TREATING VIRGINIA’S PAIN:
AN UPDATE ON NON-OPIOID AND ADJUNCTIVE
MEDICATIONS FOR CHRONIC PAIN

9:00 - 10:15AM

ACPE UAN: 107-000-14-012-L01-P
Activity Type: Application-Based
0.125 CEU/1.25hr

Learning Objectives for Pharmacists: Upon completion of this CPE activity participants should be able to:
1. Describe the latest safety information concerning non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen
2. Implement rational use of topical medications in chronic pain patients
3. Discuss the latest evidence-based options for the treatment of neuropathic pain
4. Apply information learned to the patient case

Speakers: Geoffrey C. Wall, PharmD, FCCP, BCPS, CGP, is a Professor, Department of Clinical Sciences, College of Pharmacy at Drake University. His clinical practices include the Internal Medicine and Medical Intensive Care Teaching Services at Iowa Methodist Medical Center in Des Moines, IA. Dr. Wall received his Bachelor of Science in Pharmacy from the University of Utah in 1992 and his Doctor of Pharmacy from Idaho State University in 1998. He completed an ASHP-accredited Internal Medicine Specialty Residency at Scott and White Memorial Hospitals and Clinics in 1999. He is Board-Certified in Pharmacotherapy and is a Certified Geriatric Pharmacist. He is a Fellow of the American College of Clinical Pharmacy. Dr. Wall has written a number of peer-reviewed papers and textbook chapters on a variety of topics, and has designed or participated in several clinical trials. His research interests include drug treatment of gastrointestinal disorders, including inflammatory bowel disease (IBD), clinical evaluation of drug allergy and rheumatologic disorders.

William J. Yost, MD, FACP, is the Director of Internal Medicine Residency Program at Iowa Methodist Medical Center in Des Moines, IA and Dr. Yost is also a consulting partner for Medical Intelligence Group, PLLC, also in Des Moines. Dr. Yost attended medical school at the University of Iowa College of Medicine and graduated in 1988.

Speaker Disclosure: Geoff Wall and John Yost report no actual or potential conflicts of interest in relation to this CPE activity. Off-label use of medications will be discussed during this presentation.
Non-Opioid And Adjunctive Medications For Chronic Pain

GEOFFREY C. WALL, PHARM. D. FCCP, BCPS, CGP
WILLIAM JOHN YOST, M.D. FACP
MEDICAL INTELLIGENCE GROUP, PLLC

Faculty Disclosure

• Geoff Wall, Pharm.D.
  o I do not have actual or potential conflicts of interest associated with this presentation
  o I will discuss the off-label use of medications during this presentation.

• W. John Yost, M.D.
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Meet Virginia

- 29 year-old female presenting with ongoing knee pain which is affecting her ability to ambulate.
- She was a star athlete in high school on the soccer team, but suffered a knee injury during her senior year
- She attended a junior college in Kansas, and is now living in a small town in Iowa. She is a Current Smoker
- She works at a locally-owned retail store downtown, and is a waitress at the local pizza place 3-4 nights per week and on the weekends. She notes ongoing pain especially when on her feet for long periods of time.
Pre-Assessment Questions

- Would NSAIDs be your first choice for Virginia’s pain? Which route? For how long?

Introduction

- Pain = An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
- Physicians, health-workers and others have “fought” pain for centuries
- For mild acute pain or early chronic pain (like Virginia has) non-opioids are often used
  - Update on information
- Neuropathic pain options are expanding
  - Ditto

Part 1: Safety Considerations of Non-Opioid Drugs

GEOFFREY C. WALL, PHARM. D. FCCP, BCPS, CGP

Acetaminophen Safety

- In use since 1950 (OTC 1959)
- At the time considered much safer than the only other oral non-opioid pain medication (ASA)
- Reports of hepatotoxicity since the 1960s
- Acute OD has well known risks and treatment
- What about chronic use?
Acetaminophen hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure

- The report describes 67 patients who developed hepatic injury after ingestion of APAP with therapeutic intent.
- All were regular users of alcohol
- Doses of APAP were in the "nontoxic" range (6 g/d) in 60% of the group, within the recommended range (4 g/d) in 40%, and at 4.1 to 6 g/d in 20%
- Recently abstinent alcohol abusers seem to tolerate doses up to 4 gms/day for short courses with no biochemical signs of toxicity

Clinical Pearls for Chronic APAP Use

<table>
<thead>
<tr>
<th>Factor</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of presentation</td>
<td>Initiation of therapy &gt; 16 hours predicts worse outcome</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Toxic dose threshold probably lowered; Therapeutic doses (no more than 4.0 gm/d) appear safe</td>
</tr>
<tr>
<td>Fasting/malnourished</td>
<td>Toxic dose threshold may be lowered</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>Toxic dose threshold lowered: (eg., isoniazid, phenytoin, SMX-TMP, carbamazepine)</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>Little data to support dose reductions</td>
</tr>
</tbody>
</table>
APAP: Renal Toxicity

- Analgesic nephropathy syndrome
  - Acetaminophen may be involved but study results vary and most implicate phenacetin, and analgesic mixtures taken over years
  - National Kidney Foundation still recommends APAP as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease
  - Clinical Implication:
    - Supervise long-term analgesic use
In Vitro Selectivity: COX-2/COX-1 Ratio

Range of COX Selectivity for COX-1 and COX-2
(\log_{10} IC_{50} COX-2/COX-1)

Increasingly COX-2 Selective
Increasingly COX-1 Selective

Increased CV Toxicity?
In Vitro Selectivity: COX-2/COX-1 Ratio

Range of COX Selectivity for COX-1 and COX-2
\( \log_{10} \frac{IC_{50, COX-2}}{IC_{50, COX-1}} \)

Increasingly COX-2 Selective
Increasingly COX-1 Selective

NSAIDs: GI Toxicity

- Prevalence of gastric and duodenal ulcers
  - 9–22%

- Bleeding, perforation, or obstruction
  - 1/10 NSAID-induced peptic ulcer

- GI bleeding
  - 35% of all peptic ulcer complications
  - Most common serious ADE in US
  - 10,000-20,000 deaths/year

- Economic implications
  - 200,000-4000,000 hospitalizations each year in US
  - > $4 billion health care cost

Risk Factors for NSAID-Mediated GI Bleeding

Risk Factors

- Concomitant Corticosteroid Or Anticoagulant Use
- Previous History Of Ulcers Or GI Bleeds
- Alcohol Consumption
- Smoking

Does Gastroprotection Work?

- Meta-analysis of cohort studies
- Significant heterogeneity excluded several studies
- Found a general benefit in both PPIs and Misoprostol in preventing gastropathy

**NSAIDs: Renal Toxicity**

- **Epidemiology**
  - 90% drug-induced toxicity caused by: aminoglycosides, contrast materials, or NSAIDs (15%)
  - 1-5% of patients taking NSAIDs develop a nephrotoxic syndrome
  - 20% of NSAID using pts are considered at risk because of underlying conditions.


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**NSAIDs: Acute Renal Toxicity**

At-risk patients with decreased renal function

- Renin-angiotensin axis
  - Angiotensin II
- Adrenergic nervous system
  - Catecholamines

- Renal vasoconstriction
  - ↓ Renal function
  - "Normalized" renal function

- NSAIDs

- Compensatory vasodilation induced by renal prostaglandin synthesis
Risk Factors for NSAID-Mediated Adverse Renal Effects

- Concomitant Use Of Diuretics Or ACE Inhibitors
- ≥65 y Of Age
- Intrinsic Renal Disease
- Volume Depletion
- Congestive Heart Failure
- Hepatic Disease (cirrhosis)

Flurry of studies in early 2000s that suggested an increased risk of CV events with COX-2 drugs and other NSAIDS
- The more COX-2 Selective = the more CV risk?
- Is Naprosyn Cardioprotective?
- Latest Meta-analysis from BMJ
- **Bottom line: Avoid celecoxib and diclofenac in high risk CV patients**
- Also don’t forget worsening of CHF!!
Comparative Safety of Opioids and NSAIDS in Arthritis

- Large Medicare DB study of patients with OA or RA from 1999-2005
- New prescriptions for opioid, NSAID or COX-2 drug
- Used propensity scores and multivariate regression to adjust for confounders
- N = 36,414
- Found opioid use associated with increased risks of hospitalization associated with drug or all cause mortality


Categories with the largest number of deaths

- Sedatives-Hypnotics-Antipsychotics 382
- Opioids 307
- Cardiovascular drugs 252
- Antidepressants 210
- Stimulants and street drugs 203
- Acetaminophen (alone or combo) 352
Practical Advice

- In terms of CV effects, naproxen is associated with lowest risk and COX-2 drugs the highest
- All NSAIDs are contraindicated in active peptic ulceration, but may be considered if gastroprotection/H. Pylori treatment considered
- Always consider prescribing gastric protection in form of PPI for those at risk requiring long-term NSAIDs
- Avoid NSAIDs and COX-2 drugs in those with history of heart failure
- Avoid NSAID or COX-2 drugs in those with GFR <30, use with caution when GFR 30-60 ml/min

Part 2: Neuropathic Pain

WILLIAM J. YOST, MD FACP
Faculty Disclosure

• I do not have actual or potential conflicts of interest associated with this presentation

• I will discuss the off-label use of medications during this presentation.

Learning Objectives

Upon completion of this activity participants should be able to:

1. Understand the characteristics of neuropathic pain
2. Understand the fundamentals of evaluation of neuropathic pain
3. Know the first-line treatments of neuropathic pain, including indications and limitations
4. Recognize the importance of combination therapy
5. Know the role of adjunct agents in relief of neuropathic pain
Pre-Assessment Questions

- What are the essential elements to include in the evaluation of patients with neuropathic pain?
- What are the goals in managing patients with neuropathic pain?
- What are the drugs that are first-line agents in managing neuropathic pain?
- Describe the principal side effects associated with each of these drugs.
- Name two second-line agents in the management of neuropathic pain.

Neuropathic Pain

- Group of heterogeneous conditions without a single, unifying etiology or mechanism
- Can be classified as central or peripheral
- Often severe pain and typically resistant to standard therapy
- Aberrant signal processing is hallmark of the condition
Neuropathic Pain

• Neuropathic pain is complex and often difficult to treat

• Usually involves distal extremities and often worse at night

• Pain often described as burning, lancinating, sharp or needle-like

• May be associated with:
  o Paresthesias
  o Hyperalgesia
  o Allodynia

Neuropathic Pain – Some Examples

• Diabetic neuropathy or amyotrophy

• HZV reactivation/postherpetic neuralgia

• Brachial plexus injury/tumor invasion

• Trauma or ischemic injury to spinal cord, brainstem or thalamus

• Complex regional pain syndromes (CRPS)
### Evaluation of Neuropathic Pain

- Complete history and assessment of symptoms is essential
  - Events surrounding onset, duration, quality, location, intensity of pain
  - Factors that precipitate or relieve pain
- Must include careful psychosocial assessment
  - Effect on work and family life
  - Daily function
  - Presence or absence of psychiatric co-morbidities
  - Substance use
- If significant psychological co-morbidity or substance abuse, consider referral
- Focused physical and neurologic examination

### Evaluation of Neuropathic Pain

- No definitive test or procedure
- Consider directed lab testing, e.g. HIV, glucose/A1C, TSH
- Imaging often not helpful
- Nerve conduction studies are *not* diagnostic
- Quantitative sensory testing may be helpful
Evaluation of Neuropathic Pain

- Use of validated pain measurement tools beneficial
  - Pain Quality Assessment Scale
  - Leeds Assessment of Neuropathic Symptoms
  - Signs Pain Scale

- Consultation often a good idea, particularly if cause is unclear

Management of Neuropathic Pain

- Rarely eliminated
- Goal is to improve quality of life
  - Reduction in pain
  - Improvement in function

- Combination therapy is often necessary
- Attention to underlying condition may be helpful, e.g. good glycemic control in a diabetic
- Epidural steroids or surgical intervention sometimes of benefit
Management of Neuropathic Pain

- Inflammation is **not** at play – NSAIDs of little value

- Combination therapy usually necessary
  - Adjuvant analgesics
  - Opioids

- Set reasonable expectations

First-line Agents

- Gabapentin
- Pregabalin
- Topical lidocaine patch, 5%
- Opioids
- Tramadol
- TCAs
Gabapentin

- Approved by FDA in 1983 for treatment neuropathic pain
  - Trigeminal neuralgia
  - Post-herpetic neuralgia
- Not approved by FDA, but effective and used in the following conditions:
  - Diabetic neuropathy, mixed neuropathic pain syndromes
  - Phantom limb pain
  - GBS
  - Spinal cord injury
- Gilron et al, 2005, demonstrated combined use with morphine effective and resulted decreased dose of both

Adverse effects
- Sedation, dizziness, ataxia, weight gain and peripheral edema
- Gait or balance problems in the elderly

Dose
- Initiate 100-300 mg at hs
- Increase in 100-300 mg increments every 3-7 days
- Target dose 1800-3600 mg daily in 3 divided doses
Gabapentin

- 100% renal excretion – lower dose in patients with moderate to severe renal dysfunction

- Preferred to all other agents, if possible
  - Well tolerated
  - Minimal SE
  - Few drug interactions

Pregabalin

- Pregabalin recently recommended by American Academy of Neurology guidelines
  - Level A evidence to support its use

- Chief disadvantages: Expensive, and not always well tolerated
Topical lidocaine, 5%

- Approved by FDA in 1999 for treatment PHN
- 4 RCTs have demonstrated efficacy in PHN, other focal peripheral neuropathies1-2,3,4
- Recent open-label study demonstrated improvement in PHN, diabetic neuropathy, and low back pain5
- Minimal systemic absorption of lidocaine

1 Galer et al, Clin J Pain, 2002
2 Meier et al, Pain, 2003
3 Galer et al, Pain, 1999
4 Rowbotham et al, Pain, 1996
5 Argoff et al, Curr Med Res Opin, 2004

Topical lidocaine, 5%

- Apply to intact skin directly over painful site
- OK to cut or trim patch
- Approved Dose: up to 3 patches for 12 out of 24 hours
- Minimal SEs: mild skin reaction
- No clinically significant drug reactions
  - use with caution with Type I antiarrhythmics and “caine” local anesthetics
Opioids

- Multiple double blind, placebo controlled RCTs have demonstrated efficacy\(^1,2,3\)

- **However**, often require higher doses than patients with nociceptive pain
  - Increased risk constipation, sedation, nausea
  - Concerns re: inadvertent overdose
  - Risk of diversion or misuse

- Often used in combination therapy with adjuvant agents

1 Mystakidou et al, J Pain, 2003
2 Huse et al, Pain, 2001
3 Watson et al, Pain, 2003

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Opioids

- Initiate short-acting opioids
  - Titrate over 1-2 weeks
  - Then convert to LA agent with SA opioid for break-through pain

- Further adjustment as needed

- Constipation prophylaxis essential

- Attentive follow-up is critical
Tramadol

- Inhibits re-uptake NE and serotonin at nerve terminal
- Demonstrated reduction in neuropathic pain, including hyperalgesia and allodynia

Tramadol

- Dose: initiate 25-50 mg once or twice daily, increase by 25-50 mg increments every 3-7 days
- Maximum dose: 400 mg daily (300 mg in the elderly)
- SEs:
  - Seizures
  - Sedation, nausea, orthostatic hypotension, dizziness, constipation
  - Avoid concomitant use other serotonergic agents (e.g. SSRIs, TCAs)
    - serotonin syndrome
<table>
<thead>
<tr>
<th>TCAs</th>
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<tbody>
<tr>
<td>- Produce analgesic effect independent of effect on mood</td>
</tr>
<tr>
<td>- Inhibit re-uptake of NE and serotonin</td>
</tr>
<tr>
<td>- Strong evidence to support use, especially in diabetic neuropathy and PHN(^1)</td>
</tr>
<tr>
<td>- However, <strong>lack of evidence</strong> to support use in other neuropathic pain disorders per recent Cochrane review, and</td>
</tr>
<tr>
<td>- <strong>Ineffective</strong> in treating HIV-related neuropathies</td>
</tr>
</tbody>
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\(^1\) Cochrane Database Syst Rev, 2005

<table>
<thead>
<tr>
<th>TCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Secondary amines (nortriptyline, desipramine) preferable due to better SE profile, less anticholinergic effects</td>
</tr>
<tr>
<td>- Dose: initiate with 10-25 mg at hs, increase every few days as needed</td>
</tr>
<tr>
<td>- Maximum dose: 75-150 mg daily</td>
</tr>
<tr>
<td>- SEs:</td>
</tr>
<tr>
<td>- Sedation, dry mouth, blurred vision, dizziness, orthostatic hypotension, urinary obstruction and constipation</td>
</tr>
</tbody>
</table>
Other Antidepressants

- **Bupropion**
  - Limited data to support its use
- **SSRIs**
  - Some evidence to support use of paroxetine, citalopram in treatment diabetic neuropathy
- **Duloxetine**
  - FDA approval for treatment diabetic neuropathy
  - 60 mg once or twice daily
  - Nausea, dizziness, somnolence and fatigue most common SEs

Second-line Treatments

- **Carbamazepine**
  - First agent approved – trigeminal neuralgia
  - Limited by safety profile
- **Lamotrigine**
  - Most robust evidence supporting use diabetic neuropathy, HIV-related neuropathy, post-stroke pain
  - Again, limited by safety profile
- **Topiramate**
  - Diabetic neuropathy
- **Tizanidine**
  - One open-label trial found efficacy in painful neuropathy, and a systematic review found effective for trigeminal neuralgia
- **Capsaicin**
  - Depletes substance P from nerve terminals
When to Refer?

- The diagnosis is unclear
- The patient’s pain is refractory to medical management
- The patient does/will require opioids and has identified potential for abuse
- The patient may benefit from a procedure

Other Treatments

- Epidural or peripheral nerve blocks
- SC stimulators
- Intrathecal pumps
Summary of Neuropathic Pain Management

- Neuropathic pain is a challenging condition to treat with poorly understood pathophysiology

- Careful evaluation, with attention to history, psychosocial history, and a focused exam and testing are essential

- Successful management will usually require combination therapy with opioids and adjuvant medications

- Consider second-line agents and referral when the patient does not demonstrate adequate improvement

Part 3: The Role of Topical Drugs in Chronic Pain
### Medications Used in Transdermal Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>1-5%</td>
<td>NE Reuptake inhibitor</td>
</tr>
<tr>
<td>Baclofen</td>
<td>2-5%</td>
<td>GABA(_\text{A}_1) Agonist</td>
</tr>
<tr>
<td>Bretylium</td>
<td>1-5%</td>
<td>Sympathetic Inhibition</td>
</tr>
<tr>
<td>Bupivicaine</td>
<td>0.25-10%</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.025-0.1%</td>
<td>Substance P Blockade</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2-5%</td>
<td>NMDA Na(^+) Blocker</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1-0.3%</td>
<td>Alpha -2 Agonist</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>1-4%</td>
<td>Muscle Relaxant</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>5-10%</td>
<td>NMDA Receptor Antagonist</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Mechanism</th>
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</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>2-10%</td>
<td>Cyclooxygenase Inhibitor</td>
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<tr>
<td>Diphenhydramine</td>
<td>5-10%</td>
<td>Voltage Regulated Na(^+) &amp; Ca(^{++}) Blockade</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>5-10%</td>
<td>Voltage Regulated Na(^+) &amp; Ca(^{++}) Blockade Glutamate Antagonist</td>
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<tr>
<td>Guaifenesin</td>
<td>5-10%</td>
<td>Muscle Relaxant</td>
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<tr>
<td>Ibuprofen</td>
<td>10-30%</td>
<td>Propionic Acid NSAID</td>
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<tr>
<td>Indomethacin</td>
<td>15-20%</td>
<td>Methylated Indole NSAID</td>
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</table>
Medications Used in Transdermal Delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Ketamine</td>
<td>5-15%</td>
<td>NMDA Receptor Antagonist</td>
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<td>Ketoprofen</td>
<td>5-10%</td>
<td>Propionic Acid NSAID</td>
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<td>Lidocaine</td>
<td>2-10%</td>
<td>Anesthetic</td>
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<td>Lipoic Acid</td>
<td>2-3%</td>
<td>Antioxidant</td>
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<tr>
<td>Loperamide</td>
<td>5-10%</td>
<td>Mu agonist</td>
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<tr>
<td>Naproxen</td>
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<td>Propionic Acid NSAID</td>
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<tr>
<td>Nifedipine</td>
<td>0.2-16%</td>
<td>Non-NMDA Ca+2 Channel Antagonist</td>
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<tr>
<td>Pentoxifylline</td>
<td>5-15%</td>
<td>TNFα Inhibitor, Peripheral Vasodilator</td>
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<td>Phenytoin</td>
<td>0.5-2%</td>
<td>NMDA Na+ Blocker</td>
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What Data Supports These Formulations?

- Not Much
- In depth review in 2013 found mostly small case series and CR for modalities like compounded amitriptyline and anticonvulsant drugs with variable results
- Safety analyses rarely done
- Thus, not much evidence-base for the clinician except for:
  - Topical NSAIDs
  - Topical Lidocaine

Topical Lidocaine

- Available for over 10 years
- Approved for PHN, used in other types of neuropathic pain
- ? Use as an adjunct in somatic pain
- Relatively well tolerated
- May apply up to three patches for 12/24 hrs
- May cut patch if needed
- Cost: $10/patch

Results (n=143)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lidocaine Patch 5% (n=69)</th>
<th>Celecoxib 200 mg/d (n=74)</th>
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<tbody>
<tr>
<td>joint stiffness 0–2 Weeks</td>
<td>-0.0197</td>
<td>-0.6726</td>
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<td>-0.0264</td>
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<td>-0.1169</td>
<td>0.0159</td>
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<td>WOMAC physical function</td>
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<td>WOMAC composite score</td>
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<td>-1.0228</td>
<td>-0.9595</td>
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*WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

*No significant between-treatment differences were found.
Topical NSAIDs

- Various formulations used in Europe for over two decades
- Approved in EU for acute injury (sprains, etc) and short-term treatment of OA
- Diclofenac recently approved in US
  - Gel, Solution, and Patch

Topical NSAIDs in Chronic Pain

- In-depth 2013 review of topical NSAIDs
- In general found similar efficacy and less GI ADRs over up to 12 weeks

Effect sizes (95% confidence intervals) in pain relief between topical non-steroidal anti-inflammatory drugs and placebo.

Practical Advice

- At this point topical NSAIDs have the most data to support use in treatment of pain
- Probably safer than systemic drug, but many studies excluded patients at high risk for ADRs
- Expensive
- Topical lidocaine may be worth trying in localized somatic pain syndromes
  - Expensive so discontinue if no relief found
  - Probably subtypes of patients who respond
Questions?

MEDICAL INTELLIGENCE GROUP, PLLC

Education, Technology, Patient Care Consultations, and Protocol Development

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