Pharmacotherapy of Pain: Nonopioid Analgesics

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Defining Pain

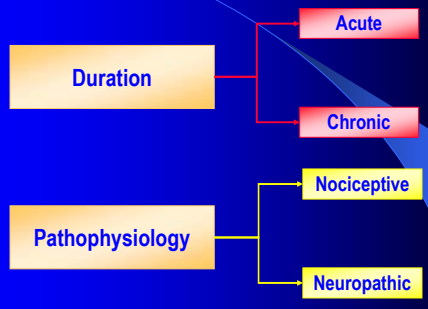
"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

International Association for the Study of Pain (IASP)

International Association for the Study of Pain Web site. Available at: http://www.iasp-pain.org/terms-p.html. Accessed September 30, 2004.

כאב מוגדר **כחווית תחושתית ורגשית סובייקטיבית**, לא נעימה על רקע פגיעה פיזית או פגיעה הנתפסת כזו על ידי הסובל.

Classifications of Pain



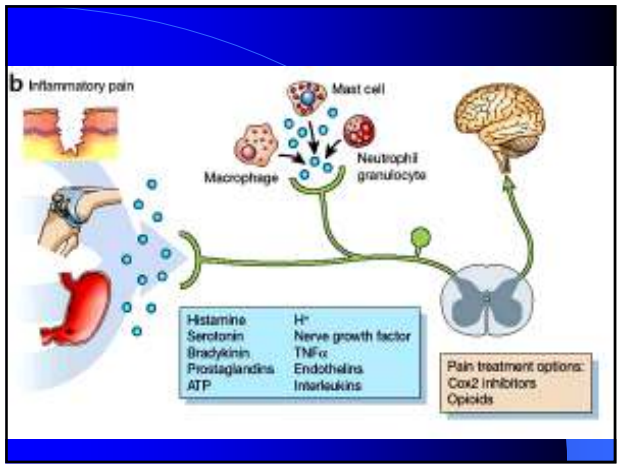
Nociceptive pain

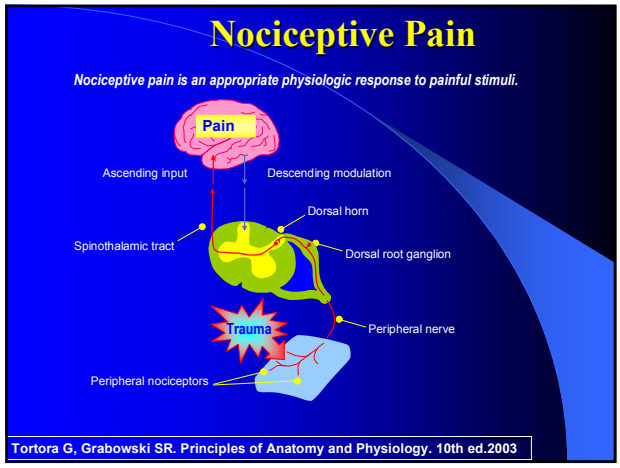
- נזק ברקמות נראה
- טיפול:

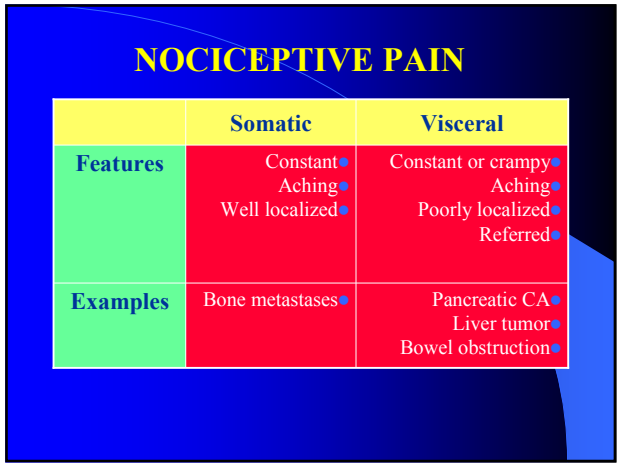
NSAID

אופיאטים

תוספות לא אופיאטיות.


b Inflammatory pain
Mast cell
Macrophage
Neutrophil granulocyte
Histamine
Serotonin
Bradykinin
Prostaglandins
ATP
H+
Nerve growth factor
TNFα
Endothelins
Interleukins
Pain treatment options:
Cox2 inhibitors
Opioids


Nociceptive Pain
Nociceptive pain is an appropriate physiologic response to painful stimuli.
Pain
Ascending input
Descending modulation
Dorsal horn
Spinothalamic tract
Dorsal root ganglion
Trauma
Peripheral nerve
Peripheral nociceptors
Tortora G, Grabowski SR. Principles of Anatomy and Physiology. 10th ed.2003


NOCICEPTIVE PAIN
Somatic
Visceral
Features
Constant
Aching
Well localized
Constant or crampy
Aching
Poorly localized
Referred
Examples
Bone metastases
Pancreatic CA
Liver tumor
Bowel obstruction

כאב ממקור עצבי...

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

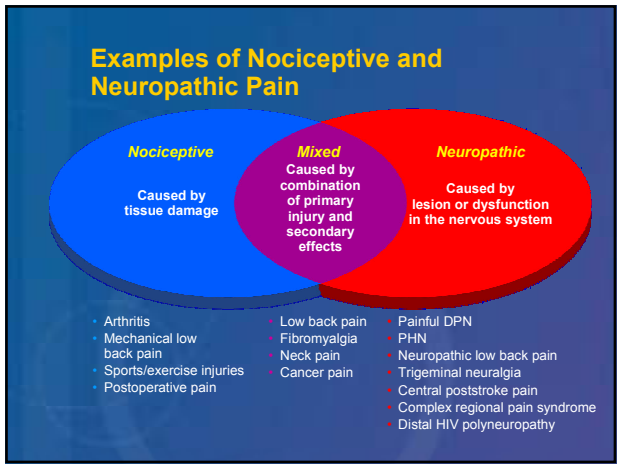
אופיאטים

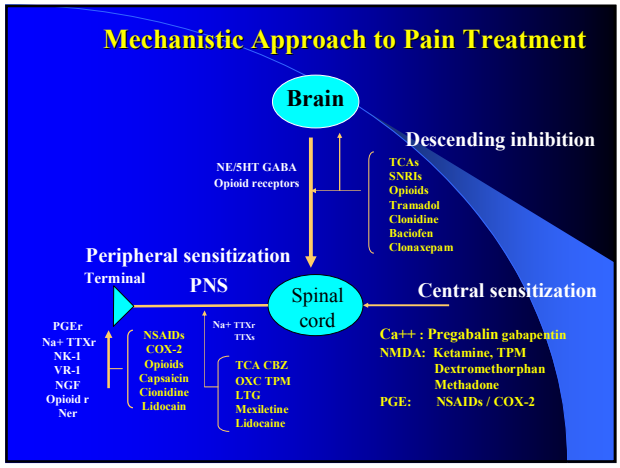
תוספות של ajuvants בד"כ מתבקש.

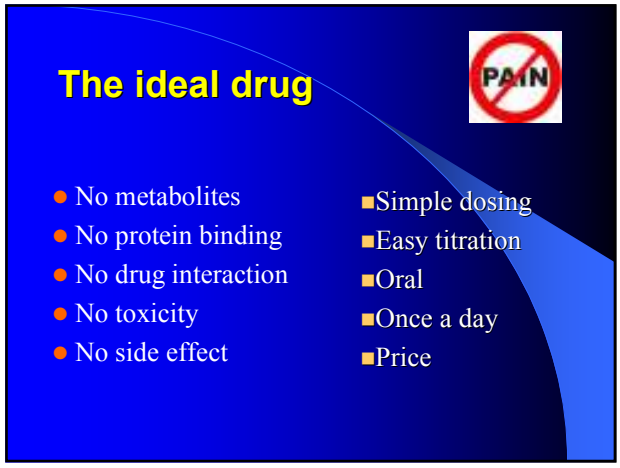
FEATURES OF NEUROPATHIC PAIN

COMPONENT	DESCRIPTORS	MEDICATIONS
Steady 	Burning, Tingling Constant, Aching Squeezing, Itching Allodynia Hyperesthesia	Gabapentin Tricyclic antidepressants Corticosteroids Mexilitene
Paroxysmal 	Stabbing Shocklike, electric Shooting	Gabapentin Baclofen Tegretol Corticosteroids Mexilitene

ביטוי הכאב הנוירופטי במגוון מחלות


Examples of Nociceptive and Neuropathic Pain
Nociceptive
Caused by tissue damage
Mixed
Caused by combination of primary injury and secondary effects
Neuropathic
Caused by lesion or dysfunction in the nervous system
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
Distal HIV polyneuropathy


Mechanistic Approach to Pain Treatment
Brain
Descending inhibition
NE/5HT GABA
Opioid receptors
TCAs
SNRIs
Opioids
Tramadol
Clonidine
Baciofen
Clonaxepam
Peripheral sensitization
Terminal
PNS
Spinal cord
Central sensitization
PGEr
Na+ TTXr
NK-1
VR-1
NGF
Opioid r
Ner
NSAIDs
COX-2
Opioids
Capsaicin
Clonidine
Lidocain
Na+ TTXr
TTXs
TCA CBZ
OXC TPM
LTG
Mexiletine
Lidocaine
Ca++ : Pregabalin gabapentin
NMDA: Ketamine, TPM
Dextromethorphan
Methadone
PGE: NSAIDs / COX-2

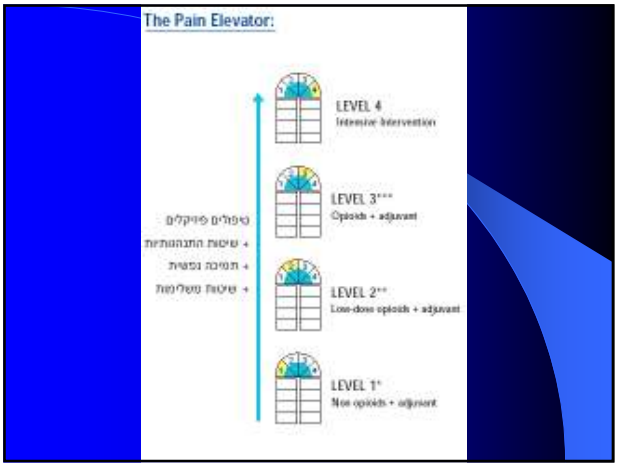

The ideal drug
PAIN
No metabolites
No protein binding
No drug interaction
No toxicity
No side effect
Simple dosing
Easy titration
Oral
Once a day
Price

רשימת תרופות

- Non Selective NSAIDs– Paracetamol
- NSAIDs - Cox 2 selective: Etoricoxib, Celecoxib
- Topical analgesic agents- NSAIDs, Capsaicin, EMLA
- Tramadol
- Antiarrythmics
- Antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA receptor antagonists

תרופות אנלגטיות לא אופיואידיות

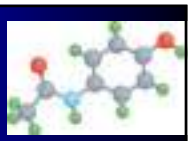
- יעילות לבד או לטיפול בכאב קל עד בינוני
- אנלגזיה אדיוטיבית במתן עם אופיואידים
- בעלות "אפקט תקרה" ("ceiling" effect)
- אינן גורמות לסבילות או תלות פיזית



WHO Method for Relief of Cancer Pain:

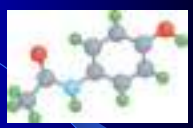
- 'By the mouth' i.e. oral
- 'By the clock' i.e. regular
- 'By the ladder' (next slide)
- Individualise treatment
- Pay attention to detail

Paracetamol (Acetaminophen)



- The most widely recommended nonopioid analgesic for mild-to-moderate acute and chronic pain states.
- Centrally mediated analgesia
- Has 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**
- **Can be used with other drugs**
- **Inexpensive**
- **Optimal dose is 1,000 mg/dose NNT= 3.8 (3.4 - 4.4)**
- **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, is the major side effect associated with overdose

50% to 75% dose reduction recommended in patients with renal/hepatic dysfunction or history of current alcohol abuse

NSAIDs: Overview

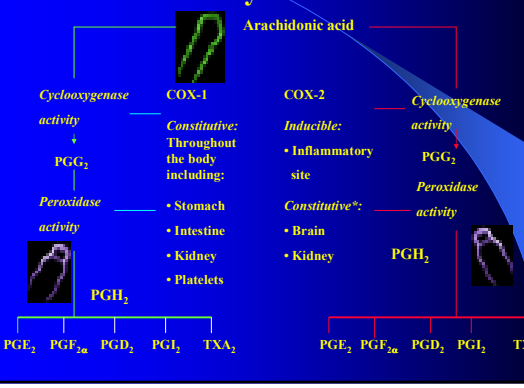
Effects:

- Anti-inflammatory
- Analgesic
- Antipyretic

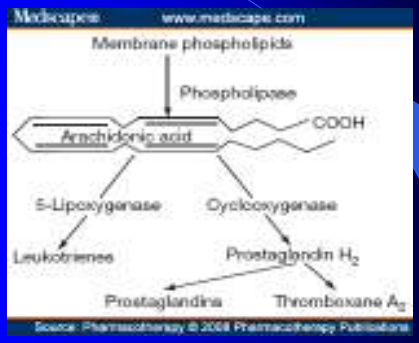
Interactions with NSAIDs include:

- Anticoagulants
- ACE inhibitors
- Antihypertensives
- Lithium
- Diuretics

Roles of COX-1 and COX-2 in Prostaglandin Synthesis



The Phospholipid Pathway



NSAID

- **Mechanism**
  - Inhibit both peripheral and central cyclo-oxygenase, reducing prostaglandin formation
  - 3 isoforms of COX
    - COX-1: Constitutive, physiologic
    - COX-2: Inducible, inflammatory
    - COX-3: Central, blocked by acetaminophen

NSAID Therapy for Various Chronic Pain Syndromes

- **Osteoarthritis and Rheumatoid Arthritis**
- **Low Back Pain**
- **Fibromyalgia**
- **Peripheral Neuropathy-Mixed Pain Syndromes**

Adverse Events Associated with NSAID Therapy

- Gastrointestinal Events
- Cardiovascular Events
- Hepatotoxicity
- Nephrotoxicity
- Central Nervous System

Gastrointestinal Events

- Dyspeptic symptoms
- Gastric or duodenal ulceration

Factors Associated With NSAID GI-ulcer

- NSAID dose
- NSAID time of treatment
- Type of NSAID
- Age > 60 years
- Past history of GI –ulcer
- Combination with steroids
- Combination with anti-coagulants
- H. Pylori present

Risk Factors for Gastrointestinal Events Associated With NSAID Therapy

Medscape www.medscape.com

Risk Factor	Risk Level for Gastrointestinal Events: Low	Moderate	High
Age (yrs)			
< 60	X		
60–64		X	
≥ 65			X
Combination therapy with NSAID			
Low-dose aspirin	X		
Anticoagulants	X		
Corticosteroids	X		
Other NSAIDs	X		
Type of NSAID			
Diclofenac	X		
Ibuprofen	X		
< 1200 mg/day			
Piroxicam			X
Ketoprofen			X
Ketorolac			X
Duration of NSAID therapy (mo)			
< 1			X
1–3		X	
> 3	X		
Helicobacter pylori infection	X		
Lifestyle			
Smoking and alcohol use*	X		
History of dyspepsia	X		

NA = not applicable.
*Smoking and alcohol use contribute to risk but are not considered independent risk factors.
Adapted from reference 10.

Relative Risk for Ulcer With Different NSAID Treatments

Generic Name	Relative risk for ulcer
Ibuprofen	1
Diclofenac	2.3
Aspirin	4.8
Sulindac	6
Naproxen	7
Indomethacin	8
Piroxicam	9
Ketoprofen	10

Who Needs Protection?

High Risk Groups

- Age >65
- Previous GI bleeding, DU
- Dyspepsia or symptoms of gastroesophageal reflux disease
- Corticosteroid use
- Heart disease

Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

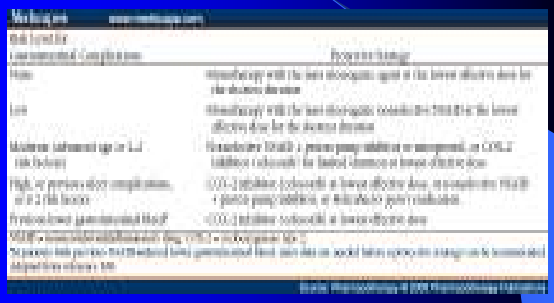
- All NSAIDs, including COX-2 inhibitors, raise the risk of GI ulcers and bleeding when combined with ASA taken chronically for cardioprotection
- Patients at increased GI bleeding risk should go on a PPI
- PPIs such as **lansoprazole** and **omeprazole** are preferred over **misoprostol**, **sucralfate**, or histamine 2 **(H2)-receptor antagonists** for both the prevention and treatment of gastroduodenal lesions associated with ASA and other NSAIDs

Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

- Patients with a history of ulcers should be evaluated and, as appropriate, treated for *Helicobacter pylori* infection before starting antiplatelet therapy.

J Am Coll Cardiol. 2008;
Circulation. 2008

Consensus Treatment Strategies



Nephrotoxicity

- Elevation of serum creatinine level
- Sodium and water retention, hyperkalemia
- Acute renal failure
- Nephrotic syndrome
- Acute tubular necrosis
- Interstitial nephritis

Nephrotoxicity

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Hepatotoxicity

- The risks appear to be rare
- The rate of hospitalization due to NSAID-induced hepatotoxicity in this review was 2.7/100,000 patients
- In the first review, diclofenac and rofecoxib were associated with the highest rate of aminotransferase level elevations

Clin Gastroenterol Hepatol 2005;3:489-98.

Cardiovascular Events

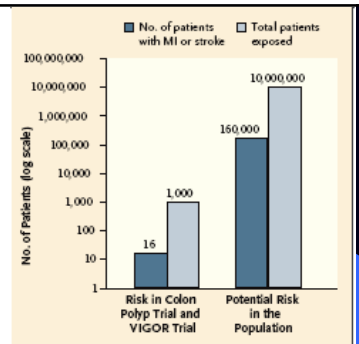
- Peripheral edema, and hypertension
- Heart Failure exacerbation
- Increase MI , cardiac arrhythmia
- COX-2 inhibition can result in an increased risk for thrombosis due to increased activity of thromboxane A2 and reduced activity of prostacyclin

תופעות לוואי COX-2 *SELECTIVE*

- פחות תופעות לוואי הקשורות למערכת העיכול , אך דיספפסיה לעיתים בשכיחות דומה ל NS-NSAIDs
- פגיעה כלייתית אפשרית כמו NS-NSAIDs
- אינו גורם לעיכוב אגרגציה של טרומבוציטים
- ROFECOXIB ו CELECOXIB דווחו כמעלים שכיחות של בעיות קרדיואסקולארית בשימוש ארוך טווח של מעל שנה וחצי

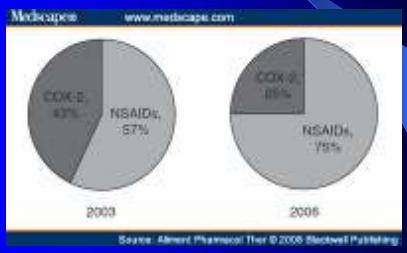
APPROVE trial (2004) evaluated the efficacy of VIOXX 25 mg in preventing reccurence of colorectal polyps.

There was an increased relative risk for heart attack and stroke in low-risk patients –**an excess of 16 myocardial infarctions or strokes per 1000 patients-** beginning after 18 months of treatment vs. placebo.



Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.
Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

What percent of the NSAID prescriptions that you prescribe are traditional NSAIDs and what percent are COX-2 selective agents?



European Medicines Agency announces regulatory action on COX-2 inhibitors

- A contra-indication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke
- A contra-indication is introduced for etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control
- A warning is introduced for prescribes to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment

Ref: EMEA/62757/2005

עמדת האיגוד הישראלי לראומטולוגיה בנושא טיפול ב- NSAIDS

- כאשר שוקלים טיפול ב-NSAID יש להיות מודעים לאפשרות של תופעות לוואי קרדיו-וסקולריות כולל יתר לחץ-דם, אי-ספיקת לב ואוטם שריר הלב, ולהעריך את התועלת הצפויה מהטיפול כנגד האפשרות לסיכונים אלו.

- בנוסף יש להתחשב בגורמי סיכון קרדיו-וסקולריים, לשקול אפשרות טיפול בתרופות אחרות, ובמידת האפשר לצמצם את מינון התרופה ומשך הטיפול.

הודעת ה-FDA : 7 באפריל 2005

U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

ה - FDA הסיק כי:

- קיימת עליה בסיכון לאירועים קרדיווסקולרים לכל התרופות ממשפחת ה-NSAID, לרבות אלו מהדור הישן (כדוגמת אתופן, וולטרן, איבופרופן ועוד). אזהרות אלו חלות גם על תכשירי NSAIDS הנמכרים ללא מרשם רופא (כדוגמת נורופן, אדוויל וכו') וגם על מעכבי קוקס-2 מהדור החדש (לדוגמא הלהוקסיב)

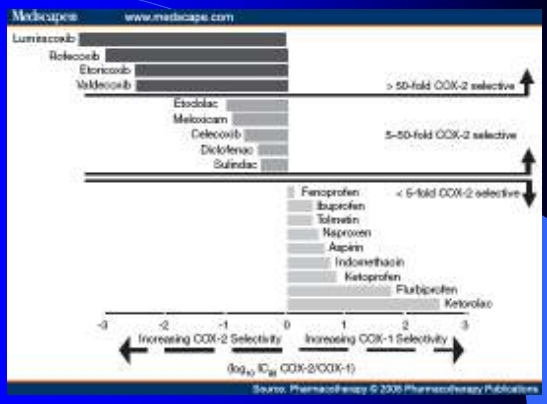
AHA Updates NSAID Advice for Heart Disease Patients

- In patients at increased risk for thrombotic events, low-dose aspirin plus a proton-pump inhibitor could be added
- COX inhibitors can lead to impaired renal perfusion, sodium retention, and increases in blood pressure, which may contribute to their adverse cardiovascular effects

February 28, 2007

AHA Updates NSAID Advice for Heart Disease Patients

- "Nonselective" NSAIDs also differ with regard to COX selectivity. Diclofenac has greater COX-2 selectivity than ibuprofen, which in turn has greater COX-2 selectivity compared with naproxen
- **Naproxen** is probably the NSAID associated with the lowest risk for thrombosis



The stepwise approach to pharmacologic therapy for musculoskeletal symptoms

1. Acetaminophen, tramadol, narcotic analgesics (short-term)
2. Nonacetylated salicylates
3. Non-COX-2 selective NSAIDs
4. NSAIDs with some COX-2 activity
5. COX-2 selective NSAIDs

סיכום

- רב ה NSAIDS חשודים בתופעות CV
- רב העבודות מצביעות על בעייתיות בשמוש ממושך מעל שנה ויותר
- לרב רופאי המשפחה משתמשים ב NSAID בשמוש אפיזודי וקצר טווח
- יש להשתמש ב-NSAID שמוש מושכל ויש לעקוב אחרי כל חולה הנוטל אותם באופן קבוע
- Coxibs יעילים באותה מידה אך גורמים לפחות תופעות גסטרואינטסטינליות ואין פגיעה בתפקוד טסיות
- אין הבדל בפגיעה הכלייתית

Topical Treatments

Topical NSAID

- widely used, OTC preparations
- effective for both acute and chronic pain conditions
- NNT =3-5
- systemic side effects were rare

"**Topical NSAIDs may be a useful alternative to oral NSAIDs**

BMJ. **December 4, 2007**

Capsaicin

- Particularly useful for neuropathy
- Topical agent from chili pepper for site-specific pain
- Interferes with reuptake of substance P
- At least 3 randomized, controlled trails show beneficial effect of capsaicin cream in the treatment of OA over 1-3 month
- Should be started at the lowest dose 0.025% every 6 hours

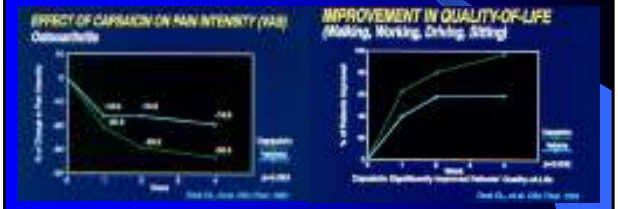
Topical Capsaicin

- Provides modest improvement in pain after 4- to 6-week use
- Opens calcium channel via the TRPV1* receptor; C-fibers die back and regrow in 6 to 7 weeks
- Has a high rate of burning sensations that are unacceptably severe
- New capsaicin 8% patch in development

Symptomatic Treatments

טיפול מקומי

מכילים NSAIDs או Capsaicin.
יכולים להביא להקלה בינונית



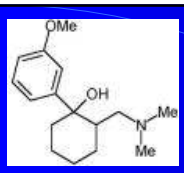
Other Topical Agents

EMLA

- a mixture of lidocaline and prilocaine
- for use:in incidental pain, venous cannula insertion, pain after circumcision and another postoperative pains

5% Lidocaine Patch

- Excellent safety and tolerability
- Systemic absorption from the patch must be considered in patients receiving oral class 1 antiarrhythmic drugs
- Two studies involving the transdermal lidocaine 5% patch show that it may have a role in both musculoskeletal and neuropathic pain
- Only adverse effect is mild skin reactions, erythema or rash



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
- 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 (transient)
  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

Questions?