Optimizing Neuropathic Pain Medications

Dermot More-O’Ferrall, MD
PAIN MANAGEMENT ≠ OPIOID DISPENSING
Objectives

Understand:
• Definition and subtypes of pain
• Pathophysiology of neuropathic pain
• Pharmacologic treatment options
• Discuss EFNS, NeuPSIG and Canadian guidelines
• APM philosophy
Definitions We Can Agree On

• Pain
  – Unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

• Neuropathic Pain
  – 1994 (IASP): “Pain initiated or caused by a primary lesion or dysfunction of the nervous system”
  – 2008 (IASP – NeuPSIG) : “Pain caused by a lesion or disease of the somatosensory nervous system”
Pain Classification

**Pain**

- **Acute**
  - Injury
  - Postoperative
  - Flare

- **Headache (migraine)**

- **Chronic**
  - **Nociceptive**
  - **Mixed**
  - **Somatic**
  - **Visceral**

- **Neuropathic**
  - Diabetic neuropathy (DN)
  - Postherpetic neuralgia (PHN)
  - Radiculopathy (RADIC)

- **Neuropathic**
  - Cancer pain
  - Low back pain
  - Fibromyalgia

- **Nociceptive**
  - Osteoarthritis
  - Rheumatoid arthritis
  - Myofascial pain

- **Somatic**
  - IBS
  - Pancreatitis
  - Bladder pain
  - Noncardiac chest pain
  - Abdominal pain syndrome
Acute Pain

- Cause of most pain
- Identifiable physical or organic cause
- Usually accompanied by actual tissue damage
- Increased autonomic activity
- Serves a protective function
- Pain resolves with healing of underlying injury
- Predictable prognosis
Chronic Pain

• Pain that extends 3-6 months beyond onset or beyond the expected period of healing
• Persistent after tissue damage has healed
• Ceases to serve a protective function
• Produces harmful psychosocial effects
• Degrades health and function
• Can result in depression
• Treatment needs to be multidisciplinary
Nociceptive Pain (Somatic/Visceral)

• Results from inflammatory, mechanical, thermal or chemical activation of peripheral nociceptors
• Mediated at nociceptors widely distributed in cutaneous tissue, bone, muscle, connective tissue, vessels and viscera
• Proportionate to the stimulation from the receptor
• Pain described as dull, aching and throbbing

E. Krames, J Pain & Symptom Mgt, 1996
Neuropathic Pain

• “Pain caused by a lesion or disease of the somatosensory nervous system”
• May be mediated by sensitization of nociceptors, abnormal activation of NMDA receptors, “wind-up” and central sensitization
• Disproportionate to the stimulation of the receptor
• Pain described as sharp, shooting, stabbing, burning, tingling and electric or lightning-like.

Physiology of Pain Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior
PAIN:

An unpleasant **sensory and emotional** experience associated with **actual or potential** tissue damage, or described in terms of such damage.
Primary afferent nociceptors convey noxious information to projection neurons within the dorsal horn.

A subset of these projection neurons transmit information to the somatosensory cortex via the thalamus, providing information about the location and intensity of the painful stimulus.

Other projection neurons engage the cingulate and insular cortices via connections in the brainstem (parabrachial nucleus) and amygdala, contributing to the affective component of the pain experience.

This ascending information also accesses neurons of the rostral ventral medulla and midbrain periaqueductal gray to engage descending feedback systems that regulate the output from the spinal cord.
Brain regions and circuits implicated in the comorbidity between pain and depression

- 60% of patients with depression have chronic pain
- 18-85% of patients with chronic pain have depression

Alterations in modulatory neuropeptides NE, 5HT, DA and alterations in glutamate signaling play a role in pain and depression

1. Normally pain is carried by small fibers: A delta and C fibers
Under Normal Conditions

1. Normally pain is carried by small fibers: A delta and C fibers

2. Touch and proprioception are carried by the larger A beta fibers
Central Sensitization Occurs Due to:

1. **Glutamate/NMDA receptor-mediated sensitization**
2. **Disinhibition: interneurons and descending inhibitory pathways**
3. **Microglial activation: morphine hyperalgesia**
Central Sensitization

- Increased excitability of spinal cord neurons (dorsal column) from peripherally sensitized afferents

- Leads to spontaneous firing and enlarging area of response (wide dynamic range neurons) and “wind-up”

- Leads to abnormal neuro-anatomical reorganization with connections between A beta, A delta and C fibers (sprouting), which spreads and involves multiple dermatomes = diffuse symptoms

- Symptoms outlast the injury/stimuli (LTP=long-term potentiation)
Central sensitization

– Increased facilitation of **ascending** pathway (increase in substance P, CGRP, glutamate)

– Decreased activity of **descending inhibitory** pathways (deficit in serotonin, norepinephrine, dopamine)
Acute to Chronic Pain Cycle

**Pathophysiology of Maintenance**
- Radiculopathy
- Neuroma traction
- Myofascial sensitization
- Brain pathology (loss, reorganization)

**Psychopathology of maintenance**
- Encoded anxiety dysregulation
  - PTSD
- Emotional allodynia
- Mood disorder

**Acute injury and pain**

**Central sensitization**

**Neurogenic Inflammation**
- Glial activation
- Pro-inflammatory cytokines
- Blood-nerve barrier disruption

**Peripheral Sensitization**
- Na+ channels
- Lower threshold

**Secondary Pathology**
- Muscle atrophy, weakness
- Bone loss
- Depression
- Cortical atrophy

**Disability**
- Less active, Kinesiophobia
- Decreased motivation
- Increased isolation
- Role loss
Patients with FM (n=10) had significantly less GM volume in posterior cingulate, insular cortex, MFC, and parahippocampal gyrus. Rate of age-related decline was significantly greater in patients with FM than in controls (n=10; \( P < .001 \))

Patients with FM were losing 1.5 cm\(^3\) of GM annually since the year of their diagnosis.

Patients with chronic back pain (CBP) had 5-11% less whole-brain gray matter, equivalent to 10-20 years of normal aging

The River Liffey

Dublin, Ireland
“Several guidelines agree that **first- and second-line drugs** for neuropathic pain include **anticonvulsants** (gabapentin or pregabalin), **tricyclic antidepressants**, and **SNRIs**. ... **Interventional approaches** such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain”.

Pharmacologic Treatment: Let us see how they fare in real life per 2015 review on neuropathic drugs

- Anticonvulsants
  - Lamotrigine
  - Oxcarbazepine
- Antidepressants
  - Duloxetine
  - Imipramine
  - Venlafaxine
- Sodium Channel Blockers
  - Fentanyl
  - Gabapentin
- NMDA-Receptor Antagonists
  - Clonazepam
  - Ketamine
  - Mexiletine
- Opioids
  - Oxycodone
  - Phenytoin
- Topicals
  - Baclofen
  - Lidocaine
- Antidepressants
  - Imipramine
  - Venlafaxine
- Topicals
  - Oxycodone
  - Capsaicin
- Tricyclic Antidepressants
  - Imipramine
Analgesic Drug Classes

• Acetaminophen
• NSAIDs
• COX-2 Inhibitors
• Steroids
NSAID classes

• **Carboxylic Acid**
  A. Acetic Acid: Diclofenac, Etodolac, Indomethacin, Sulindac
  B. Salicylic: Aspirin, Salsalate
  C. Proprionic Acid: Ibuprofen, Naproxen, Ketoprofen, Oxaprozin

• **Enolic Acid**
  A. Pyrazalones: Phenylbutazone
  B. Oxicam: Meloxicam, Piroxicam

• **COX 2 Inhibitors: Celecoxib**
Analgesic Drug Classes

• **Muscle relaxants:**
  – Cyclobenzaprine (Flexeril, Amrix)
  – Tizanidine (Zanaflex)
  – Metaxolone (Skelaxin)
  – Baclofen (Lioresal)
  – Orphenadrine 100mg bid
  – Methocarbamol (robaxin) 4500mg/day
  – Diazepam (Valium)
  – Carisoprodol (Soma)
Neuropathic Pain

- **TCADs**
  - (NNT 3.6); Amitriptyline, Nortriptyline

- **SNRIs**
  - (NNT 6.4); Duloxetine, Venlafaxine

- **AEDs**
  - (NNT 7.2); Gabapentin, Lyrica

- **SSRIs**
  - (No benefit - pain)

- **Topicals**
  - Capsaicin, Lidocaine
  - Finnerup N. Lancet Neurology, 2015
• ALPHA 2 Adrenergic Agonists
  — Clonidine, Tizanidine

• NMDA Rec Antagonists
  — Ketamine, Dextromethorphan

• Cannabinoids

• Botulinum Toxin
Opioids

Short-Acting Opioids

- Tramadol
- Codeine
- Hydrocodone
- Morphine
- Oxycodone
- Tapentadol (Nucynta)
- Oxymorphone
- Hydromorphone
- Fentanyl

Long-Acting Opioids

- Tramadol ER
- Hydrocodone (Zohydro, Hysingla)
- MS Contin/ER
- Oxycontin
- Nucynta ER
- Oxymorphone (Opana ER)
- Hydromorphone (Exalgo)
- Fentanyl
- Methadone
- Buprenorphine
Combination Analgesics

Rationale

• Multiple sites of action target multiple pain pathways
• Complementary pharmacokinetic activity
• Potentially synergistic analgesic effect
• Reduced adverse event profile with comparable efficacy

Anticonvulsants - Mechanisms Of Action

• Sodium channel blockers

• Calcium channel blockers

• Increase in GABA activity
Gabapentin and Pregabalin: Mechanism of Action

• Binds to a subunit of voltage-gated calcium channels
  – Reduces Ca2+ influx during depolarization
  – Analgesic, anxiolytic and anticonvulsant activity

• Reduces release of excitatory neurotransmitters (glutamate, substance P)
# Second Generation Anticonvulsants

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<tr>
<th>Drug Name</th>
<th>Dosage</th>
<th>Metabolism</th>
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<tr>
<td><strong>Gabapentin</strong> (neurontin)</td>
<td>100-3600 mg/day</td>
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<td><strong>Pregabalin</strong> (Lyrica)</td>
<td>150-600 mg/day</td>
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<td>Oxcarbazepine (trileptal)</td>
<td>150-2400 mg/day</td>
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<tr>
<td>Zonisamide (Zonegran)</td>
<td>100-600 mg/day</td>
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<tr>
<td><strong>Topiramate</strong> (Topamax)</td>
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# Antiepileptics and Membrane Stabilizers

<table>
<thead>
<tr>
<th>Membrane stabilizers for pain control</th>
<th>Starting dose/day</th>
<th>Target dose/day</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Carbamazepine Tegretol®</td>
<td>200</td>
<td>600-1200</td>
<td>sedation, ataxia, diplopia, leukopenia, ↓Na⁺</td>
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<tr>
<td>Valproate Depakote®</td>
<td>400-500</td>
<td>1000-3000</td>
<td>↑weight, ↓platelets, liver failure</td>
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<td>Pregabalin Lyrica ®</td>
<td>75</td>
<td>300-600</td>
<td>↑weight, somnolence</td>
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<tr>
<td>Gabapentin Neurontin®</td>
<td>100-300</td>
<td>1800-3600</td>
<td>↑weight, dizziness, somnolence, edema</td>
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<tr>
<td>Lamotrigine Lamictal®</td>
<td>50</td>
<td>300-500</td>
<td>rash, Stevens-Johnson syndrome</td>
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<tr>
<td>Levetiracetam Keppra®</td>
<td>1000</td>
<td>3000</td>
<td>recurring infections</td>
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<tr>
<td>Oxcarbazepine Trileptal®</td>
<td>300</td>
<td>600-2400</td>
<td>↓Na⁺</td>
</tr>
<tr>
<td>Tiagabine Gabitril®</td>
<td>4</td>
<td>32-56</td>
<td>nervousness, flu-like symptoms</td>
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<tr>
<td>Topiramate Topamax®</td>
<td>25-50</td>
<td>200-400</td>
<td>↓weight, renal calculi</td>
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<tr>
<td>Zonisamide Zonegran®</td>
<td>100</td>
<td>600</td>
<td>↓weight, renal calculi</td>
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# Tricyclic Antidepressants; Dosage

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<tr>
<th>Tertiary Amines</th>
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<tr>
<td>Amitriptyline 10-300mg</td>
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<tr>
<td>Doxepin 10-300mg</td>
<td>Desipramine 10-300mg</td>
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<tr>
<td>Imipramine 10-300mg</td>
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</table>
TCAs: Mechanisms

• Serotonin and norepinephrine reuptake blockade\(^1\)
• Blockade of \(\alpha\)-adrenergic receptors\(^2\)
• Antihistaminic
• Sodium and potassium channel modulation\(^1,2\)
• Modulation of monoamine neurotransmitters\(^1\)
• ? NMDA-receptor antagonism\(^1\)

TCAD (side effects)

- Sedation
- Dryness of eyes and mouth
- Constipation, urinary retention
- Weight gain
- Orthostatic hypotension, tachycardia
- Increased QT interval
- Decreased libido
SNRI Antidepressants – Mechanisms Of Actions

• Inhibit reuptake of NE and 5HT

• Watch for serotonin syndrome (Triptans, Tramadol, SSRIs)

• Avoid use with MAOIs
Mechanism of Action of Antidepressants

- Presynaptic neuron
  - Biogenic amines (NE + 5HT)
  - Synaptic cleft
    - Release
    - Reuptake

- Postsynaptic neuron
  - Receptor

Antidepressant Classes:
- TCAs
- SSRIs
- SNRI
- SSNRIs
SNRI (side effects)

- Nausea, constipation, diarrhea, anorexia
- Dry mouth
- Sedation, fatigue
- Headache
- Dizziness
- Sweating
- Loss of libido
SNRIs Dosage

- Venlafaxine 75mg qd increasing to bid
- Duloxetine 20 mg or 30 mg, titrating to 60 mg qd (Max dose 120 mg/day)
Lidoderm Patch

- 5% lidocaine in a patch form
- Max 3 qd, remove after 12 hours
- No side effects
- Applied locally
- Effective in controlling postherpetic neuralgia pain, knee pain from osteoarthritis, post-thoracotomy pain and CRPS pain
Miscellaneous Drugs

- Capsaicin (0.025% – 8%)
- Clonidine patch
- Ketamine (NMDA receptor antagonist)
Diabetic Neuropathy

• First Line
  – SNRIs e.g., Venlafaxine and Duloxetine
  – TCADs e.g., Nortriptyline, Amitriptyline
  – Gabapentinoids- Gabapentin and Pregabalin

• Second Line
  – Opioids
  – Tramadol
Attal, N. EFNS Guidelines on the Pharmacologic Treatment of Neuropathic Pain: 2010 Revision

PHN

• First Line
  – Gabapentinoids - Gabapentin and Pregabalin
  – TCADs e.g., Nortriptyline, Amitriptyline
  – Lidoderm

• Second Line
  – Capsaicin
  – Opioids
Central Pain

• Gabapentinoids- Gabapentin and Pregabalin
  – TCADs e.g., Nortriptyline, Amitriptyline

• Second Line
  – Lamotrigine
  – Opioids
  – Tramadol (SCI)
  – Cannabinoids (MS)

### Table 3: Summary of GRADE recommendations

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>First-line drugs</th>
<th>Second-line drugs</th>
<th>Third-line drugs</th>
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<tbody>
<tr>
<td>High</td>
<td>Serotonin-noradrenaline reuptake inhibitors, duloxetine and venlafaxine</td>
<td>Tricyclic antidepressants, pregabalin, gabapentin, gabapentin extended release or enacarbil</td>
<td>Tramadol, Capsaicin 8% patches, Lidocaine patches</td>
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**Neuropathic pain conditions: All**

**Values and preferences:**
- **Quality of evidence:** High, Moderate, Low
- **Balance between desirable and undesirable effects:** High, Moderate, Low
- **Effect size:** Moderate, Low-moderate, Low
- **Tolerability and safety:** Moderate, Low, Low-moderate
- **Cost and resource allocation:** Low-moderate, Low, Low
- **Strength of recommendation:** Strong, Moderate, Weak
- **Neuropathic pain conditions:** All

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*Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues."

**First, Second, Third Line**

- **FIRST LINE AGENTS**
  - SNRIs e.g., Venlafaxine and Cymbalta
  - TCADs e.g., Nortriptyline, Amitriptyline
  - Gabapentinoids - Gabapentin and Lyrica

- **SECOND LINE AGENTS**
  - Tramadol
  - Lidocaine
  - Capsaicin

- **THIRD LINE AGENTS**
  - Strong Opioids
  - Botox

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Table 3: Summary of GRADE recommendations

GRADE—Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidoacaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain, see the appendix for further information about safety issues.
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</table>

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.
Algorithm for the pharmacological management of neuropathic pain. *Topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin; *Limited randomized controlled trial evidence to support add-on combination therapy. TCA Tricyclic antidepressants; SNRI Serotonin noradrenaline reuptake inhibitors
FLOP: Functional level of pain

- **Interventionally:** Diagnostic or therapeutic
- **Physically:** PT, chiropractic, bracing, TENS
- **Psychology:** P3, SOAPPr, biofeedback, counselling, cognitive behavior program
- **Non-opioid management:** AED, TCAs, SNRIs, topicals, NSAIDs, muscle relaxants, etc.
Objectives

Understand:

• Definition and subtypes of pain
• Pathophysiology of neuropathic pain
• Pharmacologic treatment options
• Discuss EFNS, NeuPSIG and Canadian Guidelines
• APM Philosophy
Asanas with Props

The ancient yogis used logs of wood, stones, and ropes to help them practice asanas effectively. Extending this principle, Yogacharya Iyengar invented props which allow asanas to be held easily and for a longer duration, without strain.

Yogacharya Iyengar in Setubandha Sarvangasana
This version of the posture requires considerable strength in the neck, shoulders, and back, requiring years of practice to achieve. It should not be attempted without supervision.
THANK YOU
Duloxetine and Venlafaxine NNT 6.4

Gabapentin and Pregabalin: NNT 7

NNT Gabapentin is 7.2
NNT Pregabalin is 7.7

**Recommendations**

<table>
<thead>
<tr>
<th></th>
<th>Comparisons</th>
<th>Participants</th>
<th>Active pain relief</th>
<th>Placebo</th>
<th>Number needed to treat (95% CI)</th>
<th>Susceptibility to bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>15</td>
<td>948</td>
<td>217/473</td>
<td>85/475</td>
<td>3.6 (3.0-4.4)</td>
<td>1973</td>
</tr>
<tr>
<td>Serotonin-noradrenaline reuptake inhibitors</td>
<td>10</td>
<td>2541</td>
<td>676/1559</td>
<td>278/982</td>
<td>6.4 (5.2-8.4)</td>
<td>1826</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>25</td>
<td>5940</td>
<td>1359/3530</td>
<td>578/2410</td>
<td>7.7 (6.5-9.4)</td>
<td>2534</td>
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<tr>
<td>Gabapentin</td>
<td>14</td>
<td>3503</td>
<td>719/2073</td>
<td>291/1430</td>
<td>7.2 (5.9-9.1)</td>
<td>1879</td>
</tr>
<tr>
<td>Tramadol</td>
<td>6</td>
<td>741</td>
<td>176/380</td>
<td>96/361</td>
<td>4.7 (3.6-6.7)</td>
<td>982</td>
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<tr>
<td><strong>Strong opioids</strong></td>
<td>7</td>
<td>838</td>
<td>211/426</td>
<td>108/412</td>
<td>4.3 (3.4-5.8)</td>
<td>1326</td>
</tr>
<tr>
<td>Capsaicin 8%</td>
<td>6</td>
<td>2073</td>
<td>466/1299</td>
<td>212/774</td>
<td>10.6 (7.4-18.8)</td>
<td>700</td>
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<tr>
<td>Botulinum toxin A</td>
<td>4</td>
<td>137</td>
<td>42/70</td>
<td>4/67</td>
<td>1.9 (1.5-2.4)</td>
<td>678</td>
</tr>
</tbody>
</table>

Data are number, unless otherwise indicated. *Number of comparisons with placebo in published trials and unpublished trials included in the meta-analysis; results from registries were included if they reported numbers of responders. †Total number of patients treated with active treatment and placebo; patients were counted twice if the study had a crossover design. ‡Number of patients needed to be treated in a new study showing no effect to make the number needed to treat (NNT) greater than 11, which is the cutoff for clinical relevance; susceptibility to publication bias implies that a new study with fewer than 400 participants with no effect might increase the NNT to greater than 11. §Including gabapentin extended release and enacarbil. ¶Susceptible to publication bias.

Table 1: Analysis of susceptibility to bias in published and unpublished trials

**Strong Opioids NNT 4.3**