Date:          Saturday, October 10, 2015
Time:          1:30 pm – 3:00 pm
Location:      Gaylord National Harbor Resort and Convention Center, Chesapeake 7/8/9
Title:         Compounding for Pain Management - How to turn Turmoil into Opportunity
               Sponsored by Medisca Network, Inc.
               ACPE # 207-000-15-105-L04-P • 0.15 CEUs

Activity Type: Application-based
Speaker:       Ken Speidel, RPh, BS Pharm, PharmD, Gates Healthcare Associates

Pharmacist Learning Objectives:
Upon completion of this activity, participants will be able to:
1. Discuss novel “targeted” approaches for the treatment of pain.
2. Describe a multi-modal approach to pharmacotherapeutics to intercept deleterious afferent pain signal elicitation and subsequent excitation, inhibition, cessation and modulation though compounded analgesic therapy.
3. Highlight select pharmacodynamic differences within specific chemical classifications that will allow the compounding specialist to individualize pharmacotherapy, not only on patient parameters but also on known chemical activities.
4. Discuss ideas about how to differentiate your compounding practice in order to sustain compounding for pain management as a viable niche offering.
5. Describe how the recent changes in third party reimbursement have affected patient access and suggest potential strategies to counter patient access challenges.

Disclosures:
Ken Speidel is receiving an honorarium Medisca Network, Inc. for this program. The conflict of interest was resolved by peer review of the slide content.

NCPA’s education staff declares no conflicts of interest or financial interest in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
Compounding For Pain Management: How to Turn Turmoil Into Opportunity

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Disclosure

Kenneth R. Speidel is a consultant/facilitator of Medisca Network's copyright program materials. The conflict of interest was resolved by peer review of the slide content.

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Material presented during this CPE Activity reflects current literature on the subject and is presented without commercial bias, prejudice or influence.

Any personal opinions on the part of the presenter will be notably specified.

Content Disclaimer

Information contained in this educational activity, including treatment modalities, diagnostic and therapeutic information, is for educational purposes only and should not be taken as a treatment regimen, product indication, or suggested treatment modality. Any treatments or therapy must be fully investigated and prescribed only by a duly licensed medical practitioner in accordance with accepted professional standards and compendia.

Content Disclaimer

Due to the very nature of compounding pharmacy practice, content may address therapeutic options that may or may not be approved by Governmental regulatory bodies or medical associations.

Participants of this Activity should verify all information and data before advocating any therapies described in this educational activity.
• Discuss the current compounding pain market and payer challenges.
• Describe how the recent changes in third party reimbursement has affected patient access.
• Suggest potential strategies to counter patient access challenges.
• Emphasize the need to return to the “custom” of the customization of pharmacotherapy for the treatment of advanced pain syndromes.
• Reveal a novel “targeted” approach for the treatment of pain.
• Highlight potential evidence that may assist in the justification for compounded options for pain management.
• Describe a multi-modal approach to pharmacotherapeutics to intercept deleterious afferent pain signal elicitation and subsequent excitation, inhibition, cessation and modulation though compounded analgesic therapy.

Learning Objectives

• Highlight select pharmacodynamic differences within specific chemical classifications that will allow the compounding specialist to individualize pharmacotherapy, not only on patient parameters but also known chemical activities.
• Discuss ideas as to how to differentiate your compounding practice in order to sustain compounding for pain management as a viable niche offering.

Compound Pain Creams Make Headlines For Unethical Marketing/Billing Scheme

February 23, 2015

CBS News aired a story about unethical marketing and billing of compounded pain creams.

The report exposed telemarketing scheme:
• Get physicians to write prescriptions for patients who mentioned they were experiencing pain.
• The company would bill extremely high amounts of money to the patient’s insurance company and ship the medication.
• They often did not charge the co-pay to the patient.
April, 2015 – CBS News

Reported that a man got a call from a telemarketer about an alternative treatment for pain:

- The person on the phone asked him if he ever has pain and if he has needs for medication.
- He gave the caller permission to speak to his doctor but did not authorize them to seek a prescription—which is why he and his wife were surprised when jars of prescription creams and gels showed up three months later.
- "Our immediate reaction was, Oh my goodness, someone else ordered medication and they sent it to us by mistake."
- According to the man, it totaled $18,680.00!

May 11, 2015 – CBS News

The Department of Defense has seen evidence of unscrupulous marketing and sales activities to military beneficiaries:

- In some cases, fraudulent activity is suspected and we are investigating those reports.
- CBS News has recently highlighted this issue; the Defense Health Agency has provided CBS with on-air interviews to communicate our concern and the actions we are taking to address potential fraud and targeting of TRICARE beneficiaries.

Former NFL quarterback pitched the benefits of a compounded pain gel on Sirius XM’s NFL show last year:

- "It’s a safe way to treat some of your ailments,” said Favre.
- "It even works with cramps, stomach pain. It’s amazing.”

He predicted the compounded gel would "revolutionize" the treatment of sports injuries.
Compound Pain Creams Make Headlines For Unethical Marketing/Billing Scheme

Work Comp Doctors Make $20,000+ a month to prescribe pain creams. (Los Angeles)

Third Party Marketing pushing prescribers and patients.

- May 14, 2015 - Louisiana House Bill 568 passed 94 to 0.
  - Bill enables the Louisiana Board of Pharmacy to investigate and take disciplinary action against a pharmacy that has financial arrangements with doctors and others prescribers that jeopardize patients' freedom of choice and could lead to increased healthcare billings.
- Other states following suit.

Payer Changes Creating Pain For Compounders

- An allowance in Tricare's prescription drug coverage policy that has drained nearly $1 billion from the Pentagon's health budget since January vanished when a new policy on compound medications went into effect.
- Starting May 1, 2015, Tricare pharmacy contractor Express Scripts will screen each ingredient in compound medications to ensure all are approved by the Food and Drug Administration.
- Under the new process, many patients who use personalized drug formulas still will have access to their medications.
Payer Changes Creating Pain for Compounders

WSJ BLOG - Wednesday, May 13, 2015

Drug Makers are Having Trouble Improving Their reputations: Survey. By Ed Silverman

REPORT: PRESCRIPTION DRUG COSTS ROSE FASTER THAN EVER FOR MANY AMERICANS:

- The report also identified compounded medicines as another contributing factor to rising spending.

- Among Americans with annual drug costs of $100,000 or more, the proportion of patients using compounded meds grew 30% in 2014, and the costs for those medicines quadrupled, according to the report.

- Express Scripts contends these drugs “add little or no value to patient outcomes” and, in some cases, may increase health risks.

Change the Paradigm

Create compelling points of differentiation:

- Acquire Accreditation
- PROVE Quality
- Promote yourself and practice...highlight training/certifications/awards
- Acquire Testimonials
- Change your formulation process to accommodate payer needs
- Affect Legislation
- Develop a Clinical (MTM) / Consultative Practice
- Individualize pharmacotherapy (Customization)
- Target for Pain
- Provide evidence of effectiveness

Change the Paradigm - Promotion

Demonstrate competence and commitment:

- Certifications/fellowships
- Seminar attendance
- CE’s
- Lectures given
- Publications
- University affiliations

Awards & Certificates
Change the Paradigm

**Testimonials**

Physicians/prescribers
Pharmacists (colleagues)
Patients/animal owners

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**Testimonial**

Military Times Commentary: Compound Medications Can Benefit Patients

Friday, May 1, 2015. By Dr. Randy Lundell who served seven years as a military family physician and did a tour in Iraq. He opened his own practice, Health Rejuvenation Institution, in Spanish Fork, Utah, in June, 2010.

Dr. Lundell stated:

- As a physician and a veteran who works closely with compounding pharmacies on behalf of my patients, I found that the accusations in the April 10 Military Times article, 'Compound Pharmacies Marketing Directly to Tricare Users,' painted an unfair picture of the overall industry.

- A few bad actors can do a lot of damage, but I can assure you that these aggressive marketing practices are spearheaded by the minority.

- As a practitioner who focuses on a comprehensive approach to treating patients, I know that some will benefit greatly from compounded medicine while others will benefit greatly from manufactured drugs.
Dr. Lundell stated:

- Many times, the pharmacist, patient and I have discussions on the treatment and work together to adjust the dose and application of the medicine to ensure it is tailored to address the patient's need. This is what we call the "triad" relationship, and it's an important one.

- Protecting access to compounded medications is vital for many patients (veterans and active-duty members included) to maintain their quality of life. We shouldn't let the bad business practices of a few cast a shadow on the rest of the industry.

**Change the Paradigm - Formulation**

**Change the method by which you formulate to accommodate payer needs...**

**Use manufactured products as Active Ingredients**

- When using a coated tablet to compound a final preparation, make sure that the API(s) and excipient(s) remain stable when the coating is removed when compounding the tablet into another dosage form.
- Caution: When crushing extended-release tablets, any extended-release properties are lost.
- It can be difficult to break tablet coating systems, therefore an appropriate mortar and pestle, or even a Blender or Grinder, will have to be used along with powder containment.

**Use manufactured products as Active Ingredients**

- After breaking the tablet coating system, a calibrated sieve must be used to remove the coating and reduce particle size of the tablet content. Note that it is also extremely important to pass the excipient(s) that will be used to compound the formula through the same sieve, as well, in order to keep the same particle size for all of the powder that will be used to compound the formulation.
- Specific equipment can be used to mix powders and produce a uniform powder blend of ingredients, ensuring excellent homogeneity to facilitate geometric addition.
- Some of the excipients in commercial tablets are hydrophobic, therefore use a good wetting agent as well as a surfactant (e.g.: Polysorbate 80 or Sodium docusate) to reduce contact surface between powder and liquid.
Use manufactured products as Active Ingredients - Continued

• When using the contents of a tablet to compound a topical preparation, it is important to ensure that all the active ingredients can permeate the stratum and that all ingredients be applied on the skin.

• An ultrasonic bath (sonicator) can be used to reduce the particle size of tablet content or capsules after incorporating them into a suspension, creams, gels, etc.

• When making preparations with commercial liquid-filled capsules, liquid content can be extracted using a syringe.

Change the Paradigm – Affect Legislation

US Senator David Vitter (R-La) announced legislation June 9, 2015 to protect and expand access to life saving compounded medications.

Senators Rand Paul (R- Kentucky) (an Ophthalmologist) and Sherrod Brown (D-Ohio) drafted a letter to the FDA noting the restrictive nature of the Guidance.

Change the Paradigm - Clinical Practice

INDIVIDUALIZATION
DRAW OUT THE BEST IN EACH PERSON

Personalization is the “Standard”, not the Exception

ONE SIZE DOES NOT FIT ALL.
That The CUSTOM in Compounding Has Always Been
The CUSTOMization of Drug Therapy

Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose healthcare needs cannot be met by manufactured medications.

http://www.iacprx.org/default.asp accessed 12/01/2014

Are We Losing Our Direction?

Does Compounding = Customization?

Or...

Does Compounding = Commoditization?

Are we being driven by Check boxes on a 9 x 11 template for the “Typical” Patient?
Customization Compass

1. Do you provide prescriber templates?
2. Do you have go-to common APIs?
3. Do you suggest acronyms to make prescribing easy?
   • CAG/KAT/DAG, etc.
   • Lidocaine, Gabapentin, Ketoprofen, Ketamine
4. Do most of your patients get the same delivery system?
   • PEG Troche, O/W Cream, Liposomal Emulsion, Fatty Base Suppository
5. Do your pain cocktails contain APIs that have the same MOA?

One Dose, One Delivery System DOES NOT FIT ALL

Practitioners...

• Using Manufactured Products, are trying to match a patient to a product.
• Using Compounded Preparations, match a compounded formulation to a patient.

Status Quo No More

The compounding pharmacist that will differentiate themselves from others will believe in the ideology of matching a compounded preparation to the patient.
Pharmaceutical Compounding: Individualized Patient Care

Compounding pharmacists must have proven competence in:

- pharmaceutics
- pharmacology
- pharmacogenomics
- formulations
- pharmaceutical chemistry
- medicinal chemistry
- physiology and pathophysiology
- microbiology
- non-sterile compounding & sterile compounding

The Role of the Compounding Pharmacist is the...

Individualization of Pharmacotherapy to Optimize Outcomes

Pharmacotherapeutic Customization

- Physiological Differences:
  - Skin
  - Mucus Membranes
  - Allergenicity
- Systemic Effects - Need for targeted treatment approach.
- Complex Symptom Presentation
- Social/Environmental/Occupational Differences
- Clinical Pharmaceutics
- Pharmacodynamic Differences:
  - Drug Class
  - Within the Same Class
- Pharmacogenomics
Individualize Based on Drug Pharmacodynamics, Not Name

- Why is Lidocaine the go-to "Caine"?
- What physicochemical properties are needed to enhance absorption?
  - Molecular size, ionization, pH, partition coefficient, etc.?
- Why is Nifedipine your favorite calcium channel blocker?
- What is so special about Ketamine? Ketamine is an NMDA antagonist.
- Does Ketoprofen deserve to be the topical NSAID of choice?
- Is Morphine really the way to go with opiates?

Individualize Based on a Patient’s Genomic Composition; Pharmacogenomics

- Based on the individual’s human genome.
- Better selection of drugs:
  - Coffee anyone? Sorry, does it keep you up at night?
  - CYP1A2
- Better selection of dose.
- Better selection of excipients.
- Compounding plays a major role!

How Can You Customize For Pain Management?

Intersecting Physiology with Pharmacology

Mechanism of Action → Pathophysiological Pathway
# Tools For Success: Individualizing For Pain Management

- **Know The Pharmacology** of the APIs Drug Class Mechanisms of Action (MOA)
- **Know The Physiology & Pathophysiology** (P/P)
- Utilize a **Multi-Modal Approach (MMA)** to treatment

## Know The Pharmacology

<table>
<thead>
<tr>
<th>CLASS</th>
<th>MECHANISMS OF ACTION &amp; COMMON APIs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong> (COX-1, COX-2)</td>
<td>Pre-synaptic: Blocks Initiators Inhibits the activity of both cyclooxygenase-1 and/or -2 enzymes and, thereby, the conversion of arachidonic acid to prostaglandins, which inhibits the inflammatory response mechanism. APIs: Celecoxib, Diclofenac, Etodolac, Fenoprofen, Flosulide, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meloxicam, Naproxen, Phenylbutazone, Profloxacin, Sulindac</td>
</tr>
</tbody>
</table>


| **Sodium Channel Blockers** (local anesthetics) | Pre-synaptic: Blocks sodium ion channel, preventing nerve cell membrane polarization, which prevents action potential propagation. APIs: Benzocaine, Bupivacaine, Cocaine, Dyclonine, Lidocaine, Mepivacaine, Prilocaine, Ropivacaine, Tetracaine |

### Anticonvulsants

**Pre-synaptic:** Maintains the sodium ion channel in an inactivated state which prevents action potential propagation.

**APIs:** Carbamazepine, Lamotrigine, Phenytoin, Topiramate, Valproic Acid

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### NMDA Receptor Blockers

**Pre-synaptic:** Stabilizes Magnesium connectivity to NMDA receptor sites, preventing Magnesium release and subsequent massive depolarization, thus preventing secondary messengers from exciting neighboring neurons. Are opiates sparing?

**APIs:** Amantadine, Dextromethorphan, Guaifenesin, Ketamine, Orphenadrine, Levorphanol, Methadone

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### Opioids

**Pre-synaptic:** Ca²⁺ Influx Inhibition
Pre-synaptically inhibits the release of excitatory neurotransmitters and promotes the release of inhibitory neurotransmitters.

**Post-synaptic:** Membrane Hyper-polarization
Post-synaptically hyperpolarizes the nerve cell membrane leading to decreased signal transmission.

**APIs:** Tramadol, Alfentanil, Buprenorphine, Butorphanol, Codeine, Fentanyl, Hydromorphone, Hydromorphone, Levorphanol, Methadone, Morphine, Naltrexone, Naloxone, Oxycodone, Oxymorphone, Pentazocine, Sufentanil, Sufentanil Citrate

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Know The Physiology - Your Target

- Initiators and/or Neurotransmitters
- Nerve Cell Body
- Axon
- Synaptic Bouton
- Synaptic Cleft
- Dendrite Receptors
- Muscle (Skeletal)
- Blood Vessels

The Physiology → Neurotransmitters

Substance P → Neurokinin -1 Receptor
Evolutionary GL-Analogs → NK-1<br>Precursoe in GABA
Seclon: Evophorol → NMDA Receptor
Inhibitory GABAergic <br>Receptors → GABA Receptor
GABA Transporter<br>Adenosine Receptors

Know The Physiology – Target a Trigger Point

Pharmacotherapeutic Targeting of a Trigger Point
1. Degenerative small nerve fiber neuropathy leads to formation of neuromas on differentiated axon, hyper-excitability of peripheral nerve terminals, loss of sensation and dysfunctional signaling perceived as uncontrollable itching.

2. Insulin deficiency results in less insulin, like growth factor (IGF) which protects mitochondrial function during hyperglycemia, and damages neuronal cells.

3. Constant signaling leads to central excitation through normal channels.

4. Hyperglycemia in spinal column, through increased flux in aldose reductase and induction of COX-2 and prostaglandin release, leads to central inflammation.

5. Cross talk connections between neurons overwhelms the descending nocuous inhibitory control system.

6. Decrease in some of the descending inhibitory pathways.
Successful Targeting in Pain Management

Apply a Multi-Modal Approach to Pharmacotherapy

The multimodal approach to pain management, traditionally accomplished using combination analgesics, has successfully been used in various applications to more efficiently provide analgesia. Most of the current pain medications on the market target the µ-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 multimodal therapies to be lower than that of an individual medication’s 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 in 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

Target a Region(s)
A Compounder’s Opportunity

- Peripheral Activity sensitizes the Central Nervous System and can result in difficulty to treat neuropathy.
- In order to prevent or treat many central pain syndromes clinicians must reduce peripheral nociceptive (pain receptor) afferent signaling.
- Peripheral nociceptors continue to be identified that serve to enhance the "evidence" in order to justify the off-label compounded options for pain.


Change the Paradigm: Provide Evidence of Effectiveness

Targeting Neuropathic Pain from a Peripheral Approach

Understanding the Physiology of Pain

- Local tissue injury incite the formation and release of initiators such as; Substance P, Prostaglandins, C-GRP, histamine and others.
- This mixture of "chemical" initiators initiate the electrical signalling to release a variety of neurotransmitters towards the CNS.
- Sodium and calcium channels are upregulated that further enhances the afferent sensory impulse to the CNS.
- Knowing the physiological targets allows us to "hunt" the perpetrator(s) down with the specific weapon (drug).


Understanding the Physiology of Pain

- Initiators (Prostaglandins)
- Channel Upregulation
- Neurotransmitter Release (ex: Botox®, Keppra®, etc.)
- Sympathetic Activation
- NMDA receptor activation
- Inflammatory Immune Cytokines
- Transient Receptor Potential Channels (TRP) (ex: vanilloid)
Nociceptive Response Mechanisms

- Mast Cell
- CGRP Substance P
- Histamine
- Bradykinin
- Prostaglandin
- CGRP Substance P
- Dorsal Root Ganglion Neuron
- K+
- 5-HT
- Substance P
- CGRP
- Mast Cell

Peripheral Sensitization

- Tissue Damage
- Inflammation
- Sympathetic Terminals

SENSITIZING “SOUP”
- Hydrogen ions
- Histamine
- Noradrenaline
- Potassium ions
- Bradykinin
- Prostaglandins
- 5-HT
- Leukotrienes
- Purines
- Cytokines
- Neuropeptides

- Decreased threshold of nociceptors
- Ectopic discharges
- Abnormal accumulation of Na+ channels

Common Delivery Methods in the Treatment of Peripheral Nociception

- The skin can be a very effective portal for drug delivery both locally, as well as systemically.
- The molecular characteristics of the drug and the solvent can favor either local (topical) or more systemic (transdermal) distribution.
- Topical formulations typically focus the medication to the localized region of the skin where it is applied.
- Advantages of this approach include drug delivery in a focused manner and potentially hundred to thousand times greater concentrations than through oral or parenteral routes.
- Additionally, systemic side effects would be limited as well.
### Targeted Compounded Options for Pain Management

- Can intersect the pathophysiology of the pain syndrome with the pharmacology of the drug(s).
- Reduce potential systemic side effects commonly seen in the treatment of chronic pain.
- Can concentrate the drug(s) at the peripheral site of the signal elicitation and propagation.


### Agents Used In Blocking Nociceptive Pain Signals

- **Local Anesthetics**
- **Anti-inflammatory Agents**
  - COX-1 / COX-2
  - TNF Inhibition
- **Sympatholytic Agents**
- **Transient Receptor Potential Channels (TRP)**
- **Opiates**
- **NMDA antagonists**

### Local Anesthetics

- Topically applied local anesthetic drugs (sodium channel blocking agents) are the most commonly used agents to address the antegrade release of neurotransmitters leading to peripheral sensitization.
- Prevent decreased activation thresholds in nociceptors, spontaneous discharges of nociceptors and axons, and multiple other processes that will eventually increase pain signaling to the central nervous system.
- Blocks sodium ion channel, preventing nerve cell membrane polarization, which prevents action potential propagation.
- Additionally, certain antidepressants, such as amitriptyline and doxepin, can also block the sodium and calcium channels and act very similar to local anesthetics.
Mast Cell SENSITIZING “SOUP”

Purines
Cytokines
5‐HT
Leukotrienes
Nerve growth factor
Neuropeptides

Selected References - Local Anesthetics


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Selected References – COX-1 & -2


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Anti-inflammatory Agents - TNF Inhibitors

- Shortly after a regional injury, TNF alpha interleukin 6 and interleukin 1 beta are released in the area, followed shortly by elevated levels in the dorsal horn.
- These sensitizing substances may increase signaling by essentially inserting into the neurolemma of the peripheral neuron to serve as a mutant ion channel, thereby increasing sensitivity as well as potentially supporting spontaneous discharges.
- Thalidomide is a systemic drug that is well known for TNF alpha inhibition.
- Pentoxifylline is used to promote peripheral blood flow through its actions at the capillary level by inhibiting TNF-alpha, and has been shown to be analgesic as a topical agent in several studies.

Selected References - TNF Inhibitors


Sympatholytic Agents

- Sympathetic stimulation or norepinephrine can cause excitation of peripheral nociceptive fibers, and incite pain by way of the alpha-2 receptors.
- Transdermal antihypertensive agent clonidine has been shown to be analgesic for localized sympathetically-mediated pain when the patch is placed proximate to the painful region.
- Clonidine’s action on the alpha-2 receptor is not locally restricted, but also spreads, through systemic distribution, to act at the dorsal root ganglion and other coupling sites between sympathetic and sensory fibers.
- Alpha-2 receptors have been found to spread to coupling sites between the sensory and sympathetic nerves: within the neuroma at the injury site, peripheral sympathetic fibers and an uninjured sensory nerve, sympathetic fibers that sprout into the dorsal root ganglion.
- There is a growing body of evidence that suggests tizanidine may offer some of the same benefits.
### Transient Receptor Potential Channels (TRP)

- Transient Receptor Potential channels (TRP) are implicated as nociceptors for several painful stimuli.
- These channels allow increased electrolyte conductance as a result of several stimuli, such as changes in temperature, osmolality, peptides, and hydrogen ion content surrounding the neuron.
- There is an expanding number of identified TRP types, with the TRPV (vanilloid) as the most studied.
- The TRPV1 is a non-selective cation channel that is specifically activated by heat greater than 43 degrees C; or capsaicin, the active agent in certain pepper plants. When the channels are activated, there is an increasing release of substance P (sP) and calcitonin gene-related peptide (CGRP) from peripheral and central terminals that promotes pain sensation.
- If there is repetitive TRPV channel activation, there is a desensitization process and a diminished sP and CGRP release over time.

- The TRPM-8 (melastatin) channel is activated by noxious cold sensations, near 20 degrees C and menthol.
- Interestingly, menthol activates the TRPM-8 channels, to inhibit Ca2+ influx to produce a cooling sensation and block various pain types.
- When applied shortly before capsaicin, menthol appears to reduce the burning discomfort produced by activation of the TRPV channels.
Selected References - TRP Agents


Opiates

- Evidence now supports that peripheral opioid receptors are produced in the dorsal root ganglion then transported both centrally and peripherally - especially after injury or inflammation.
- Various opioids, administered as either topical and regional preparations, have been shown to reduce pain responses.
- Local anesthetics appear to be synergistic with topical opioids as well. When applied to open ulcers, or other wounds, topical morphine has been shown to enhance healing.
- Like systemic opioids, tolerance to topical opioids has been reported. Such tolerance apparently is inhibited by co-administration of an NMDA antagonist, such as ketamine.

Opiates

- Not all opioid preparations are purely topical or local in action. Fentanyl favors a transdermal to systemic distribution pattern.
- Central side-effects of opioids including sedation, euphoria, and dependence can still result if the topical dose is significant, or if vascular uptake is considerable.
- The anti-diarrheal agent loperamide is actually a unique mu opioid agonist that lacks CNS side-effects because it does not cross the blood-brain barrier.
- Several studies have shown significant analgesic responses from topical loperamide.
- Menthol has also been proposed to act as a kappa opioid agonist as well.
Opiates

- Opioid receptors synthesized in the Dorsal Root Ganglion:
  - Transported Centrally and Peripherally
  - Peripheral axonal transport up-regulated during inflammation
- Opioids reduce action potential frequency in group III a delta fibers.
- Low doses of opioids administered peripherally to inflamed tissues elicit potent analgesic effects.
- Non-inflamed tissues will not elicit analgesic effects.
- Systemically administered centrally penetrating mu, delta and kappa agonists produced a substantial part of antinociception through peripheral opioid receptors.

Peripheral Effects of Opioids

Kappa agonists anti-inflammatory effects

- Kappa opioid actions exerted by:
  - Reduced adhesion molecule expression.
  - Inhibition of cell trafficking.
  - Reduced TNF release.
  - Alterations in mRNA expression and protein levels of sP and CGRP in joint tissue.
- Kappa opioids most effective at onset of disease.
- Inflammation disrupts perineurium:
  - Leads to more "sprouting" thus forming more terminals.
  - Inhibiting this process by controlling inflammation decreases summation and central excitation.

Selected References - Opiates

NMDA Antagonists

- The NMDA receptor has long been associated with central sensitization changes that lead to chronic neuropathic pain.
- Until recently, peripheral actions were not felt to be an active contributor to sensitization processes. NMDA receptors have been identified in peripheral C fibers in many regions, including various dermal regions.
- When activated by glutamate, which is common in inflammation and tissue injury, the NMDA receptors allow a cascade of events that include increased influx of calcium and sodium that lead to production of other sensitizing substances, such as nitric oxide and various prostaglandins.
- Topical or regional application of such NMDA antagonists, such as ketamine, memantine, or orphenadrine has been shown to considerably decrease regional pain.
- Data suggests that peripheral glutamate receptors on cutaneous axons can be manipulated to reduce certain aspects of pain of peripheral origin.

Selected References - NMDA

It’s Time to Hit The Play Button and Get The Show On The Road

Customization Services

Play Video

And When You Do……

The CUSTOM in Compounding Will Again Be……

CUSTOMization

SUCCESS AHEAD