


Non-Opioid and Adjuvant Medications for Chronic Pain

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תרופות אנלגטיות לא אופיואידיות

- יעילות לבד או לטיפול בכאב קל עד בינוני
- אנלגזיה אדיטיבית במתן עם אופיואידים
- בעלות "אפקט תקרה" ("ceiling" effect)
- אינן גורמות לסבילות או תלות פיזית

**רשימת תרופות אנלגטיות
לא אופיאודיות**

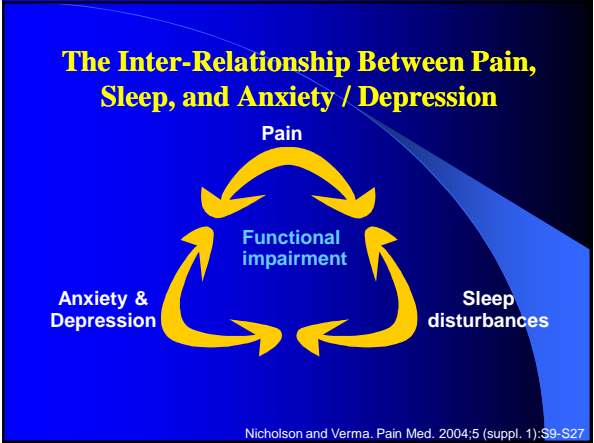
- Paracetamol
- Non Selective NSAIDs
- NSAIDs - Cox 2 selective
- Topical analgesic agents- NSAIDs, Capsaicin, EMLA
- Tramadol

הגדרה של תרופה נלוות (Adjuvant)

- תרופה משלימה משככת כאב – תרופה שההתוויה שלה אינה לשכוך כאב אבל ידוע שיש לה במצבים מסוימים השפעה אנלגטית
- תרופות משלימות כנגד תופעות לוואי שליליות של משככי כאב

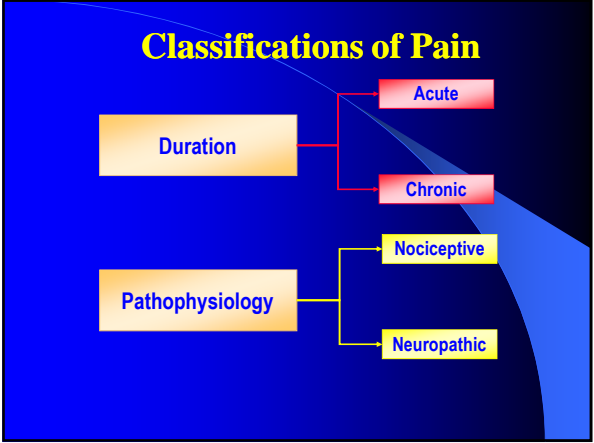
רשימה של תרופות נלוות

- תרופות משלימות משככות כאב:
 - נוגדי דיכאון
 - נוגדי כיפיון
 - סטרואידים
 - ביספוספונטים
 - חוסמי רצפטור NMDA
 - תכשירים להרדמה מקומית
 - BACLOFEN



Multipurpose Adjuvant Analgesics

| <u>Class</u> | <u>Examples</u> |
|-----------------------------|---|
| Antidepressants | amitriptyline, desipramine, nortriptyline, paroxetine, venlafaxine, citalopram, |
| Alpha-2 adrenergic agonists | clonidine |
| Corticosteroids | prednisone, dexamethasone |



Nociceptive pain

- נזק ברקמות נראה
- טיפול:

NSAID —

אופיאטים —

תוספות לא אופיאטיות. —

NOCICEPTIVE PAIN

| | Somatic | Visceral |
|----------|--|--|
| Features | <ul style="list-style-type: none"> ● Constant ● Aching ● Well localized | <ul style="list-style-type: none"> ● Constant or crampy ● Aching ● Poorly localized ● Referred |
| Examples | <ul style="list-style-type: none"> ● Bone metastases | <ul style="list-style-type: none"> ● Pancreatic CA ● Liver tumor ● Bowel obstruction |



כאב ממקור עצבי...

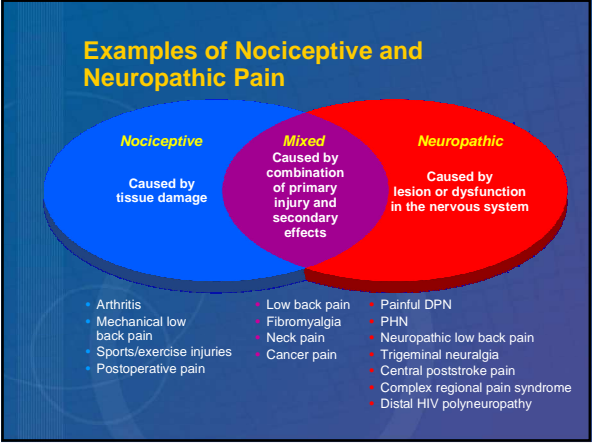
- אין תמיד קשר בין מידת הנזק ועוצמת הכאב
- אופי: שורף, חשמל, סיכות, הרדמות
- טיפול

תוספות של ajuvants בד"כ מתבקש. —

אופיאטים —

FEATURES OF NEUROPATHIC PAIN

| COMPONENT | DESCRIPTORS | MEDICATIONS |
|--|---|---|
|  Steady | <ul style="list-style-type: none"> Burning, Tingling Constant, Aching Squeezing, Itching <i>Allodynia</i> <i>Hyperesthesia</i> | <ul style="list-style-type: none"> Gabapentin Tricyclic antidepressants Corticosteroids Mexilitene |
|  Paroxysmal | <ul style="list-style-type: none"> Stabbing Shocklike, electric Shooting | <ul style="list-style-type: none"> Gabapentin Baclofen Tegretol Corticosteroids Mexilitene |



Chemicals That Increase Neuropathic Pain Signals

| Chemical | Function |
|--|--|
| <p><i>These chemicals assist in the transmission of painful impulses. Glutamate acts on NMDA receptors and opens calcium channels and other ionic receptors. Intracellular calcium stimulates a cascade of events that releases protein kinase C, arachidonic acid, endothelin-derived relaxing factor, and other mediators that facilitate NMDA modulated action.</i></p> | |
| Ca++ channels | Calcium flows across membranes of smooth muscle and causes muscle contraction ¹² |
| Glutamate | A major excitatory amino acid of the central nervous system ¹ |
| NMDA receptors (N-methyl-D-aspartate) | Play a crucial role in modulation of pain signals, the maintenance of chronic neuropathic pain, and the development of hyperalgesia and allodynia ¹ |
| Substance p | Amino acid peptide in pain fiber system; may be important in eliciting local tissue reactions ¹ |
| <p><i>These additional compounds help create an "inflammatory soup" that increases the likelihood of development of aberrant pathways and neuropathic pain:</i></p> | |
| ATP | Adenosine triphosphate - storage form of energy in muscle tissue ¹ |
| Bradykinin | Potent vasodilator ¹ |
| Hydrogen ion | Affects blood pH and ability of hemoglobin to hold oxygen ¹ |
| Interleukin B | Produced by T cells; important in inflammatory response ¹ |
| Nerve growth factor | A protein whose hormone-like action affects differentiation, growth, and maintenance of neurons ¹ |
| Prostaglandins | Unsaturated fatty acid that affects vasomotor tone, capillary permeability, permeability, muscle tone, aggregation of platelets, endocrine and exocrine functions, the autonomic and central nervous system (includes NMDA [N-methyl-D-aspartate] in intracellular prostaglandin) ¹ |
| Tumor necrosis factor | A natural body protein produced in response to the presence of toxic substances ¹ |

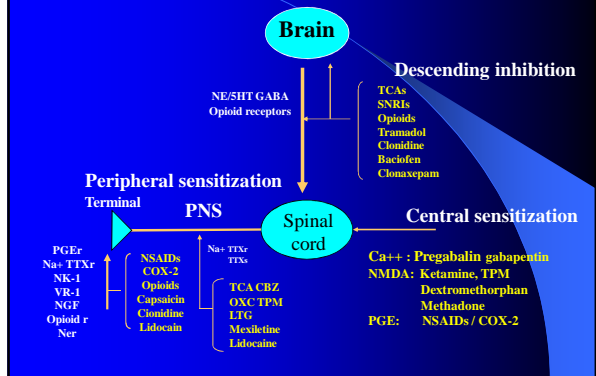
Source: American College of Nurse Practitioners © 2008 Elsevier Inc.

Chemicals in the Body that can Modulate or Decrease Pain Signals


| Chemical | Function |
|-------------------------------------|--|
| GABA (gamma-aminobutyric acid) | An amino acid that functions as an inhibitory neurotransmitter in the brain and spinal cord ¹² |
| 5HT (serotonin 5 hydroxytryptamine) | A naturally occurring derivative of tryptophan found in platelets and in cells of the brain and intestine. It acts as a potent vasoconstrictor; in the central nervous system it acts as a neurotransmitter ¹ |
| NE (norepinephrine) | An adrenergic hormone that increases blood pressure through vasoconstriction ¹² |
| Endorphins | Neuropeptides that act as a powerful analgesics ¹² |

Source: American College of Nurse Practitioners © 2008 Elsevier Inc.

Mechanistic Approach to Pain Treatment




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

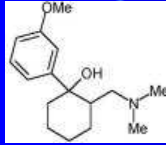
- A mixture of lidocaine and prilocaine
- For use in incidental pain, venous cannula insertion, pain after circumcision and another postoperative pains

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 situation 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
- Totalling 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

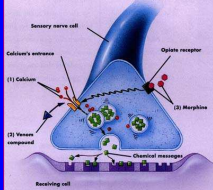
Clinical Experience with Tramadol

- 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 intolerance²

TCAs: AEs

Commonly reported AEs (generally anticholinergic)

- Blurred vision
- Cognitive changes
- Constipation
- Dry mouth
- Orthostatic hypotension
- Sedation
- Sexual dysfunction
- Tachycardia
- Urinary retention

● **Fewest AEs**

● **Most AEs**

- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

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.

ירידה ברמת נוירו-טרנסמיטורים – נוראפינפרין (NE), סרוטונין (5HT)

קיים קשר בין ירידה ברמות NE ו 5HT לבין דיכאון

ירידה ברמות NE ו 5HT בחוט השדרה ובמוח מביאה לעלייה בגירוי הכאב המגיעים למח ובתחושת כאב מוגברת

ל NE ול 5HT תפקיד מרכזי בתפקוד מערכת השתן התחתונה

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

Sindrup et al. Neurology, 2003;60:1284-1289.

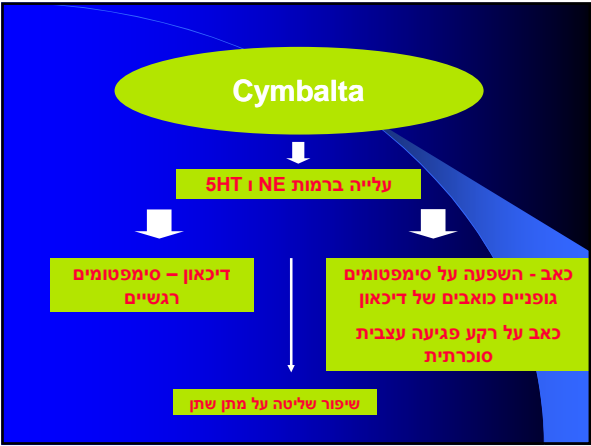
Duloxetine

- Balanced selective nor-epinephrine and serotonin reuptake inhibitor
- Lacks significant affinity for anti-cholinergic, antihistamine, α_1 -adrenergic, dopamine, and opioid receptors
- Relieves symptoms of major depressive disorder
- Results suggest 60 mg safe and effective in patients with painful DPN

SNRI – Cymbalta ברמת הסינופסה

Cymbalta פועלת על מנגנון עיכוב הקליטה מחדש של סרוטונין נוראפינפרין. באפיות גבוהה ובאופן מאוזן וכך מעלה את רמתם במערכת העצבים המרכזית

Theoretical Representation



Cymbalta – סיכום בטיחות

- Cymbalta הוכחה כבטוחה בכל המחקרים הקליניים (כאב נירופטי סוכרתי ו-דיכאון).
- תופעות הלוואי העיקריות שנצפו היו בחילה, נמנם סחרחורת.
- Cymbalta אינה גורמת לשינויים בלחץ הדם והשימוש בה בטוח גם בחולים הסובלים מ-ל.ד.
- Cymbalta אינה גורמת לשינוי ב-QTc.

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
- Phenytoin

• The Second Generation of AED

- Gabapentine
- Lamotrigine
- Topiramate
- Pregabalin

Anticonvulsants that do not block Na-Channels

- Valproic acid
- Pregabalin
- Gabapentin

Na-Channel blocking anticonvulsants

- Carbamazapine
- Phenitoin
- Lamotrigine
- Topiramate

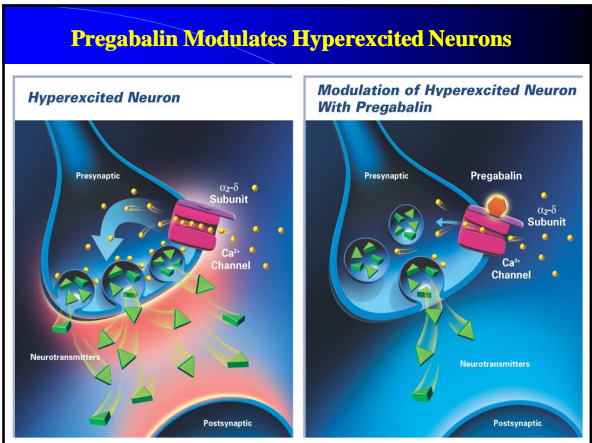
Antiepileptic Drugs

- 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

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 (Clcr < 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

| <u>Drugs</u> | <u>NNT</u> |
|--------------------------|------------|
| TCA | 2.6 |
| SSRI | 6.7 |
| Phenytoin, Carbamazepine | 2.5 |
| Gabapentin | 4.1 |

Sindrup SH et al, Meta-analysis
Neurol 2000

Muscle relaxants: Baclofen

- Used as adjuvant for patients with chronic musculo-skeletal 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. dexamethazone 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, dextromethorpan, 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

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

Adjuvant for the treatment of bone related pain

- NSAID's
- Bisphosphonates
- Calcitonin
- Radio-isotopes

הצגת מקרה

בת 52, ג+3.
לפני כ-3 חודשים נכנסה לטיפול הוספיס בשל
אבחנה סרטן לבלב גרורתי, תהליך ממושט
בבטן ואגן.
ממשיכה לקבל כימיוטרפיה GEMZAR
רקע- סוכרת מטופלת באינסולין, הפטיטיס ב,
הפרעות חרדה ודיכאון.

הצגת מקרה

- סבלה תקופה ארוכה מכאבי בטן אך התאזנה היטב עם טיפול במדבקות דורודג'זיק 100 מק"ג לשעה פעם ב-3 ימים.
- במשך שבועיים האחרונים התלוננה על החמרה בכאבי בטן וגם הופיע כאב חדש בשתי הרגליים-כאבים שורפים והרגשת נימולים בשתי כפות הרגליים.
- טיפול: באופן הדרגתי הועלה מינון של דורוג'זיק עד 400 מק"ג שהקל על כאבי בטן אך ללא שינוי הרגשת שריפה ונימולים ברגליים.
- מה הצד הבא ?

הצגת מקרה

- מה סוג הכאב החדש?
- מה הסיבות אפשריות להופעת כאב מסוג זה?
- מה אופציות טיפוליות?
- איזה טיפול אדיובנטי תבחר?

הצגת מקרה

- נוגדי דיכאון : אמייטריפטילין (אלטרול), סימבלטה.
- נוגדי פרכוסים: גבפנטין, ליריקה.
- סטרואידים.
- מטדון - ?
- לידוקאין ?
- קטאמין ?
- טיפול פולשני ?

Questions?

סוף ההרצאה!

