisms of pain
  - Emotional element to pain
  - Some clinicians may doubt pain is “real” if there is no apparent tissue damage
  - Different patients will respond differently to treatments

# Features of Neuropathic Pain

| Component                                                                                                                                                                             | Descriptors                                                                                                                                                                                                                                                                       | Examples                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| <p>Steady,<br/>Dysesthetic –An unpleasant<br/>abnormal sensation<br/>produced by normal stimuli</p>  | <ul style="list-style-type: none"> <li>• Burning, Tingling</li> <li>• Constant, Aching</li> <li>• Squeezing, Itching</li> <li>• Allodynia – Pain due to a stimulus that does not normally provoke pain</li> <li>• Hyperesthesia - Increased sensitivity to stimulation</li> </ul> | <ul style="list-style-type: none"> <li>• Diabetic neuropathy</li> <li>• Post-herpetic neuropathy</li> </ul>                    |
| <p>Paroxysmal,<br/>Neuralgic</p>                                                                   | <ul style="list-style-type: none"> <li>• Stabbing</li> <li>• Shock-like, electric</li> <li>• Shooting</li> <li>• Lancinating</li> </ul>                                                                                                                                           | <ul style="list-style-type: none"> <li>• Trigeminal neuralgia</li> <li>• May be a component of any neuropathic pain</li> </ul> |
|                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                   |                                                                                                                                |

# Common Peripheral Neuropathies

- Diabetic Neuropathy
- Postherpetic Neuralgia
- Complex regional pain syndrome
- Mechanical neuropathies
  - Entrapment neuropathies
  - Nerve compressions
- HIV-related sensory neuropathy
- Idiopathic sensory neuropathy
- Phantom limb
- Posttraumatic neuralgias
- Trigeminal neuralgia
- Cancer-chemotherapy-induced neuropathies

# Case Study

- P.N. – a 70 year old female with a history of shingles
- Has developed postherpetic neuralgia
  - Has had the pain in the area of the shingles outbreak for 4 months – just below the breast on the right side and extending towards her side in a dermatomal distribution
- Very painful to touch
  - Describes the pain as a 7-8/10 most of the time on the Visual Analog Scale
  - Sometimes goes up to 9 or 10 (a described as a “stabbing” feeling)

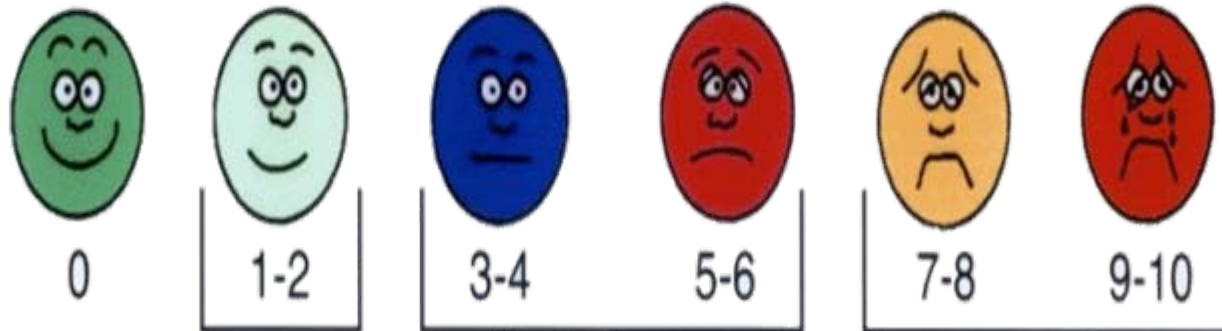
# Case Study

- Tried gabapentin
  - Could not tolerate drowsiness even at lowest dose
- She has reached her deductible & will not try pregabalin (“not covered by Pharmacare”)
- Tried amitriptyline
  - Her mouth was too dry, made her tired, and it didn’t seem to help
- Does not want to be constipated from morphine or codeine
  - Refused early acetaminophen & codeine treatment, which may have controlled the pain or prevented the escalation
- Has only been using acetaminophen 500mg 2 tabs q6h

# UNIVERSAL PAIN ASSESSMENT TOOL

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs.

Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.



WONG-BAKER  
FACIAL  
GRIMACE SCALE

MILD

MODERATE

SEVERE

ACTIVITY  
TOLERANCE  
SCALE

NO  
PAIN

CAN  
BE  
IGNORED

INTERFERES  
WITH  
TASKS

INTERFERES  
WITH  
CONCENTRATION

INTERFERES  
WITH BASIC  
NEEDS

BEDREST  
REQUIRED

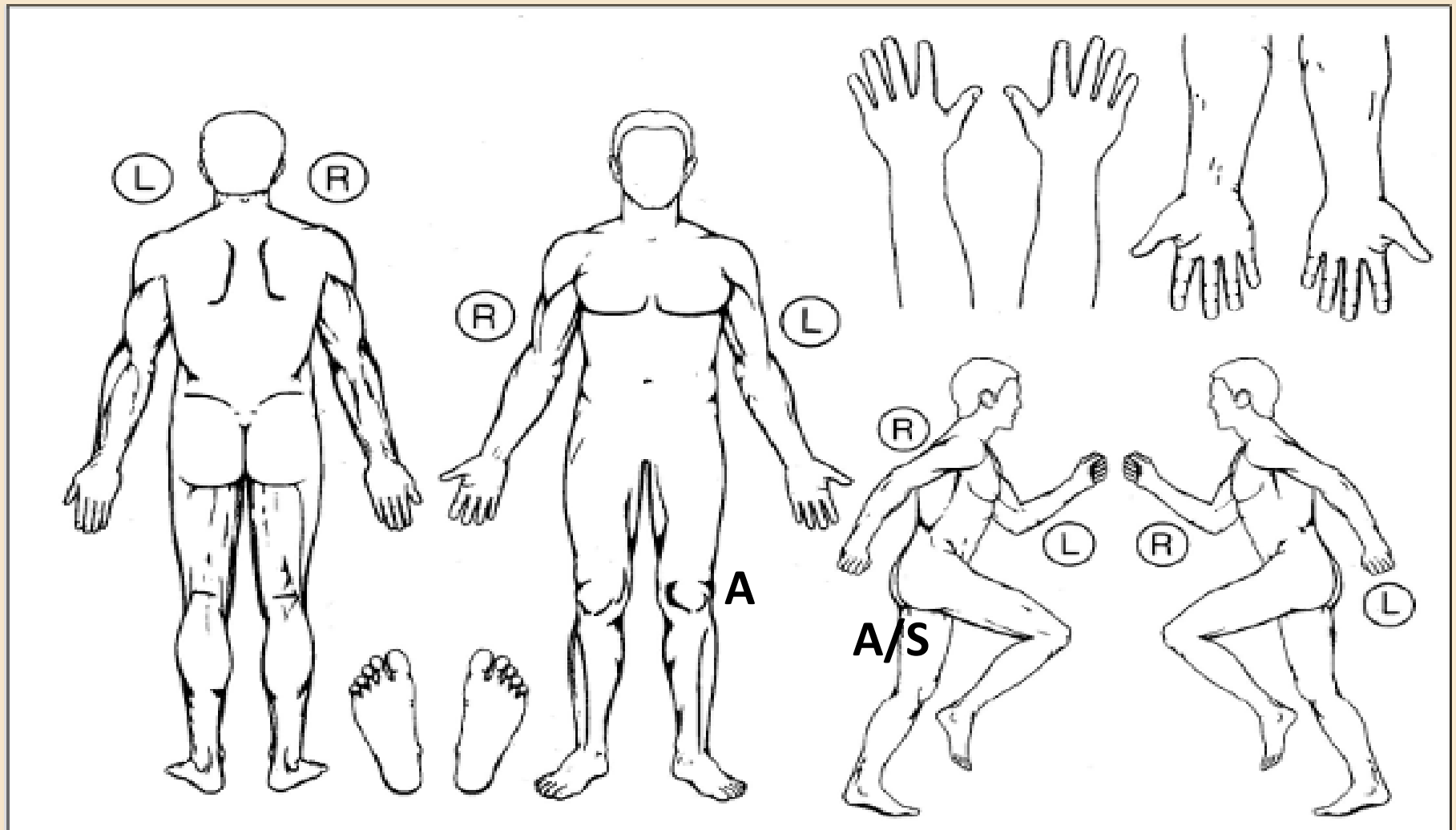
## Brief Pain Inventory (Short Form) - Modified

Name \_\_\_\_\_

Date \_\_\_\_\_

On the diagram below, shade in the areas where you feel pain. Put an "X" on the areas where it hurts the most. (*S=sharp/stabbing, B=burning, N=numbness, P=pins and needles, A=aching, Arrows = shooting pain.*)

*Use colours if you have more than one type of pain)*



What things make your pain feel worse?

What things make your pain feel better?

What treatments or medications are you currently receiving for your pain?

Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.

|            |   |   |   |   |   |   |   |   |   |   |    |                                  |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|
| No<br>pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst pain<br>you can<br>imagine |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|

Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.

|            |   |   |   |   |   |   |   |   |   |   |    |                                  |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|
| No<br>pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst pain<br>you can<br>imagine |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|

Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**.

|            |   |   |   |   |   |   |   |   |   |   |    |                                  |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|
| No<br>pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst pain<br>you can<br>imagine |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|

Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW**.

|            |   |   |   |   |   |   |   |   |   |   |    |                                  |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|
| No<br>pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst pain<br>you can<br>imagine |
|------------|---|---|---|---|---|---|---|---|---|---|----|----------------------------------|

In the last 24 hours, how much relief have your pain treatments or medications provided?

Please circle the one percentage that shows most how much **RELIEF** you have received.

|           |    |     |     |     |     |     |     |     |     |     |      |                 |
|-----------|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----------------|
| No relief | 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% | Complete relief |
|-----------|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----------------|

Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

**A. General Activity:**

Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

**B. Mood:**

Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

**C. Walking Ability:**

Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

**D. Normal Work (includes both work outside the home and housework)**

Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

**E. Relations with other people:**

Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

**F. Sleep:**

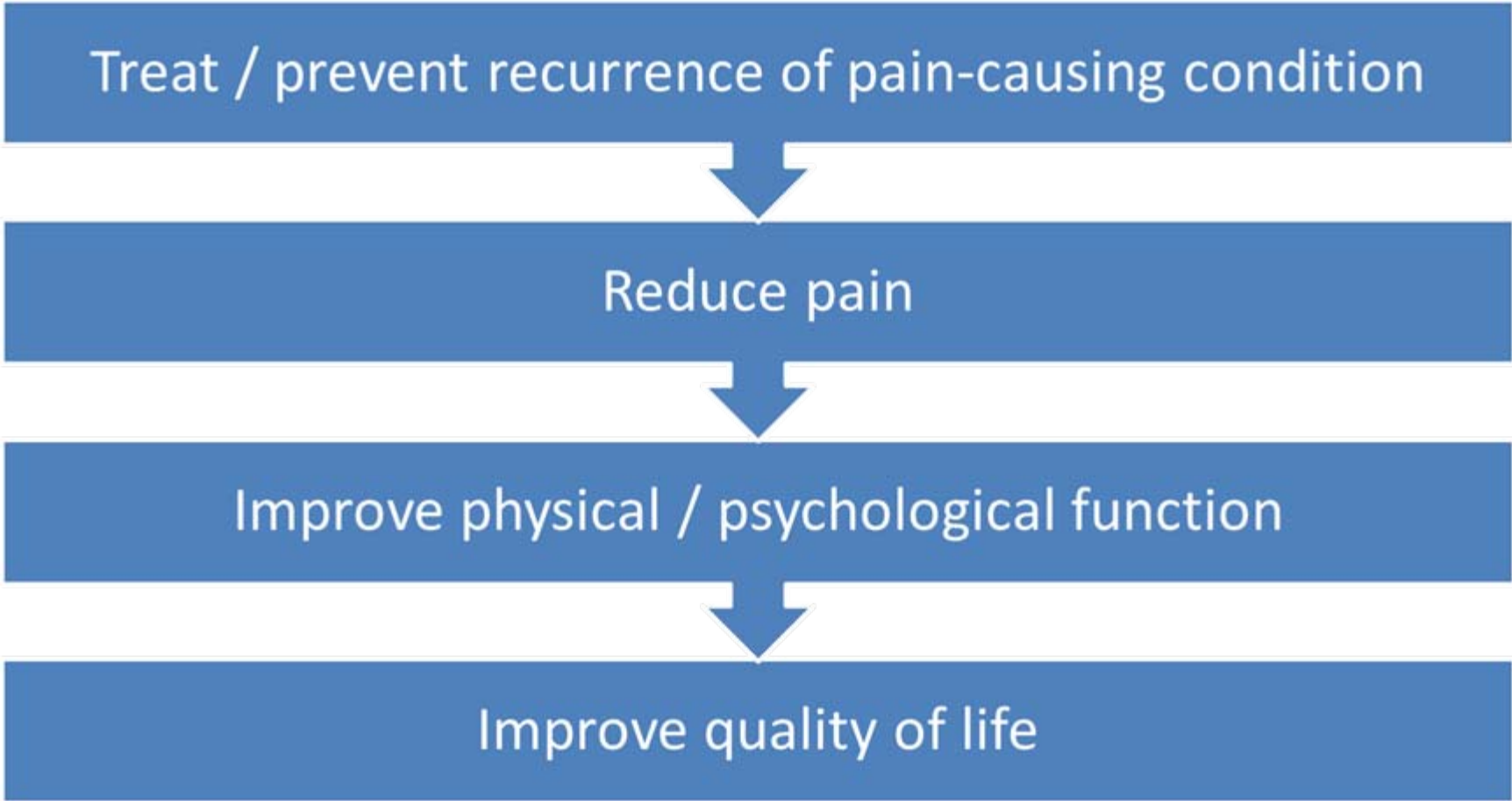
Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

**G. Enjoyment of Life:**

Does not interfere    0    1    2    3    4    5    6    7    8    9    10    Completely interferes

# Goals of Neuropathic Pain Management

Treat / prevent recurrence of pain-causing condition



```
graph TD; A[Treat / prevent recurrence of pain-causing condition] --> B[Reduce pain]; B --> C[Improve physical / psychological function]; C --> D[Improve quality of life];
```

Reduce pain

Improve physical / psychological function

Improve quality of life

# Biochemical Individuality



# What is Compounding?

- Compounding is the art and science of customizing medications to fit the needs of the individual patient
- The standard methods of delivery, dosage form, strength and flavour can all be adjusted to suit the needs of the patient

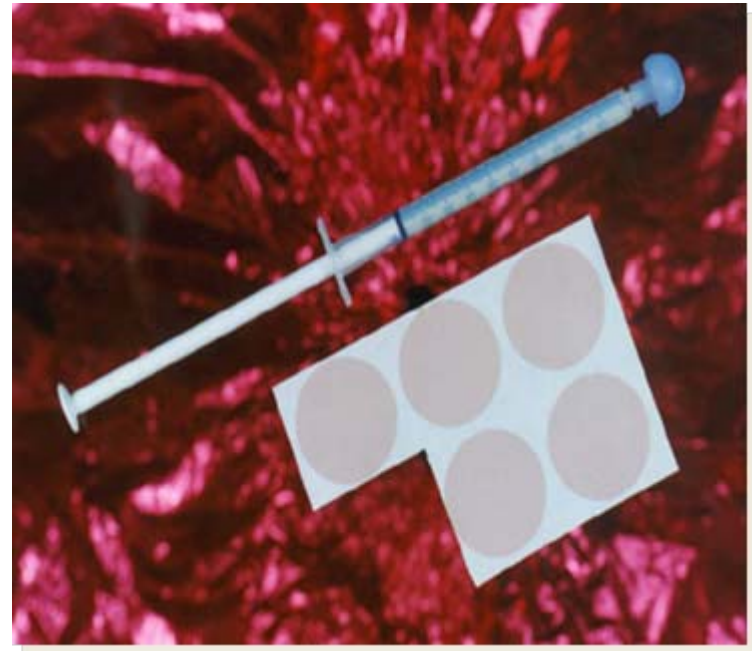
# Customized Compounding – Helping patients from a different perspective

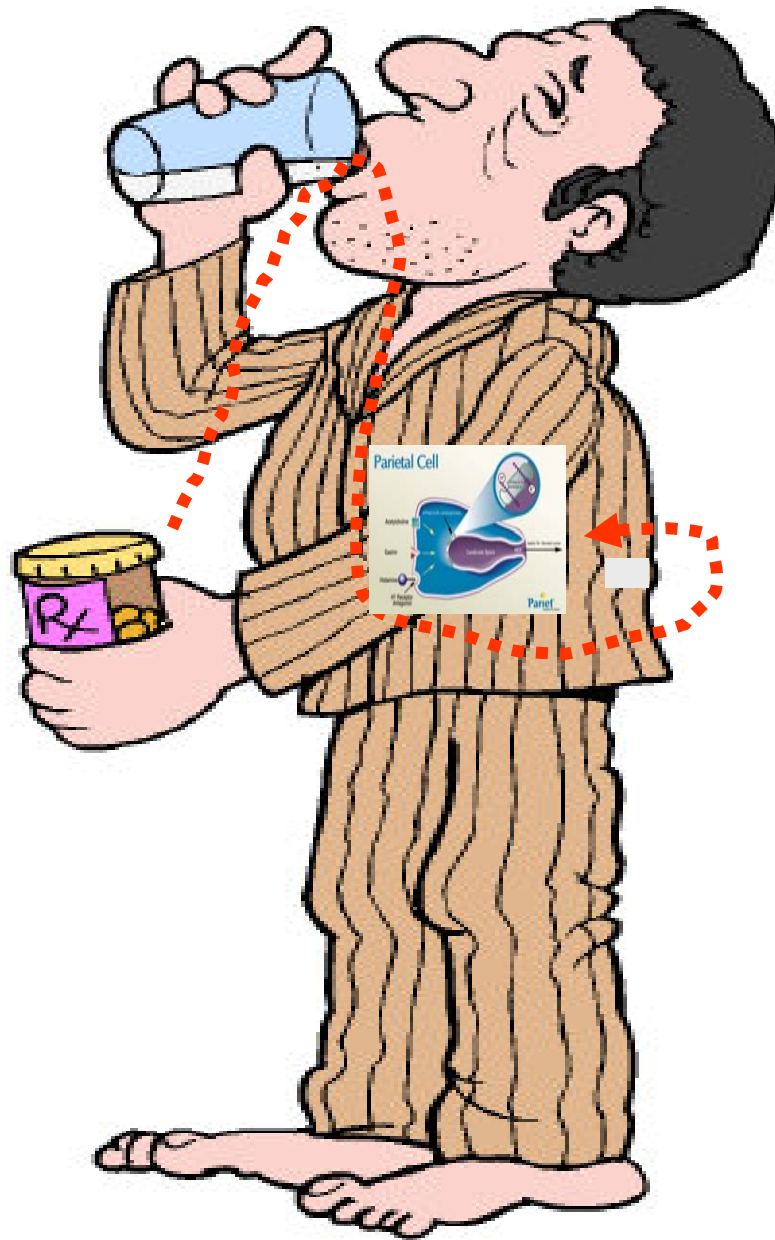
t h i n k i n g



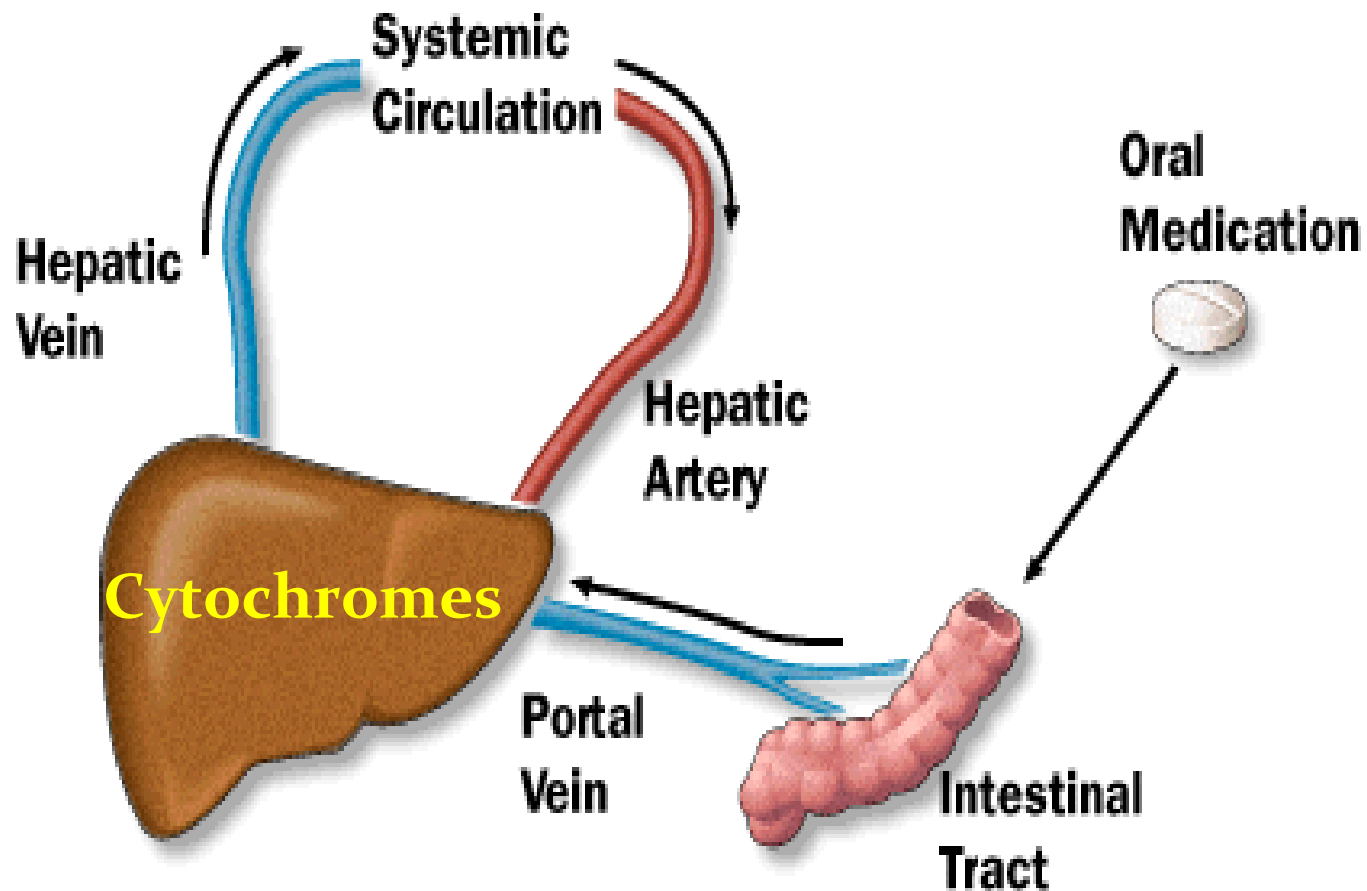
# How Can Compounding Help?

- Compounding is the art and science of preparing customized medications
  - Alternate dosage forms
    - For example, a transdermal may provide targeted treatment with optimal results and less GI irritation
  - Combined formulations
    - A variety of medications mixed synergistically to help address pain
  - Strength variations
    - Because patients vary in size, symptoms and pain tolerance





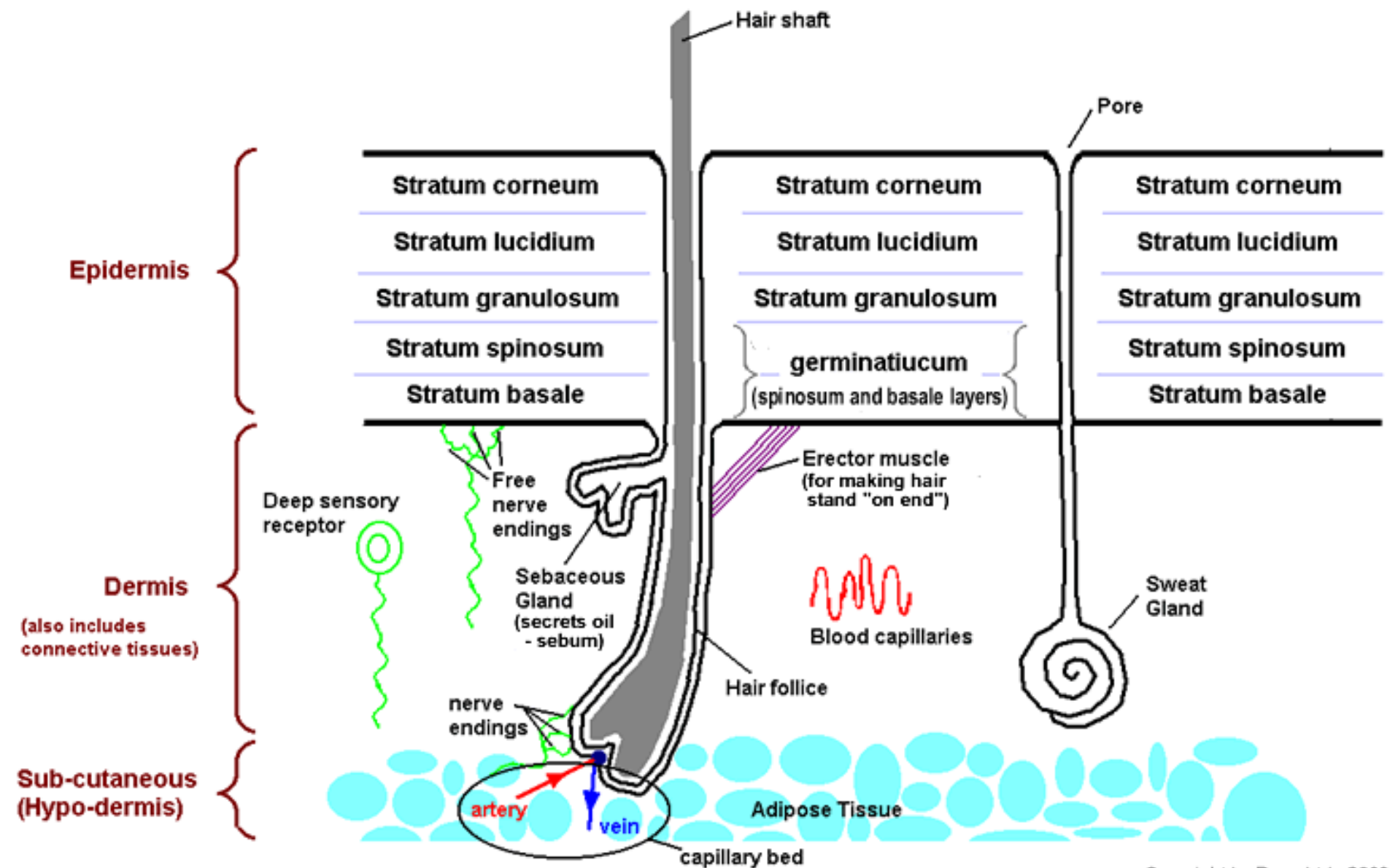
# Metabolism



# Factors for Drug Absorption Transdermally

- Transcutaneous flow of compounds across the stratum corneum is directly proportional to the concentration gradient & therefore can be attributed to passive diffusion
- As surface area  $\uparrow$  & thickness of epidermis  $\downarrow$ , the rate of transdermal flux  $\uparrow$
- The underlying epidermal layers & the dermis area are an aqueous environment

# The Structure of Skin



# Factors for Drug Absorption Transdermally

- Highly hydrophilic drugs will absorb poorly through the stratum corneum but better in the aqueous layers of the epidermis
- Highly lipophilic drugs will absorb better through the stratum corneum, which is composed of a lipid-heavy intercellular matrix, but slowed when they reach the aqueous layers of epidermis

# Factors for Drug Absorption Transdermally

- Highly hydrophilic drugs will absorb poorly through the stratum corneum but better in the aqueous layers of the epidermis
- Highly lipophilic drugs will absorb better through the stratum corneum but slowed when they reach the aqueous layers of epidermis

# Site Permeability

- Generalized rank order of site permeabilities (i.e. Where better absorption may occur):
  - genitals > head/neck > trunk > arm > leg
  - Preterm infant > term infant > young adult > elderly

Klein & colleagues,. Transdermal Clonidine Therapy in Elderly Mild Hypertensives;  
Hypertension Suppl 1985;3;581-584

# Finding a Suitable Carrier

- For compounds used exclusively for the treatment of a skin condition, passive diffusion into the superficial epidermis may be sufficient
  - Using a vehicle such as Glaxal Base© or Vaseline©
- For a drug to be delivered deeper or to the general circulation, the drug/vehicle must maintain affinity for both aqueous and lipid environments to absorb effectively

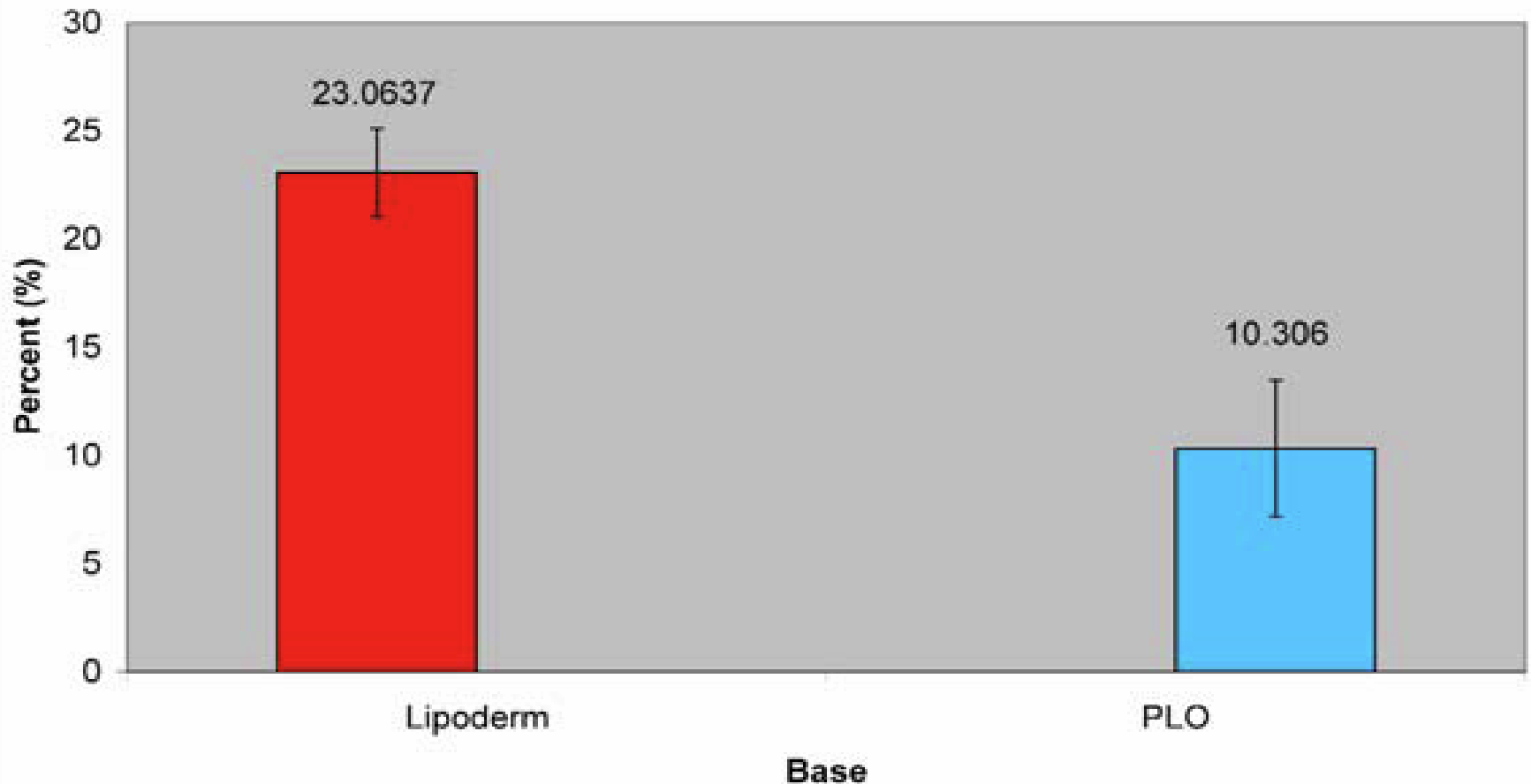
# PLO or Diffusimax<sup>®</sup>

- PLO – Pluronic Lecithin Organogel
  - Pluronic → hydrophilic phase
  - Lecithin Isopropyl Palmitate → lipophilic phase
  - Mixing Pluronic Gel & Lecithin Isopropyl Palmitate under pressure (with the drug) will form an amphiphilic phase containing drug micelles
- Was the gold standard → available at many Rx
  - Note: not all pharmacies can mix the drug into it properly
- Provides good penetration into skin
- Works well with a variety of lipophilic/hydrophilic agents
- Need to rub in well
- “Greasy” base → can leave a “tacky” feeling
- The 2 phases can separate under cold conditions
  - Ideal storage between 15°C – 25°C

# Lipoderm®

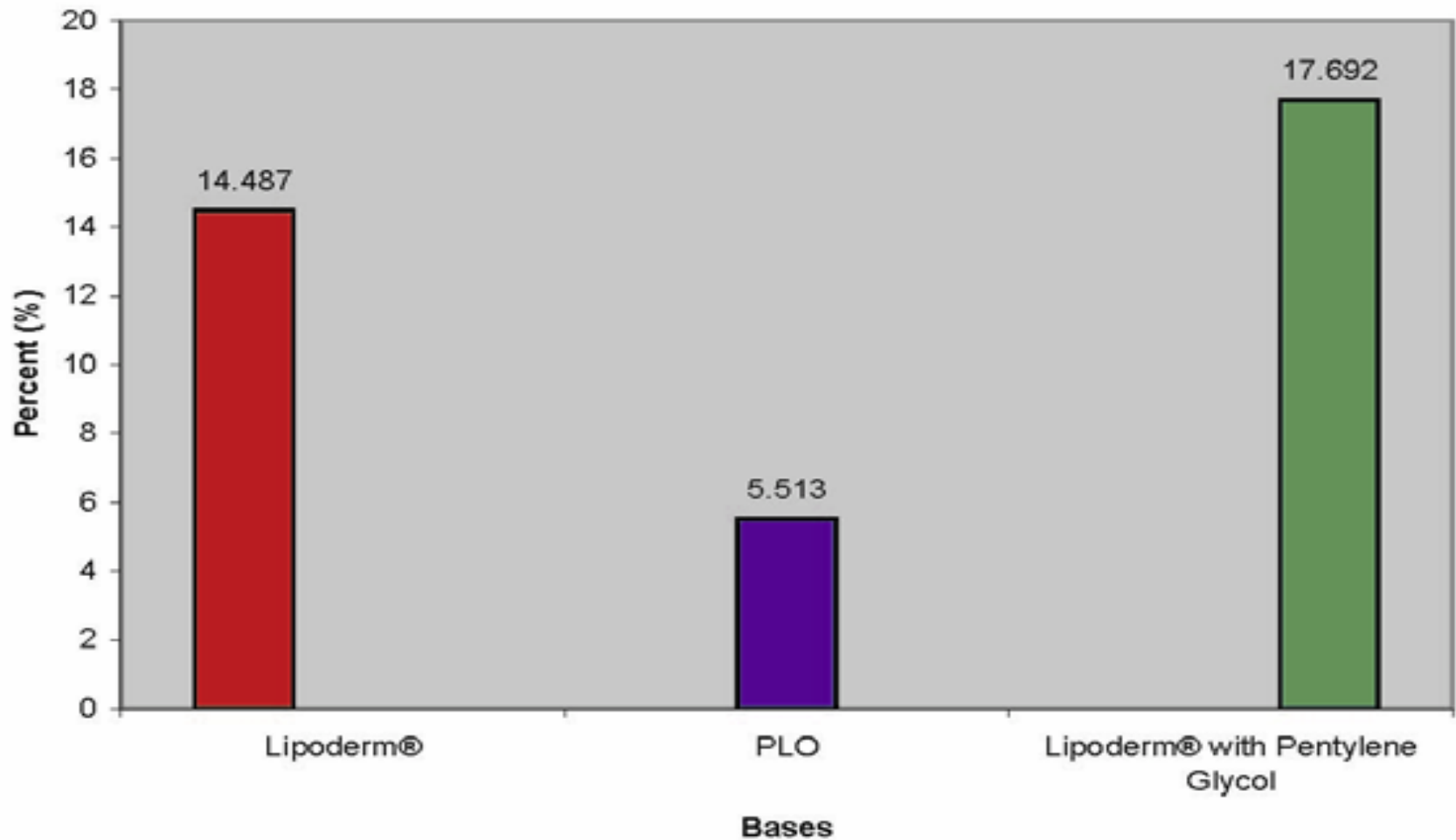
- Lipoderm
  - Creamier base than PLO
    - Cosmetically more elegant
    - Less sticky
    - Less smell
  - Not as temperature sensitive as PLO
    - Cold temperatures PLO may separate
  - Less chance of rash vs. PLO
  - Improved absorption of medication
  - Only compounding pharmacies belonging to PCCA have availability to this

## Percent Permeation of Promethazine HCL Through the Stratum Corneum



The percent of applied dose that penetrated past the Stratum Corneum with PCCA Lipoderm® was 2.24 times more than PLO.

## Percent Permeation of Ketoprofen Through Human Skin & into Receptor Solution after Single Application



Percent of applied ketoprofen dose that was delivered completely through human skin *in vitro* was *significantly better with PCCA Lipoderm®* versus PLO.

# Why Try the Topical/Transdermal Route?

- Oral route not desirable or not available
  - Inability to swallow
  - Mucositis
  - Nausea/vomiting
- Can be used to obtain a localized or a systemic effect
- Lowers systemic absorption when choosing to apply for a local effect
- Sites with high vascularity → good systemic absorption
  - Inner part of the wrist, behind the ears, over carotid artery, large volumes applied over major muscles

# Topical vs. Transdermal

- Topical
  - Looking for a delivery system to act locally
  - Superficial, low penetration
  - Minimizes systemic effects
  - E.g. hydrocortisone on the site of a rash

# Topical vs. Transdermal

- Transdermal
  - Looking for a delivery system to act systemically or to penetrate deeper to get local peripheral action
  - For systemic action, apply to inside of the wrist, behind the ear, carotid artery, femoral artery
  - For local action, apply at the site of pain, the site of the original injury, the corresponding dermatome, and any trigger point location
  - E.g. fentanyl patch, nicotine patch, scopolamine gel, ketamine cream

# Advantages of Transdermal Pain Compounds

- Various medications and concentrations
- Direct delivery to pain receptors
- Avoid first-pass effect & reduces organ toxicity
- Rapid termination & likely to produce fewer side effects
- Lowers adverse drug interactions
- Minimizes abuse and addiction
- Reduces opioid tolerance
- Potential greater effectiveness and results for a localized pain
- May improve patient compliance

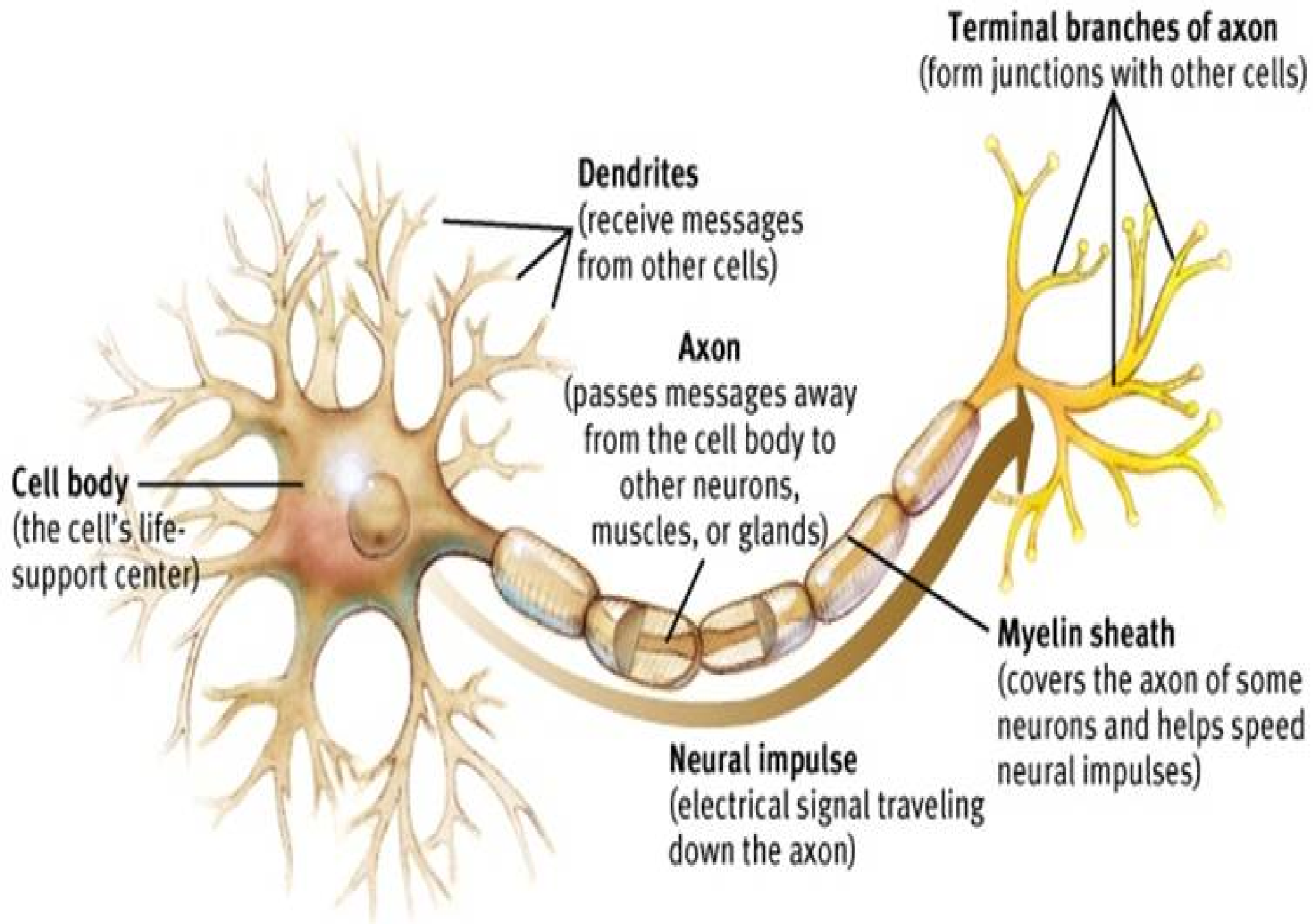
# Advantages of Transdermal Formulations

- Bioavailability of transdermal NSAID reported to be generally less than 5 – 15% in sites with lower absorption
- Drug concentration at the site of administration can be 30 fold higher than with an oral dose
- Decreased potential for systemic side effects when targeting specific areas with a transdermal

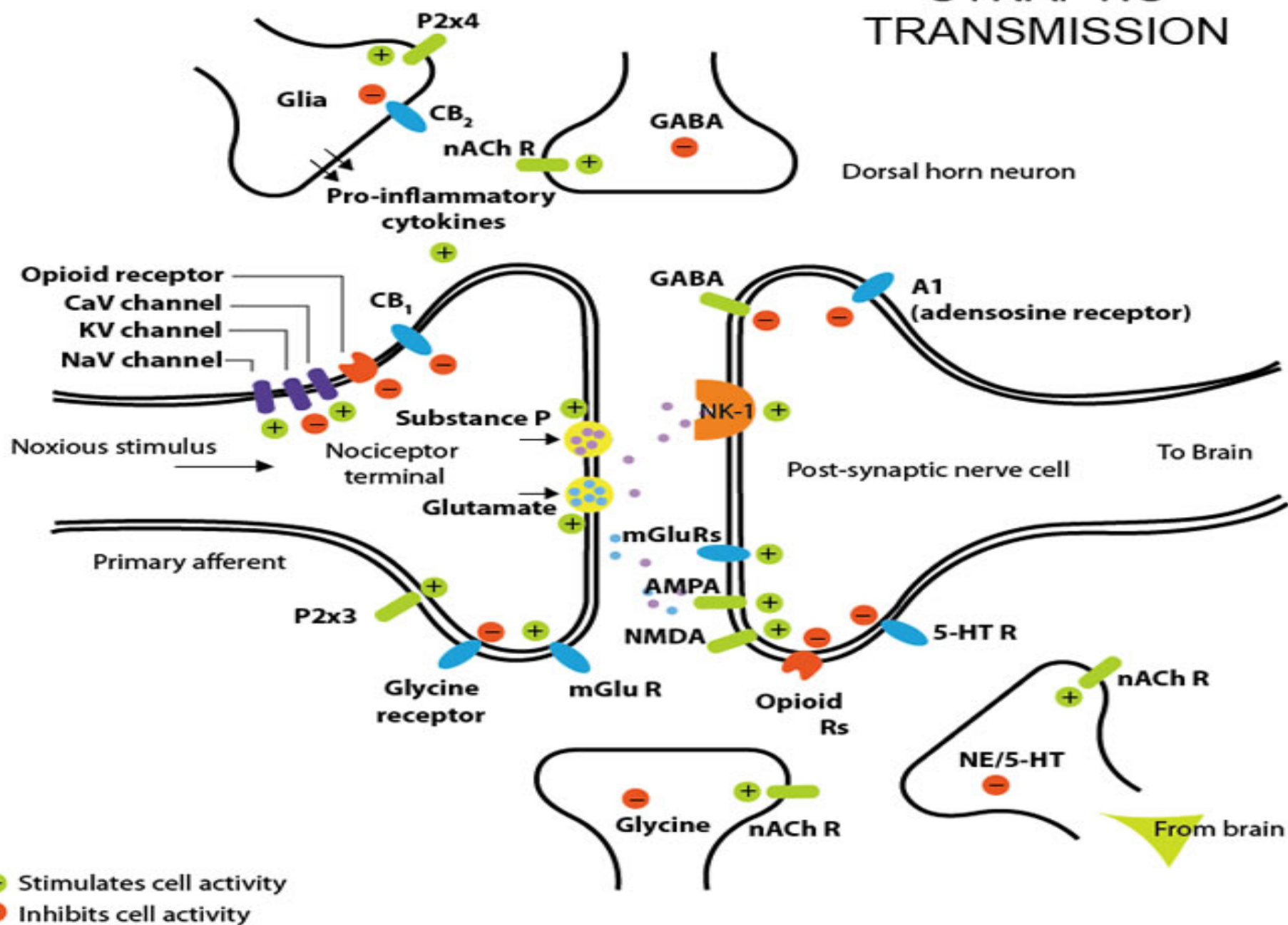
Sawynok J. Topical analgesics in neuropathic pain.  
Curr Pharm Des 2005; 11(23):2995-3004

# Transdermal Route: Drawbacks

- Possible irritation at application site
- Drying of the skin with transdermal products
- Variations in the stratum corneum barrier → variable absorption
  - May need to add penetration enhancers
- Need to concentrate dosage form to accommodate therapeutic response
- Rate of absorption may vary



# SYNAPTIC TRANSMISSION



# Multimodal Analgesia Attacks Different Points Along the Pain Pathways

*The multimodal approach to pain management, traditionally accomplished using combinations of analgesics, has successfully been used in various applications to more efficiently provide analgesia. **Most of the current pain medications on the market target the  $\mu$ -opioid, COX, serotonin, or norepinephrine receptors on the ascending and/or descending pathways. When these pathways are utilized at the same time, the analgesic effect can often be reached at a lower dose, partially allowing the side effect profile of multi-modal therapies to be lower than that of an individual medications therapy.** Because opioid-related side effects are undesirable, it is likely that a preference of newer multimodal medications that are opioid-sparing is warranted. Though the currently available multimodal therapies have made great strides on helping to manage pain, continued research is needed to develop new pain medications that provide at least the same or more effective analgesia with fewer side effects.*

*- Perry Fine, MD, Professor of Anesthesiology, University of Utah School of Medicine*

# Algorithm for Chronic Pain (by mode of action)<sup>1,2</sup>

| Drug             | Strength    | Proposed Mechanism      |
|------------------|-------------|-------------------------|
| Clonidine        | 0.1-0.3%    | Alpha-2 Agonist         |
| Phenoxymethamine | 1.5-5mg/day | Alpha-2 Agonist         |
|                  |             |                         |
| Carbamazepine    | 2-10%       | AMPA-Na Channel Blocker |
| Gabapentin       | 4-10%       | AMPA-Na Channel Blocker |
| Lidocaine        | 2-5%        | AMPA-Na Channel Blocker |
|                  |             |                         |
| Diclofenac       | 2-10%       | Anti-inflammatory       |
| Ibuprofen        | 10-20%      | Anti-inflammatory       |
| Ketoprofen       | 5-20%       | Anti-inflammatory       |
| Naproxen         | 10-20%      | Anti-inflammatory       |
| Piroxicam        | 2-4%        | Anti-inflammatory       |

# Algorithm for Chronic Pain (by mode of action)<sup>1,2</sup>

| Drug           | Strength | Proposed Mechanism               |
|----------------|----------|----------------------------------|
| Baclofen       | 2-5%     | GABA Agonist                     |
|                |          |                                  |
| Pentoxifylline | 2-15%    | Increase Blood Flow              |
| Sildenafil     | 2-4%     | Increase Blood Flow              |
|                |          |                                  |
| Loperamide     | 5-10%    | μ - Agonist                      |
| Methadone      | 0.1-1%   | μ - Agonist                      |
| Morphine       | 0.1-5%   | μ - Agonist                      |
|                |          |                                  |
| Nifedipine     | 2-16%    | Non-NMDA Calcium Channel Blocker |

# Algorithm for Chronic Pain (by mode of action)<sup>1,2</sup>

| Drug             | Strength | Proposed Mechanism                                             |
|------------------|----------|----------------------------------------------------------------|
| Dextromethorphan | 5-10%    | NMDA-Ca Channel Blocker                                        |
| Ketamine         | 5-15%    | NMDA-Ca Channel Blocker                                        |
| Magnesium Cl     | 10-15%   | NMDA-Ca Channel Blocker                                        |
| Methadone        | 0.1-1%   | NMDA-Ca Channel Blocker                                        |
|                  |          |                                                                |
| Cyclobenzaprine  | 1-4%     | Skeletal Muscle Relaxant,<br>Norepinephrine Reuptake Inhibitor |
| Guaifenesin      | 5-10%    | Skeletal Muscle Relaxant                                       |
|                  |          |                                                                |
| Capsaicin        | 0.025-2% | Substance P Depletion? – in question                           |
|                  |          |                                                                |

# Algorithm for Chronic Pain (by mode of action)<sup>1,2</sup>

| Drug               | Strength | Proposed Mechanism                                                       |
|--------------------|----------|--------------------------------------------------------------------------|
| Glucosamine        | 10%      | Supplement                                                               |
|                    |          |                                                                          |
| Amitriptyline      | 1-10%    | Tricyclic Antidepressant<br>(Norepinephrine Reuptake Inhibitors – NERI)) |
| Desipramine        | 2-10%    | Tricyclic Antidepressant (NERI)                                          |
| Nortriptyline      | 2-10%    | Tricyclic Antidepressant (NERI)                                          |
|                    |          |                                                                          |
| Cetyl Myristoleate | 2%       | Unknown – various theories                                               |
|                    |          |                                                                          |
| Diphenhydramine    | 5-10%    | Voltage-regulated Na <sup>+</sup> & Ca <sup>++</sup><br>Channel Blocker  |

# The “Shotgun Approach”

- Since neuropathic pain is generally complex, we generally treat it with the “Shotgun Approach”
- Block the various physiologic pathways with various mechanisms
  - NMDA antagonist
  - $\mu$ -receptor agonist
  - Calcium channel blocker
  - Alpha-2 Agonist
  - AMPA antagonist
  - GABA agonist
  - NERI
- Not uncommon to have 3-4 active ingredients in each formulation

☐ Lipoderm      ☐ PLO      ☐ Other (specify)\_\_\_\_\_

**+ DMSO**         5%         7.5%         10%         20%

### Check the Ingredient & Strength:

### Other Strength:

☐ Ketamine   5%    10%   15% 

\_\_\_\_\_ %

**(requires a duplicate Rx with this Rx)**

☐ **Gabapentin**        6%          8%        10%

\_\_\_\_\_ %

☐ **Clonidine** \_\_0.1% \_\_0.2%

\_\_\_\_\_ %

☐ Lidocaine   2%     5%  

\_\_\_\_\_ %

**Tetracaine** 2% 5%

\_\_\_\_\_ %

☐ **Morphine** 0.1% 0.2% 1% 2%

\_\_\_\_\_ %

**(requires a duplicate Rx with this Rx)**

☐ **Ketoprofen**        5%         10%        20% 

\_\_\_\_\_ %

☐ **Diclofenac** 2% 4% 5%         %

☐ **Carbamazepine**      2%      5%      10%      \_\_\_\_\_ %

| Medication | 2% | 5% | % |
|------------|----|----|---|
| Baclofen   |    |    |   |

|                                        | 2% | 5% | % |
|----------------------------------------|----|----|---|
| <input type="checkbox"/> Amitriptyline |    |    |   |

|                                         | 5% | 10% | 15% | % |
|-----------------------------------------|----|-----|-----|---|
| <input type="checkbox"/> Pentoxifylline |    |     |     |   |

☐ **Nifedipine**    **2%**        **5%**        **10%**        **%**

☐ **Dextromethorphan** 10% ☐ **Guaifenesin** 5% 10%

☐ **Menthol** 0.5% ☐ **Camphor** 0.25%

**Additional Ingredients:** \_\_\_\_\_ % \_\_\_\_\_ %

**Directions:** Apply \_\_\_\_ mL to affected area(s) (specify) \_\_\_\_\_

(frequency) \_\_\_\_\_.

**Mitte:** \_\_\_\_\_ mL (Total %  $\leq 30\%$ ) Refill x \_\_\_\_\_

# Medications Used in Transdermal Delivery

Drugs listed in percentages

1% Solution = 1000mg/100ml

OR

10mg/ml

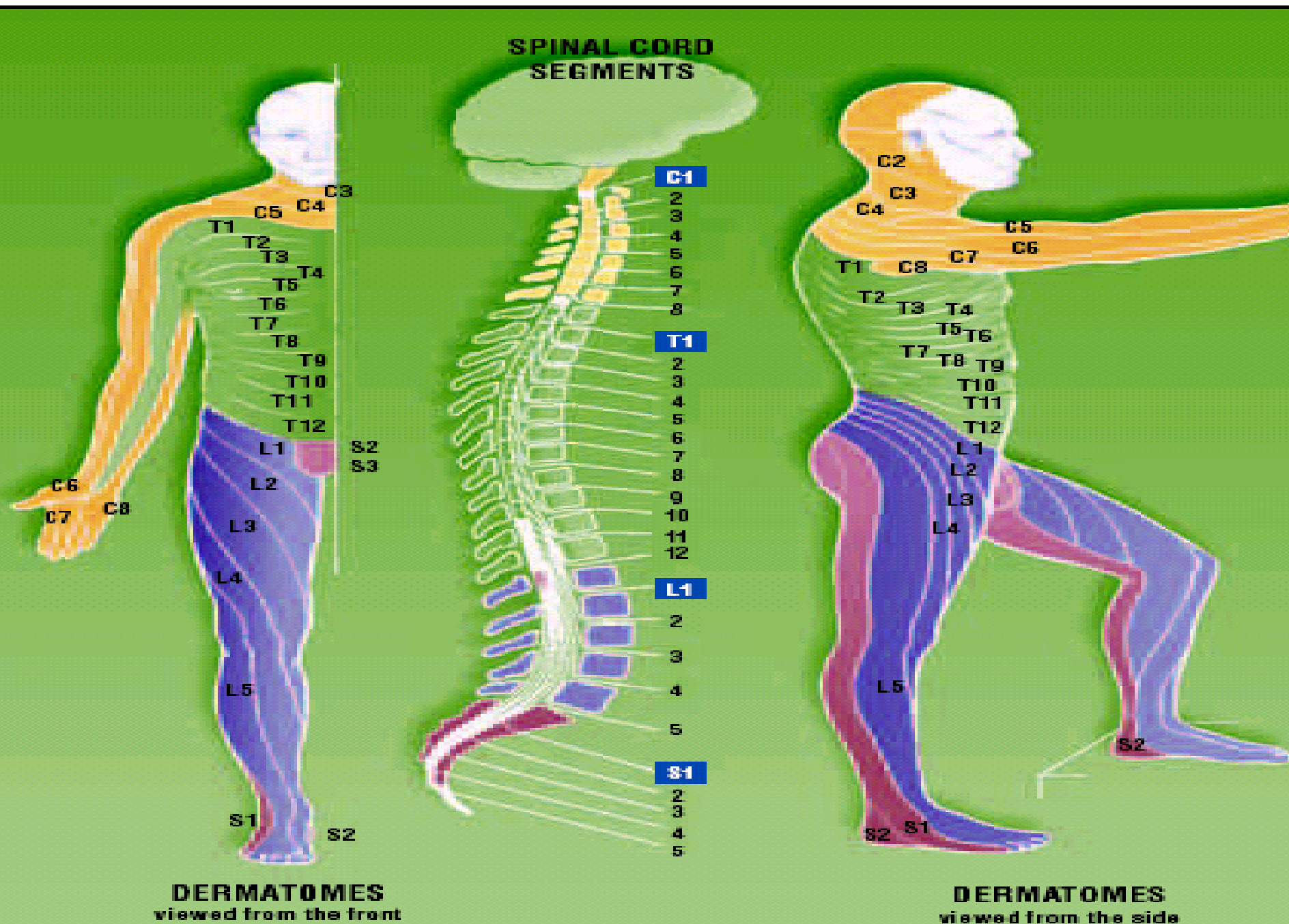
Hydromorphone 1% solution

10mg/ml

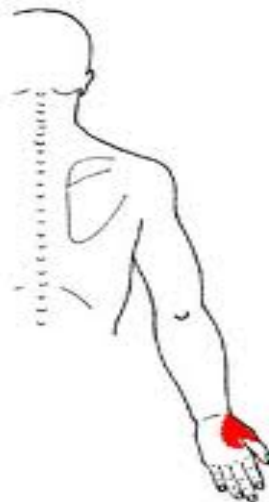
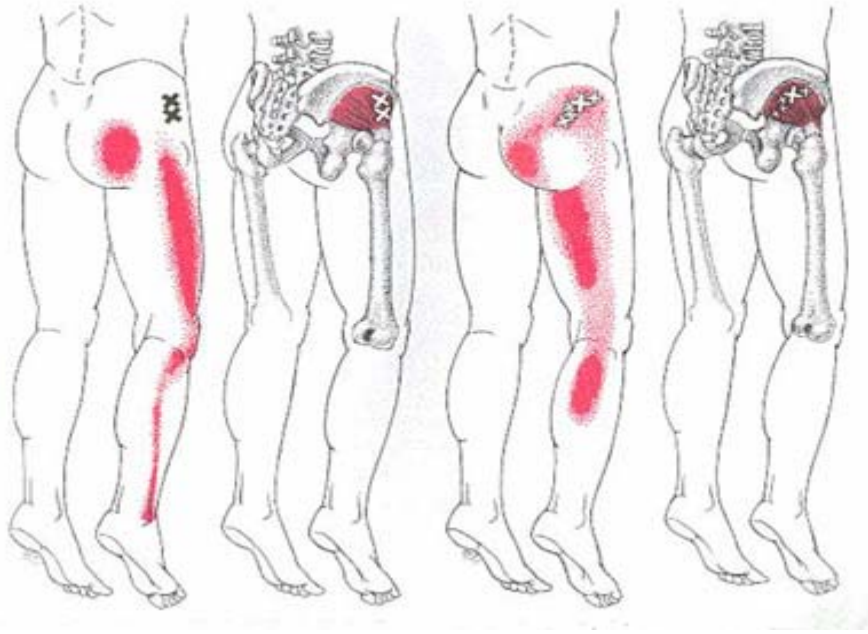
# Dosing

- Applied 2 - 4 times daily on a regular basis
  - With regular application, there may be a “depot” effect that takes place
    - Increases the efficacy of the cream
    - May allow decreasing the frequency of application in future
  - Apply :
    - To the painful site
    - To the site of the original injury
    - To the corresponding dorsal horn of the dermatome involved
    - Any trigger point locations
      - Trigger points may not play as large a part in neuropathic pain as in other types of pain
- Also may be applied every 1-2 hours when needed

**Figure 1. Map of the Human Dermatomes.**



# Trigger Point Map Examples



# Dosing (cont)

- If response is short in duration:
  - DMSO for penetration enhancement
  - Increase dosing frequency
  - Add more agents to cream
  - Maximize concentrations of agents in cream
  - Apply a larger amount of cream if area to treat is larger than originally determined
- Rule of Thumb
  - 0.5mL covers 2" x 2" area
  - 1ml covers 4" x 4" area

# Dosing (cont)

- Try and ask a lot of questions:
  - What medications have been used in the past
  - What type of pain are we treating
  - What medications are you currently on
- Once using a formulation
  - Any pain relief → Pain scale 1-10
  - How fast pain relief starts
  - How long pain relief lasts
  - Side effects? - reduce dose by  $\frac{1}{4}$ - $\frac{1}{2}$  until tolerated if possible
  - Keep a running log of conversations
  - Ideally, do continual Brief Pain Inventories

# Dosing (cont)

- This gel is not to REPLACE current pain treatment but is an ADJUNCT to your pain treatment
  - Treating shingles may be an exception
- There may not be complete resolve of pain but pain may change from, for example, an 8/10 to a 4/10
- Can we come up with a combination for treatment of good days and bad days

# Ketamine

- Widely used as an anesthetic agent
  - Given IV, IM, PO, PR, intranasally or spinally (Chia et al., 1998; Gehling and Tryba, 1998; Malinovsky et al., 1996; Mercandante et al., 2000; Walker et al., 2002)
- Safety and efficacy of ketamine as an analgesic well documented (Malinovsky et al., 1996; Reich & Silvay, 1989; White et al., 1982)
- Tx in neuropathic pain (Edie et al., 1994, 1995; Jackson et al., 2001; Kannan et al., 2002; Kjepstad & Borchgrevnik, 1997; Mercandante et al., 1995, 2000; Mercandante & Arcuri, 1998)
- Phantom limb pain (Knox et al., 1995)
- Post-operative pain and other post-traumatic pain (Dick-Neilsen et al., 1992; Gurmani et al., 1996; Hirlinger & Dick, 1984; Hirlinger & Pfenninger, 1987; Lauretti & Azevedo, 1996; Owen et al., 1987)
- Control pain during dressing changes (Bookwalter, 1994; Humphries et al., 1997; Kulbe, 1998; Pal et al., 1997)
- Low doses of ketamine have minimal adverse effects on cardiovascular or respiratory function (Miller et al., 2000)

# Ketamine

- **REQUIRES A M3P** (Manitoba Prescribing Practices Program (M3P) - **Duplicate Rx**)
  - High potency NMDA antagonist
  - NMDA receptors are one of the most common receptors involved in transmission of pain

# Shingles

- Ketamine 15%, amitriptyline 2-5%, loperamide 5-10%, lidocaine 2-10%
- Take out loperamide and add morphine 0.1 – 2% if pain is 5/10 or higher (unless patient is opiophobic)
- If the physician does not want to write a triplicate:
  - Gabapentin 6%, baclofen 2%, loperamide 10%, amitriptyline 2%, lidocaine 5%

# Case Study

- It is decided between the patient (P.N.), the physician and the pharmacist that a transdermal formulation will be tried
  - Ketamine 15%, amitriptyline 3%, morphine 0.2%, lidocaine 5% in Lipoderm©
    - Apply to affected area 2mL four times a day
    - Also apply to the corresponding dermatome – approx T6 – T8
- Upon returning home with the cream, the patient is unable to use the cream as she cannot put enough pressure on the area to rub the cream in
  - Too painful to touch

# Shingles (continued)

- If the area is too painful to apply a cream to begin with, can try using a topical spray on the area first
  - Ketamine 10%, bupivacaine 0.5%
  - Ketamine 4%, morphine sulfate 4% (good for allodynia)
  - Hydromorphone 1 – 5%, lidocaine 1 – 5%
  - Lidocaine 4%, tetracaine 4%
- Spray bottles
  - Spray 0.1ml → morphine 4% OR 40mg/ml = 4mg/spray
- Spray 3-6 sprays on area 10-30 minutes prior to applying cream
- Some patients may only require the spray
- A foam could also be utilized
  - Ketamine 2% + morphine sulfate 2%

# Case Study

- A pre-spray of ketamine 4% & morphine 4% is decided upon
  - Patient is instructed to spray 3 sprays on the affected area 20 minutes prior to applying the cream
  - She is now able to touch the area after allowing the spray to take effect
- After using the cream for 5 days, P.N. now describes the pain as a 1/10 most of the time with almost no stabbing pains.
  - Even when there is a slight stabbing feeling, she only describes it as a 3/10
- She promises a big batch of cookies for the pharmacy (still waiting for these)

# Sensory Neuropathy

## “Tingling” Sensation

- Gabapentin 6%, loperamide 10% & lidocaine 2%
  - + Amitriptyline 2 – 5%
  - + Clonidine 0.1 – 0.2%
  - + Ketamine 5%
  - +Baclofen 2% or clonidine 0.1%
- Apply to affected areas two to three times a day for 2 – 4 weeks
- It is not uncommon to have numbness as well. The numbness may not go away.

# Radiation Burns

- Skin quite inflamed → greater drug absorption because of ↑ permeability
- ↑ drug concentration in epidermis → ↑ systemic levels
- Skin can be more sensitive to touch → greater care if applying medication topically
- Do not use PLO as this is far too sticky and would further irritate the skin
- Ketamine 5%, gabapentin 6%, morphine 0.5%, lidocaine 1%
  - Apply 2-4 times a day as needed
  - Watch for systemic side effects (drowsiness)
- May need to use a pre-spray as well, or a spray instead

# Cutaneous Ulcers/Open Wounds

- Topical opioid concentrations are either undetectable or no more than 20% of SC dose
- No tolerance developed with topical treatment with opioids
  - Methadone 0.1 – 1% in Stomahesive® powder
  - Morphine 0.1 – 2% in Intraspine Gel®
  - Ketamine 0.3-1% gel
- Usually applied with each dressing change
- Hydromorphone 0.5-2% & ketamine 0.5-2% may also be used
  - Can also be formulated into a topical spray
- If odor present, may add metronidazole to the formulation, or sprinkle metronidazole powder directly on the wound

# Cannot be afraid to try new ideas

- Spring 2013 – treatment of a 78 year old female patient with vulvar cancer
  - Extremely painful to the touch & itchy
  - Unable to control pain with oral medication and standard interventions
  - Prepared a formulation of amitriptyline 1%, gabapentin 3%, lidocaine 0.5%, morphine 0.1%, sucralfate 7% in a less penetrating base (looking for a more local effect)
    - Backed off on strengths of medications to prevent systemic absorption and side effects
  - Patient had major relief of pain and discomfort shortly after first applications

# Knee Pain

- Diclofenac 5-10% + Lidocaine 5% + DMSO 10-20%
  - Ketoprofen 5-20% may be substituted in place of diclofenac if pruritis develops
  - Pain may be from muscle above the knee, so make sure cream is applied to both spots
  - Can add
    - Gabapentin 6% for any burning sensation
    - Baclofen 2% or clonidine 0.1%
- Ketorolac 8% + Tetracaine 5% + CMO 4% + DMSO 20%
- Arthritic pain is likely the #1 pain issue that we see

# Sciatica Pain

- Sciatica may occur when a herniated disk or a bone spur on the spine compresses part of the nerve. This causes inflammation, pain and often some numbness in the affected leg.
- Focus on applying the mixture over the L1-L5 area of the spine (very commonly affected area). Also cover at least 4 inches over on each side of the spinal column
- Gabapentin 6%, Diclofenac 4%, Lidocaine 2%, DMSO 5%

# Raynaud's Disease

- Nifedipine 6% (2-10%) +
- Pentoxifylline 10% (5 – 15%) +
- Sildenafil 4% (1 – 5%)
  - Apply 1ml to each hand and each foot 2-4 times daily

## TMJ (temporomandibular joint disorder)

- Potassium complex 18% gel
  - Applied twice daily

# Transdermal Gel/Cream

- **Common Uses:**

- This medication may be used for relief of diabetic neuropathy, trigeminal neuralgia, Post-herpetic neuralgia, neuropathic (nerve) pain, fibromyalgia, arthritic pain, allodynia

- **Instructions for Use:**

- Wash hands before using (you may want to wear a rubber glove)
- Take cap off of syringe (Place syringe in left hand and turn counter-clockwise with right hand)
- Squeeze out the prescribed volume onto affected area or onto hand
- Rub into area **gently** until gel/cream is no longer visible and then continue to rub **gently** for another **60 seconds** as this will aid in a deeper penetration.
- **Do not apply a lot of pressure** as this may increase someone's pain.
- Replace cap on syringe and wash hands well after applying
- Avoid getting the application site wet for at least 1 hour after application
- You do not need to apply an occlusive dressing/bandage over the applied area

- **\*\*\*FOR EXTERNAL USE ONLY\*\*\*    \*\*PLEASE NOTE EXPIRY DATE ON LABEL\*\***

- **Possible Side Effects:**

- Redness or irritation at the site of application
- Fatigue, nausea, lightheadedness, dizziness, or mood changes are also possible, but rare in occurrence. If any of these symptoms occur, contact your physician or pharmacist

- **Storage of Medication:**

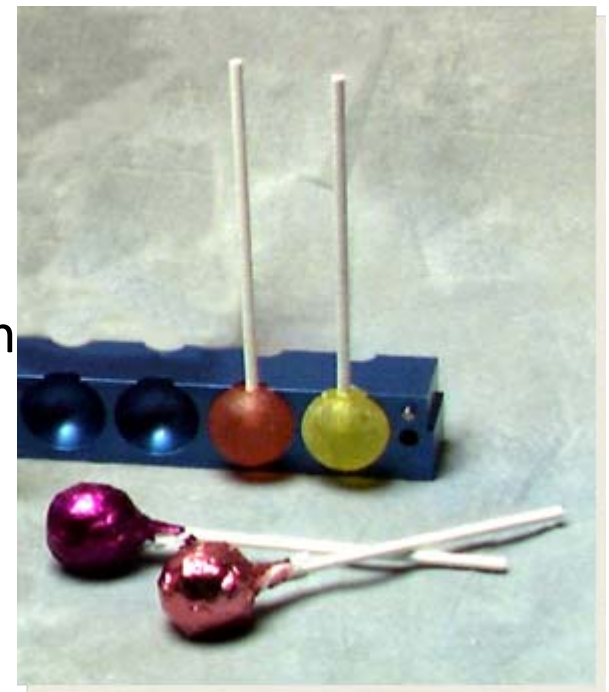
- Keep the medication at room temperature. Do not expose to any extremely hot or cold temperatures. Keep out of bright light and excessive moisture. If there is any discoloration or separation of the product, contact the pharmacy.

# We can be more successful if we:

- Get a complete pain history, including
  - Beginning of the pain, intensity, what improves or worsens it
  - Where the pain is
  - A measure of the pain
  - Medications used in the past and what degree of effectiveness
- Keep score
  - Of the response to therapy, of the dose used
- Use a stepped care approach
  - Realize that the first attempt will likely not be perfect (get over it!)
- Realize that chronic pain that lasts longer than 6 months is more difficult to treat

# Other Applications

- Neuropathic pain located elsewhere on the body
  - Oral cavity
    - Mouth rinses
    - Lollipops or lozenges
      - Hydrocortisone 1% + lidocaine 2% + diphenhydramine 25mg combo
  - Rectally
    - Suppositories – watch the base with colostomy patients
      - Ketamine, tetracaine, hydrocortisone
    - Ointments – e.g. ketamine 5% , hydromorphone 0.5%, lidocaine 2%, nifedipine 0.2%
  - Vaginally
    - Suppositories & Creams



# Other Applications

- Preparation of oral dosage forms of medications not commercially available
  - Oral capsules
    - e.g. ketamine
  - Oral liquids
    - e.g. gabapentin suspension
- Capsules with strengths of ingredients not commercially available
  - E.g. various strengths of methadone, diazepam, etc.



## Magic mouthwash –

## Super Magic Mouthwash –

**Tetracaine 0.5%, hydrocortisone 1%, clotrimazole 2%, sucralfate 15.6%**

**Ketamine 0.03%, tetracaine 0.5%, sucralfate 15.6% (requires a duplicate Rx)**

### Pink Lady - Xylocaine Viscous 2% : Maalox, 1:1

**Modified Pink Lady – Xylocaine Viscous 2% : Maalox: Benadryl Elixir, 1:1:1**

- **OR**

- **Check the Ingredient & Strength:**

**Other Strength:**

|   |                          |                 |              |             |                                  |          |
|---|--------------------------|-----------------|--------------|-------------|----------------------------------|----------|
| ● | <input type="checkbox"/> | <b>Ketamine</b> | <b>0.03%</b> | <b>0.4%</b> | <b>(requires a duplicate Rx)</b> | <b>%</b> |
|---|--------------------------|-----------------|--------------|-------------|----------------------------------|----------|

■ **Gabapentin** 6%

● ☐ **Lidocaine**      **0.4%**      **1%**      **2%**      **%**

☒ ☐ **Tetracaine** 0.5% 1% %

|                 | 0.075% | 0.125% | 0.2% | % |
|-----------------|--------|--------|------|---|
| Diphenhydramine | 0.075% | 0.125% | 0.2% | % |

|                | 0.125% | 0.5% | 1% | % |
|----------------|--------|------|----|---|
| Hydrocortisone |        |      |    |   |

| Drug          | Percentage |
|---------------|------------|
| Dexamethasone | 0.00033%   |

| Medication | Percentage |
|------------|------------|
| Sucralfate | 15.6%      |

| Clotrimazole | 2% | % |
|--------------|----|---|
|--------------|----|---|

|          | 7500 $\mu$ /ml | $\mu$ /ml |
|----------|----------------|-----------|
| Nystatin |                |           |

| Antibiotic   | Concentration | % |
|--------------|---------------|---|
| Tetracycline | 1.25%         | % |

| Medication  | Percentage | Percentage |
|-------------|------------|------------|
| Misoprostol | 0.0034%    | %          |

| Additional Ingredients: |  | % | % |
|-------------------------|--|---|---|
|                         |  |   |   |

● **Flavour (if applicable):** ☐ Bubble gum ☐ Grape ☐ Unflavoured ☐ Other (please specify) \_\_\_\_\_

- **Directions:** Swish and spit 10-15mL or \_\_\_\_\_ mL q 2-3 hours or \_\_\_\_\_ (frequency) as needed.

● Or Swish and swallow \_\_\_\_\_ mL \_\_\_\_\_ (frequency) as needed.

- (consider systemic effects when determining volume and frequency if swallowing)

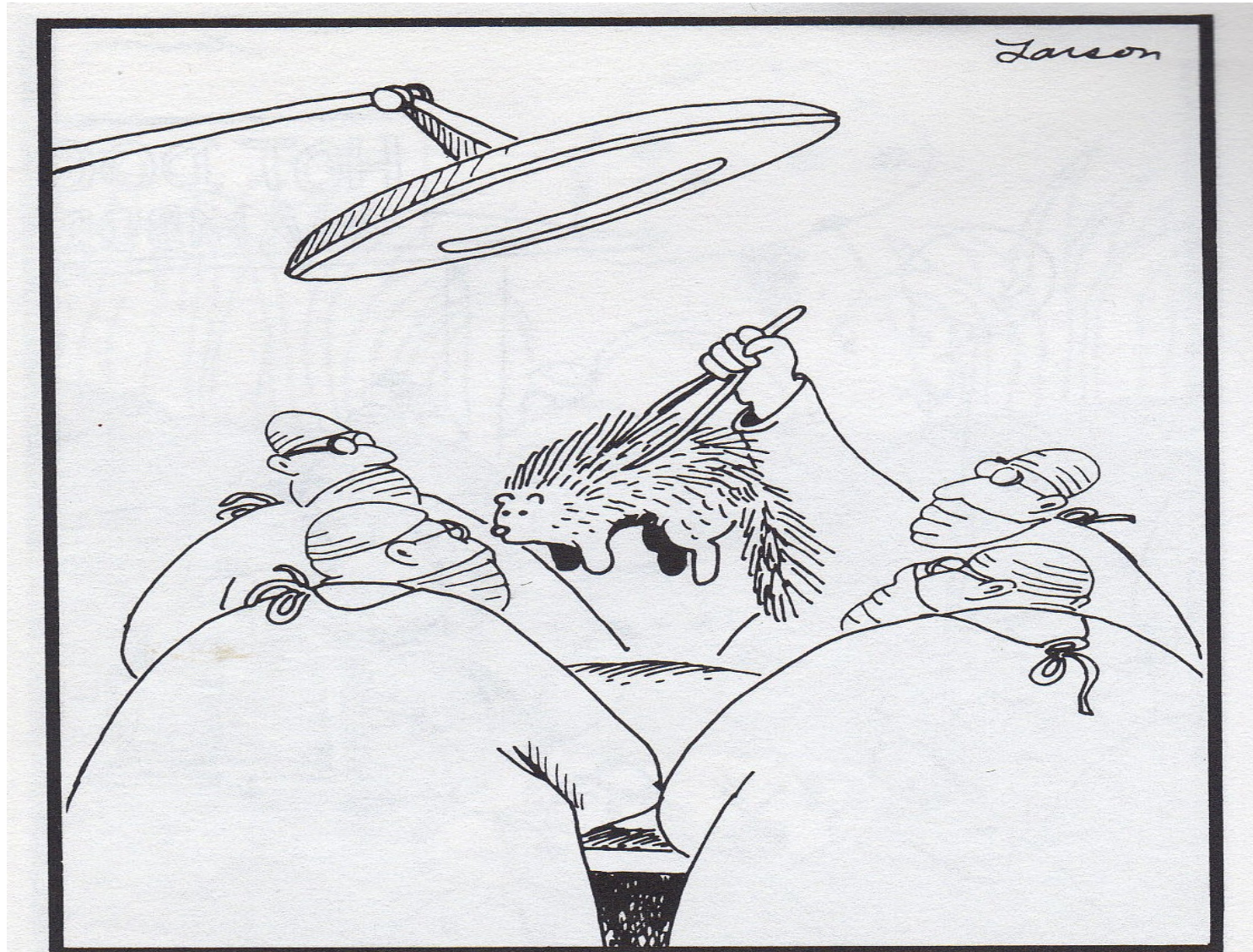
● **Mitte:** \_\_\_\_\_ mL      Refill x \_\_\_\_\_

# Mucositis

- Ketamine 0.4% in artificial saliva
  - 5mL swish for 1 minute & spit<sup>1</sup>
- Ketamine 0.03%, Tetracaine 0.5%, Sucralfate 15.6%
  - Swish & spit can be used more often as you do not have to consider total dose being swallowed
    - Use 5-10ml q2-3h as needed
- Modified Pink Lady – Xylocaine Viscous® 2% : Maalox®: Benadryl® Elixir, 1:1:1
  - Can be a simple & effective pain reliever
    - Xylocaine = lidocaine
    - Benadryl = diphenhydramine – local oral analgesic
    - Maalox = good vehicle to enhance the coating of the local analgesics in the mouth

1) Neal E. Slatkin and Michelle Rhiner, CASE REPORT  
Topical Ketamine in the Treatment of Mucositis Pain,  
Pain Medicine Volume 4, Number 3, 2003

# Let Us Try & Help You Find the Solution!!



**"Well, I guess that explains the abdominal pains."**

# References

- 1) Jones M. Chronic Neuropathic Pain: Pharmacological Interventions in the New Millenium – A Theory of Efficacy. *International Journal of Pharmaceutical Compounding*. Jan/Feb 2000; 4(1): 6-15.
- 2) Jones M. Clinical Nuggets and Pearls: Chronic Neuropathic Pain and Opioid Tolerance. *International Journal of Pharmaceutical Compounding*. Jan/Feb 2002; 6(1): 4-6.

# Questions?

