Non-Opioid and Adjuvant Medications for Chronic Pain

Dr Semionov Valentina
Pain and Palliative Care Unit
Department of Family Medicine,
Clalit Health Services-South District
Ben-Gurion University of the Negev

- Non-Opioid and adjuvant medications for chronic pain
  - Effective alone or for mild to moderate pain
  - Adjuvant analgesia with opioids
  - "Ceiling effect" (an effect that limits the pain relief)
  - May not result in sedation or physical dependence
רשימה של תרופות נלוות

- Paracetamol
- Non Selective NSAIDs
- NSAIDs - Cox 2 selective
- Topical analgesic agents - NSAIDs, Capsaicin, EMLA
- Tramadol

הגדרה של תרופה נלוות

תרופה משילימה משככת כאב - תרופה שהתחיה שלה היאشتוק למשככת כאב
- תרופה אחריםיה שליה לא ידוע ידוע לשכוך את המג自有ית

 huhghvhgh

תרופה משילימה נוגד תופעות לוואי שלושיות
- שמיסי
- BACLOFEN

רשימה של תרופות נלוות

- נוגגי דייכאא
- נוגגי דייכאא
- מומר
- פסו
-ופסי
- NMDA
- הסמארטרופיסות
- הסימטרופיסות
- הקינאמיט
- BACLOFEN
The Inter-Relationship Between Pain, Sleep, and Anxiety / Depression

Pain

Sleep disturbances

Functional impairment

Anxiety & Depression


Multipurpose Adjuvant Analgesics

Class
Antidepressants
Examples
amitriptyline, desipramine, nortriptyline, paroxetine, venlafaxine, citalopram,

Alpha-2 adrenergic agonists
clonidine

Corticosteroids
prednisone, dexamethasone

Classifications of Pain

Duration

Acute

Chronic

Pathophysiology

Nociceptive

Neuropathic
Nociceptive pain

damage to the tissues

Treatment:

NSAID, opioids, adjuvants as needed.
Features of Neuropathic Pain

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>DESCRIPITORS</th>
<th>MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady</td>
<td>Burning, Tingling, Constant, Aching, Squeezing, Itching, Allodynia, Hypersthesia</td>
<td>Gabapentin, Tricyclic antidepressants, Corticosteroids, Mexilitene</td>
</tr>
<tr>
<td>Pain</td>
<td>Stabbing, Shocklike, electric, Shooting</td>
<td>Gabapentin, Baclofen, Tegretol, Corticosteroids, Mexilitene</td>
</tr>
</tbody>
</table>

Examples of Nociceptive and Neuropathic Pain

- Arthritis
- Mechanical low back pain
- Sports/exercise injuries
- Postoperative pain
- Low back pain
- Fibromyalgia
- Neck pain
- Cancer pain
- Painful DPN
- PHN
- Neuropathic low back pain
- Trigeminal neuralgia
- Central poststroke pain
- Complex regional pain syndrome
- Dextral HIV polyneuropathy
Chemicals That Increase Neuropathic Pain Signals

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>An inhibitory neurotransmitter in the brain and spinal cord.</td>
</tr>
<tr>
<td>Serotonin</td>
<td>A naturally occurring derivative of tyrosine that acts in the brain and</td>
</tr>
<tr>
<td></td>
<td>spinal cord.</td>
</tr>
<tr>
<td>NE/5HT</td>
<td>A neurotransmitter that activates neurons in the brain and spinal cord.</td>
</tr>
<tr>
<td>Endorphins</td>
<td>Neurotransmitters that act as a natural painkiller.</td>
</tr>
</tbody>
</table>

Mechanistic Approach to Pain Treatment

- **Brain**: descending inhibition
  - TEA: TAA, opioids, FK866
  - Clonidine, sumatriptan, capsaicin
  - NMDA: ketamine, TPM, Dextromethorphan, methadone

- **Peripheral Sensation**: PNS
  - PGE: NSAIDs/Cox-2

- **Spinal Cord**: Sensation
  - GABA: excitation

- **Central Sensation**: Opioid receptors
  - Opioids: tramadol, clonidine, methadone
  - Tricyclics: mexiteline
  - Calcium: mexiletine, Lidocaine
  - PDE: gabapentin, pregabalin
  - COX-2: ketamine, TPM, Dextromethorphan
The ideal drug

- No metabolites
- No protein binding
- No drug interaction
- No toxicity
- No side effect

Simple dosing
- Easy titration
- Oral
- Once a day
- Price

Paracetamol (Acetaminophen)

- The most widely recommended non-opioid analgesic for mild-to-moderate acute and chronic pain states.
- Centrally mediated analgesia
- Analgesic, antipyretic properties and minimal anti-inflammatory effects
- The ACR guidelines for the medical management of osteoarthritis recommend paracetamol as the preferred first-line therapy in patients with symptomatic osteoarthritis of the knee.

Acetaminophen

Advantages:
- Readily available OTC
- Safe
- Inexpensive
- Optimal dose is 1,000 mg/dose
- The initial drug of choice at a dose of up to 4 g daily.
Acetaminophen

Adverse Effects

Disadvantages:
• Helpful for only mild pain
• Poor compliance with higher doses
• Hepatotoxicity, including progressive, irreversible hepatic failure
• 50% to 75% dose reduction recommended in patients with renal/hepatic dysfunction or history of current alcohol abuse

Topical Agents

EMLA
• A mixture of lidocaine and prilocaine
• For use in incidental pain, venous cannula insertion, pain after circumcision and another postoperative pains

Topical Lidocaine
• A sodium channel blocker
• Reduces the ectopic impulses in afferent fibers to provide pain relief
Lidocaine Patch

- Excellent safety and tolerability
- Only adverse effect is mild skin reactions, erythema or rash
- First-line therapy for treating localized neuropathic pain, especially for older adults

Tramadol

Centrally acting synthetic codeine analog
Useful for moderate to moderately severe pain

Two mechanism of actions:
- Weak interaction of tramadol with the μ-opioid receptor
- Inhibiting the reuptake of norepinephrine and serotonin

Tramadol: Indications

- Fibromyalgia
- Chronic low back pain
- Degenerative Joint Disease
- Painful diabetic neuropathy
- Tramadol has shown effectiveness in number of acute pain situations as well.
Tramadol: Dosing and Adverse Effects

- The typical dosing for healthy adult is 50 to 100 mg every 8 to 12 hours as needed.
- Totaling not more than 400 mg /d (300 mg/d in patients aged 74 years and older).
- The most common adverse effects (dose related and transient): nausea and vomiting, constipation, headache and drowsiness, very low risk of seizures.

Clinical Experience with Tramadol

- Atypical opioid
- Not toxic to organs
- Efficacy at least as good as NSAID’s, Coxibs, Percocet
- Less opioid related side-effects than other opioids (sedation, GI)

Cautions with Tramadol

- Reduce dosage in renal failure
- Avoid Use with MAO inhibitors
- Advise patients of potential drug interactions with SSRI/SNRIs
- Advise patients of potential of lowering seizure threshold
Neuropathic Pain Treatment

Pharmacological treatments:
- Anticonvulsants
- Antidepressants
- Ion channel blockers
- Capsaicin
- Opioids
- NMDA receptor antagonists
- Other (GABA-A,B agonists, calcitonin, levodopa, steroids, NSAID)

Tricyclic antidepressants
- Widely used for chronic pain syndromes.
- Meta-analyses have confirmed the efficacy of TCA in the treatment of neuropathic pain.
- 3 targets at once: analgesics, antidepressants, and sleeping aids.
- The TCAs, the class with strong evidence of analgesic effect independent of antidepressant effect.

TCAs: Mechanisms
- Relief of pain through serotonin and norepinephrine reuptake blockade
- Blockade of α-adrenergic receptors
- Sodium and potassium channel modulation
- Modulation of monoamine neurotransmitters
- NMDA-receptor antagonism [?]
TCAs

- Amitriptyline studied most extensively
  - Limitations due to anticholinergic AEs
    - Constipation and pseudodementia
  - Potential cardiac conduction abnormalities

- Nortriptyline and desipramine
  - Better AE profiles
  - High doses cause anticholinergic AEs
    - Affect cardiac conduction
  - Desipramine an alternative to amitriptyline intolerance

TCAs: AEs

- Commonly reported AEs (generally anticholinergic)
  - Blurred vision
  - Cognitive changes
  - Constipation
  - Dry mouth
  - Orthostatic hypotension
  - Sedation
  - Sexual dysfunction
  - Tachycardia
  - Urinary retention

Amitriptyline, Nortriptyline

- One of the true analgesic antidepressants.
- Relieves pain in undepressed patients independent of mood alteration.
- Best effects in patients with burning pain, paresthesias, painful numbness, or hyperalgesia.
- No advantage to increasing over 100 mg daily
- Anticholinergic side effects, postural hypotension, sedation, delirium, constipation, weight gain, cardiac arrhythmias.
Serotonin and Norepinephrine Reuptake Inhibitors

Venlafaxine and duloxetine

- Inhibit nor-epinephrine and serotonin reuptake and increase synaptic availability

- Minimal anti-cholinergic AEs

Venlafaxine

- SNRI
- Serotonin/weak norepinephrine reuptake inhibitor
  - Randomized, double-blind, placebo-controlled, 3-way crossover study (N=40)
    - Venlafaxine (225 mg/d) vs imipramine (150 mg/d)
    - As effective as imipramine
    - Pain scores lower than placebo

Duloxetine

- Balanced selective nor-epinephrine and serotonin reuptake inhibitor
- Lacks significant affinity for anti-cholinergic, antihistamine, α₁-adrenergic, dopamine, and opioid receptors
- Relieves symptoms of major depressive disorder
- Results suggest 60 mg safe and effective in patients with painful DPN

Cymbalta

Cymbalta operates on a balanced mechanism of delay in the reuptake of serotonin and noradrenaline, thereby increasing their levels in the central nervous system.

Theoretical Representation

SNRI – Cymbalta

Cymbalta, SNRI – Serotonin and Noradrenaline Reuptake Inhibitor

Cymbalta improves control of sweating in diabetic patients.
Cymbalta – סיכום בטיחות

Cymbalta\(^\circ\) הווקה בטיחותה בכל המחקרים הקליניים (כאמור נידודים וסוכרי-ילויים).\(^\circ\)

תкупעת להבנאל הsteryורית שעופה הوحدה, כעומד.

אינה גורמת לשינויים בלחץ הדם והשימוש \(^{\circ}\) בטוח גם בחולים הסובלים מי Cymbalta.\(^\circ\)

אינה גורמת לשינויי QTc.\(^\circ\)

Why Anticonvulsants for pain?

- Anticonvulsants for epilepsy
- Similarities to neuropathic pain
- Specific Pharmacological mechanisms
- Less tolerance
- Less side effect
- High safety profile

Anticonvulsant mechanisms

- Voltage gated Ion Channel blocker
  - Na Channel blocker
  - Ca Channel blocker
- NMDA Antagonism
- GABA inhibitory effect Agonism
Antiepileptic Drugs

The First Generation of AED
- Carbamazepine
- Valproic Acid
- Phenyltoin

The Second Generation of AED
- Gabapentin
- Lamotrigine
- Topiramate
- Pregabalin

Anticonvulsants that do not block Na-Channels
- Valproic acid
- Pregabalin
- Gabapentin

Na-Channel blocking anticonvulsants
- Carbamazapine
- Phenitoin
- Lamotrigine
- Topiramate
Antiepileptic Drugs

- Is there a drug of choice
- If one is ineffective should we try another
- No correlation between serum levels and effect.
- The initially dose should be a low one, at bedtime, increased slowly up to the therapeutic level over 4-8 weeks.

Gabapentin

Best documented efficacy in the treatment of neuropathic pain!!!

- Painful diabetic neuropathy
- Postherpetic neuralgia
- Not interact with other drugs
- The usual starting dose is 100 to 300 mg bid
- Max dosing from 1200 mg/d to 3600 mg/d
- Side effects: drowsiness, somnolence, nausea, fatigue

Pregabalin Modulates Hyperexcited Neurons

*Does not affect Ca++ influx in normal neurons*
Pregabalin

Indications
- Pregabalin is indicated for the treatment of peripheral neuropathic pain in adults

Contraindication
- Hypersensitivity to the active substance or to any of the excipients

Adverse events
- The most common adverse events in the entire clinical development program were dizziness and somnolence

Renal impairment
- Pregabalin dosage reduction is necessary in patients with renal impairment (CrCl < 60 mL/min).

Anticonvulsants in Neuropathic Pain: Conclusions

- Anticonvulsants are effective in a variety of peripheral & central forms of neuropathic pain
- An average pain reduction of 35%- 45% can be expected
- NNT range of 2.1-3.2; roughly equivalent to TCA’s
- Given their efficacy & superior safety profile, the new anticonvulsants should become available for the treatment of neuropathic pain in Israel

Comparative Efficacies of Antidepressants and Antiepileptic drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>NNT</th>
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<tbody>
<tr>
<td>TCA</td>
<td>2.6</td>
</tr>
<tr>
<td>SSRI</td>
<td>6.7</td>
</tr>
<tr>
<td>Phenytoin, Carbamazepine</td>
<td>2.5</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Sindrup SH et al. Meta-analysis
Neurol 2000
Muscle relaxants: Baclofen

- Used as adjuvant for patients with chronic musculoskeletal pain in presence of muscular spasm mainly due to spinal cord injury.
- A specific GABA-receptor (type B) agonist
- Approved for treatment of spasticity in multiple sclerosis or spinal cord injury, neuropathic pain, trigeminal neuralgia, atypical facial pain, LBP.
- Side effects: sedation, nausea, vomiting

Local anaesthetic-like drugs

- Mexiletene
- Lignocain (IV and intranasal)
- Oral tocainide
- 17 RCT’s

Lidocaine

- Local anesthetic drug
- Membrane-stabilizing agent that work by blocking voltage-gated Na channels
- IV lidocaine produced moderate reductions in pain in patients with diabetic neuropathy
- Best effective dose 5mg/kg. Over 30 min
**Mexiletene**
- Peripheral nerve injury
- Diabetic neuropathy, dysesthesia

**Steroids**
- Beneficial by direct blocking nociceptive input (block C-fiber transmission) and by anti-inflammatory action.
- Important for pain due to increased intracranial pressure, spinal cord compression and cluster headache
- Beneficial in cancer neuropathic involvement
- Rarely use doses over 20 mg. dexamethasone per day. For spinal cord compression need for high doses.
- Potentially serious effects in prolonged use

**NMDA-receptor antagonists**
- N-methyl-D-aspartate receptor involved in neuropathic pain
- Commercially-available drugs are analgesic: ketamine, dextromethorphan, amantadine
**Ketamine**

- NMDA antagonist
- For severe neuropathic pain in patients with advanced cancer
- 0.1-0.15 mg/kg as bolus or as continuous s.c infusion per hour. Raise the dose gradually.
- Principal side effects are hallucinations

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**α-2 Agonists**

- Multifactorial mechanisms the analgesia produced via α-2 adrenergic receptors
- Clonidine can be beneficial in chronic headache, neuropathic pains including cancer related
- Oral, transdermal route and epidural administration can favorable effects

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**Adjuvant for the treatment of bone related pain**

- NSAID’s
- Bisphosphonates
- Calcitonin
- Radio-isotopes
הצגת מקרה

בת 52, לחם 3+.
מלחי B וል.keyboardを選ぶ ליטול החפיפת בסל
אבקת טרהול לבלב ורחתי, התפלל למושט
בכפות אצבעות.

GEMZAR, ממסיב מלקב כימיופרופה
רקר - סוכרת ו الجنوب ביסופוטן, הפטיסיוו, ב',
הרעתה זרה וד unpopular.

הצגת מקרה

סבלה תקופה ארוכה מכאבי בטן אך התאזהד отлично
עם טיפול ב bác' הקדומים וرار' 100 מ' ג' לעשונה פעמים
בכל יום.
במרחEK משנייה, היא נוטלת ההנהלה על המרכז
בכפיף ב דובgypt מהפיים ובש in בולוט הקולטיים-כאמים
ושופほぼ וرفع השמיעות ב שцитל העדכניות.
adaptiveStylesLATED: באזון הדדי והנהלה מיומן של דור'גר' 7 100
400 מ' ג' מה 400 מ' ג'.
שופג על fas של אבק' ב דובgypt.

מה הצלになった?}

הצגת מקרה

מה סימן הגב הדתי?}

מה הסימן עלולות להושם כב' קדום?}

מה אופייניים לסופי?}

איך טיפולי נוספים נבחרים?}

מה הצל חזה?}
הצגת מקרה

נגדי דיכאון: אמפיריפטילין (אלטרול)
טריאבירית ליריקה, גבפנטין: נוגדי פרכוסים
סטרואידים
מטדון
לידוקאין
קטאמין
טיפולי פולשנים

Questions?

סוף ההרצאה!