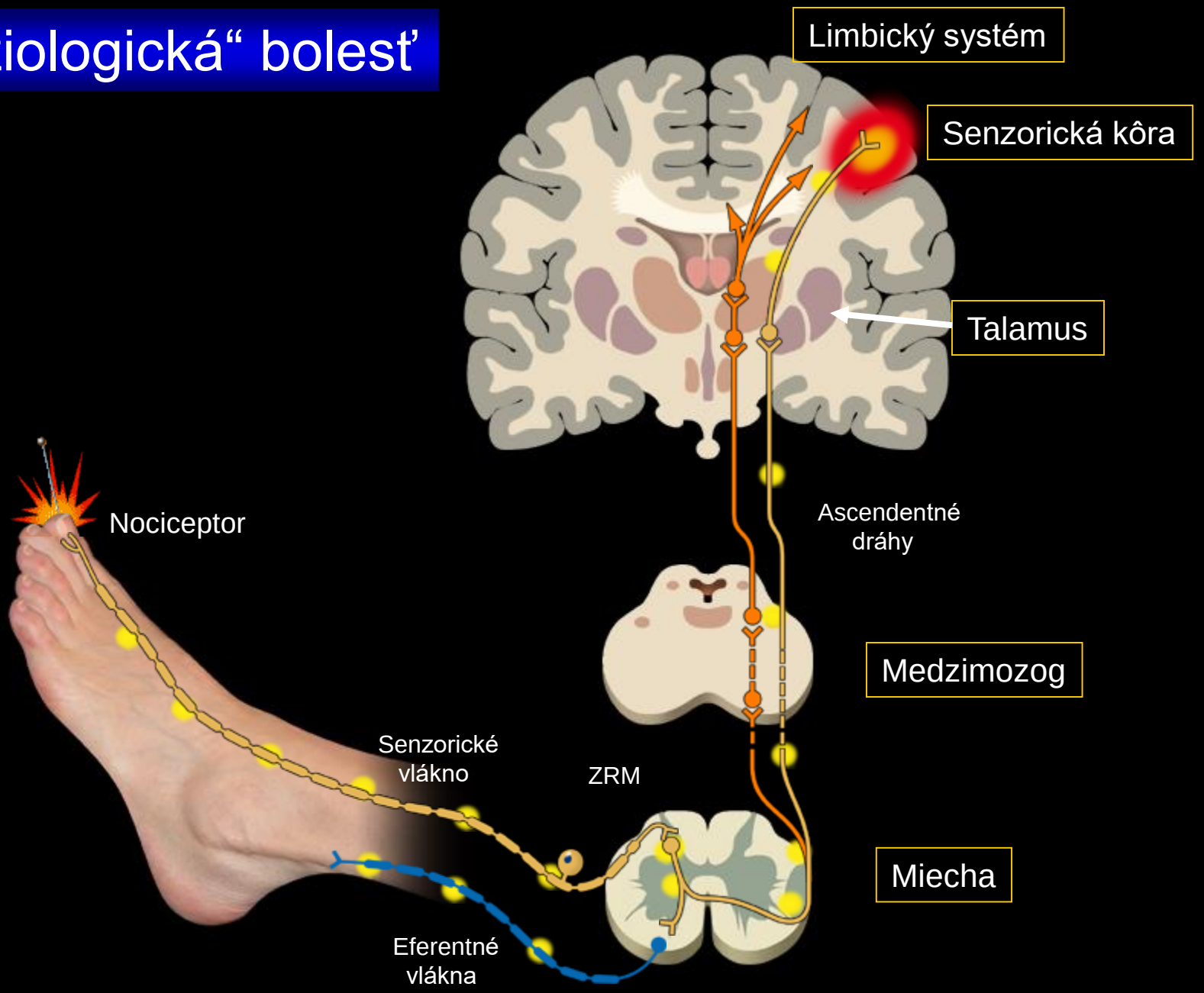
Analgetiká, koanalgetiká

Jana Šimonová

KAIM UPJŠ LF a UNLP Košice

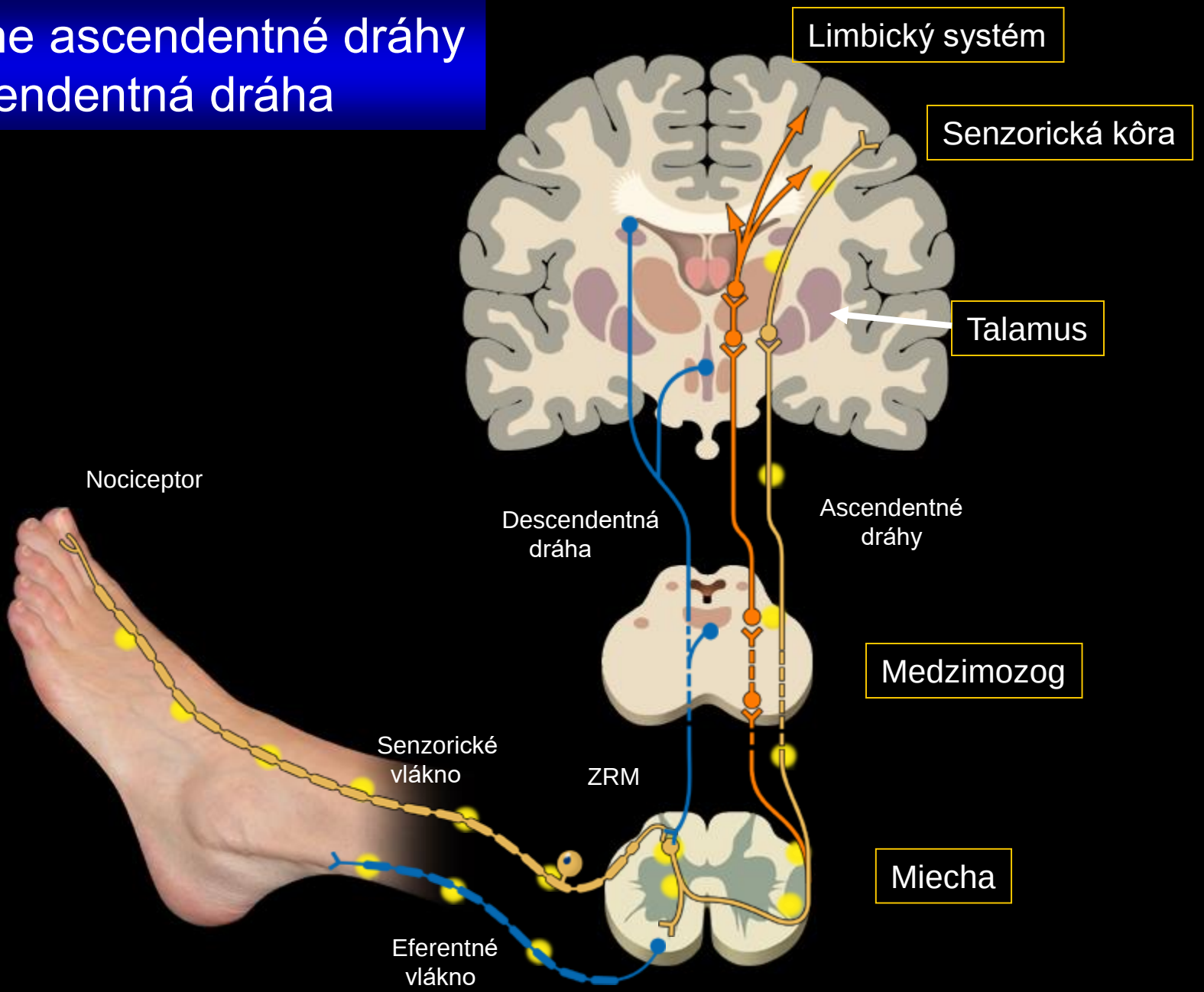
CEEA, Košice 29.11.2019

„Fyziologická“ bolesť



Raymond Sinatra

Duálne ascendentné dráhy
Descendentná dráha



Raymond Sinatra

Farmakologické ovplyvnenie bolesti

1. Na úrovni nociceptorov: LA, analgetiká-antipyretiká a NSA

2. Membrána nervových vláken: LA, niektoré antiarytmiká

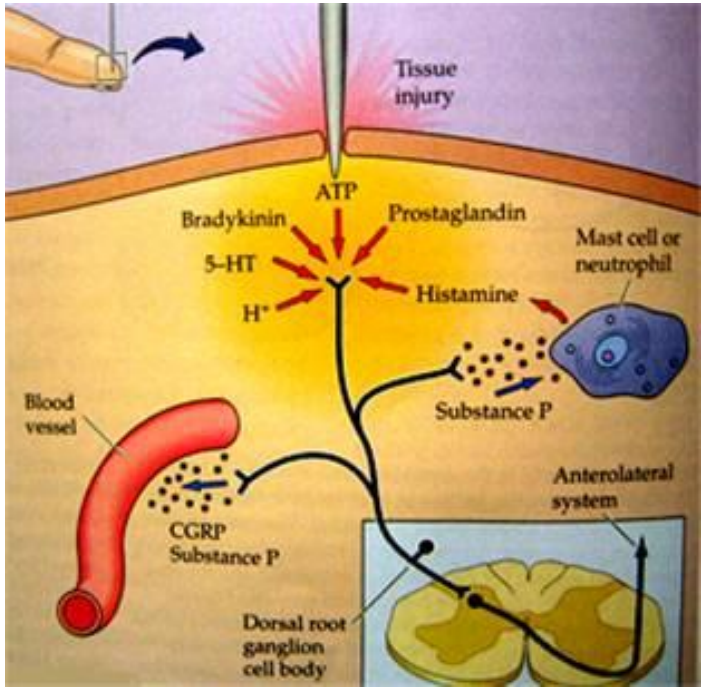
3. ZRM: EA/SA - opioidy, LA, klonidin; systémovo podané opioidy

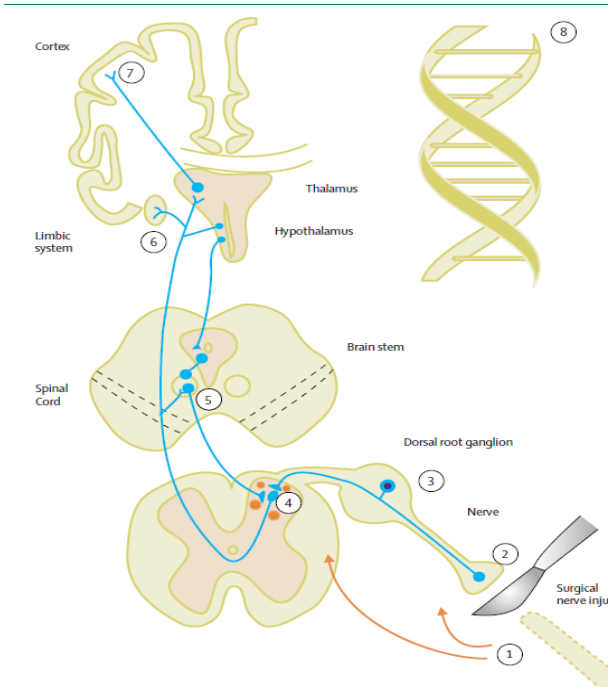
4. Hypotalamo-limbická oblasť (afektívna zložka): opioidy, AD, AE

5. Aktivácia DIS: opioidy, antidepresíva

6. Na úrovni talamo-kortikálnej: opioidy, niektoré analgetiká-antipyretiká

Patofyziológia





Nociceptívna komponenta

Neuropatická komponenta
rez, útlak, ischemizácia, ťah, termolézia, RTG

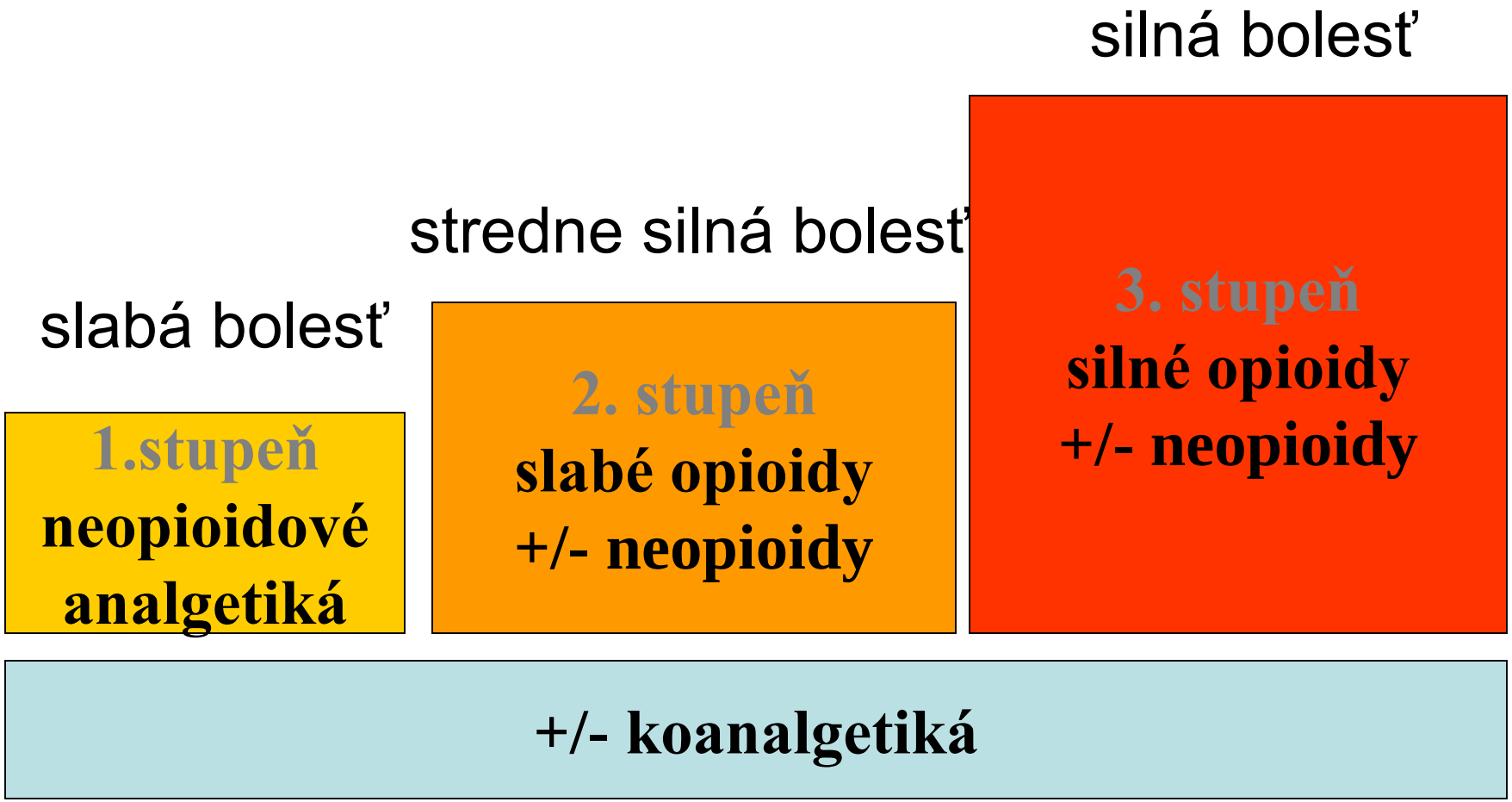
Benefit viacerých mechanizmov účinku

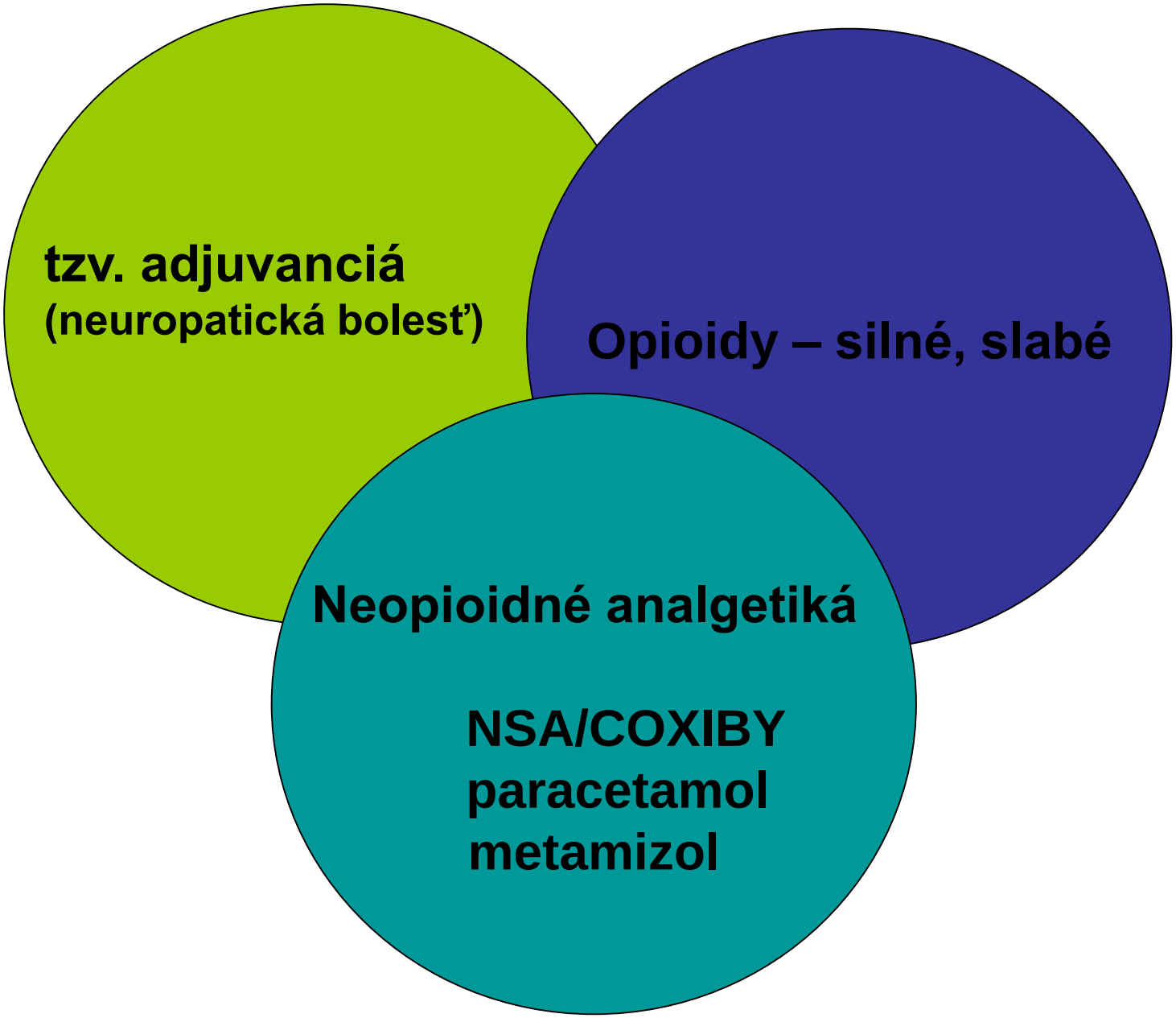
- príčinou nižšej účinnosti liekov s jedným mechanizmom účinku hlavne pri zmiešaných typoch bolesti je fakt, že nociceptívna a neuropatická bolesť nemajú rovnaké patogenetické mechanizmy a vyžadujú odlišné terapeutické prístupy

- mnohé štúdie podľa Cochrane databázy vykazovali vyššiu efektívnosť liekov s rôznymi mechanizmami účinku

COLUZZI F, et al. European Review for Medical and Pharmacological Sciences. 2017; 21: 1672-1683

Analgetický rebrík WHO (1986)




tzv. adjuvanciá
(neuropatická bolesť)
Opioidy – silné, slabé
Neopioidné analgetiká
NSA/COXIBY
paracetamol
metamizol

Princípy aplikácie analgetík

1. Akútna bolesť

- Obrátený analgetický rebrík
- Od najsilnejších – k najslabším analgetikám
- Od invazívnejších spôsobov aplikácie k menej invazívnym

2. Chronická bolesť – 5P

1. Perorálne
2. Podľa hodín (pravidelné časové intervaly)
3. Podľa vzostupného rebríka
4. Dávku individuálne titrovať proti bolesti
5. Venovať pozornosť detailom (NÚ)

Farmakokinetika ideálneho analgetika

K liečbe akútnej bolesti:

- on demand
- rýchla absorpcia a vysoká biologická dostupnosť
- nízky first-pass efekt
- rýchly nástup účinku (krátky t_{max})
- nízky potenciál liekových interakcií (kombinácie)

K liečbe chronickej bolesti:

- podľa hodín (around the clock)
- dlhý T 1/2 - stabilná pl. hladina
- nízky potenciál liekových interakcií (kombinácie)

Lieková forma

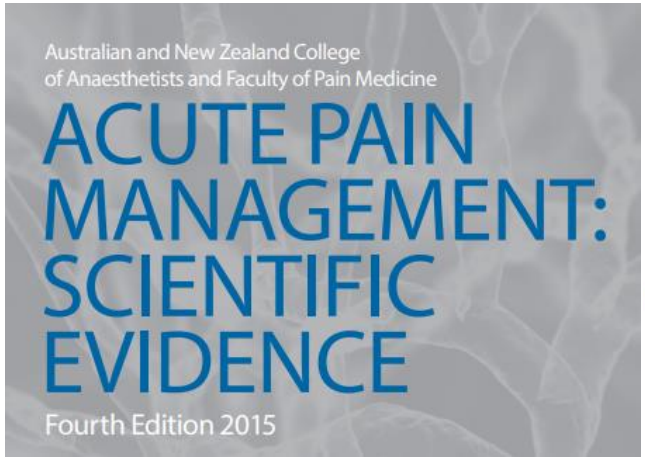
- Rýchly nástup účinku IR – krátke trvanie

(i.v., p.o. – tbl, kvapky)

- Retardované formy SR– s postupným uvoľňovaním – účinok 12-24 hodín

(p.o. - tbl, cps)

www.postoppain.org
www.anzca.edu.au/documents/apmse4_2015_final



State of the Art Safety Standards in RA
THE EUROPEAN SOCIETY OF REGIONAL ANAESTHESIA & PAIN THERAPY

prospect
procedure specific postoperative pain management

Better Postoperative Pain Management

Recommendations on this website are in the process of being updated. Please check back regularly for both updated content and new procedures

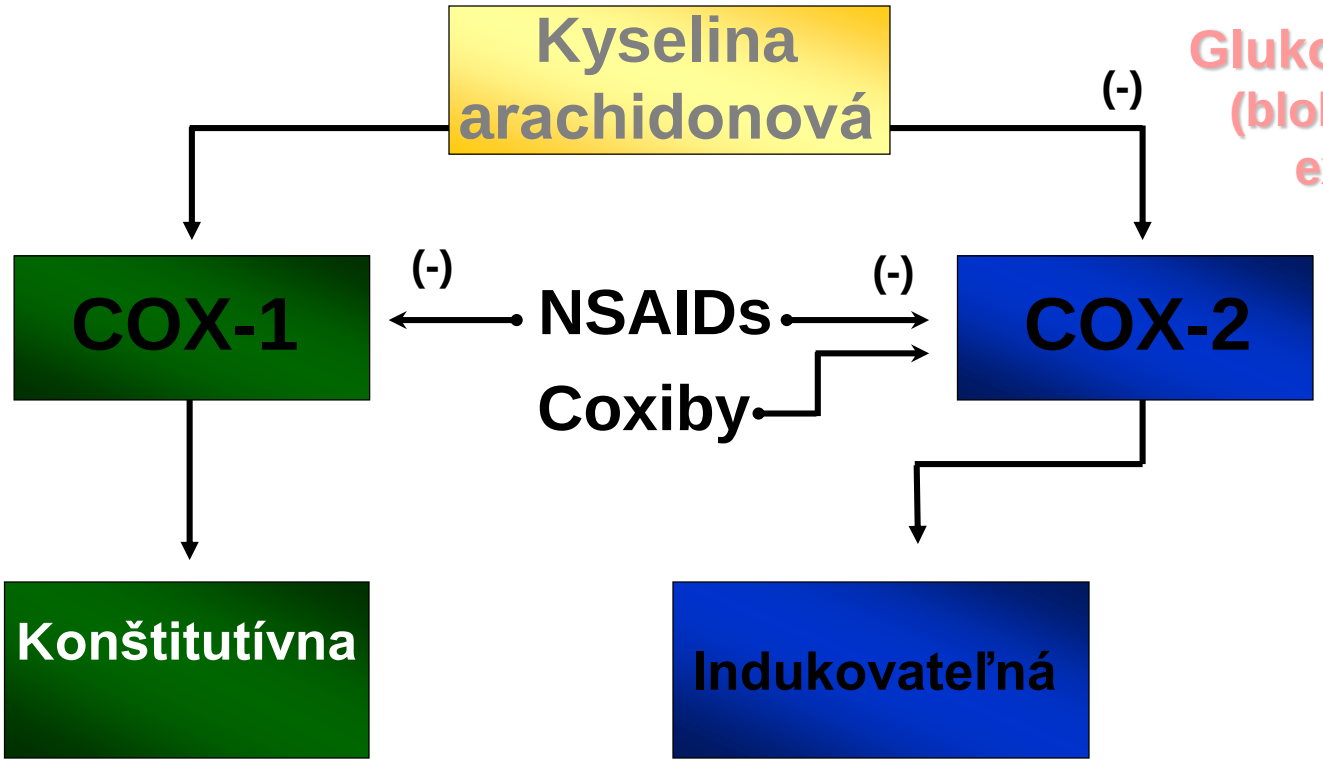
1. NSA, paracetamol, metamizol

História vývoja NSAIDs

- **Predprostaglandínové obd. (1949 - 1971)**
  - fenylbutazón, indometacín, ...

- **Prostaglandínové obd. (1971 – doteraz)**
  - 2 izoformy cyklooxygenázy — **COX-1**
    COX-2 (1991)
    Cox 3 CNS

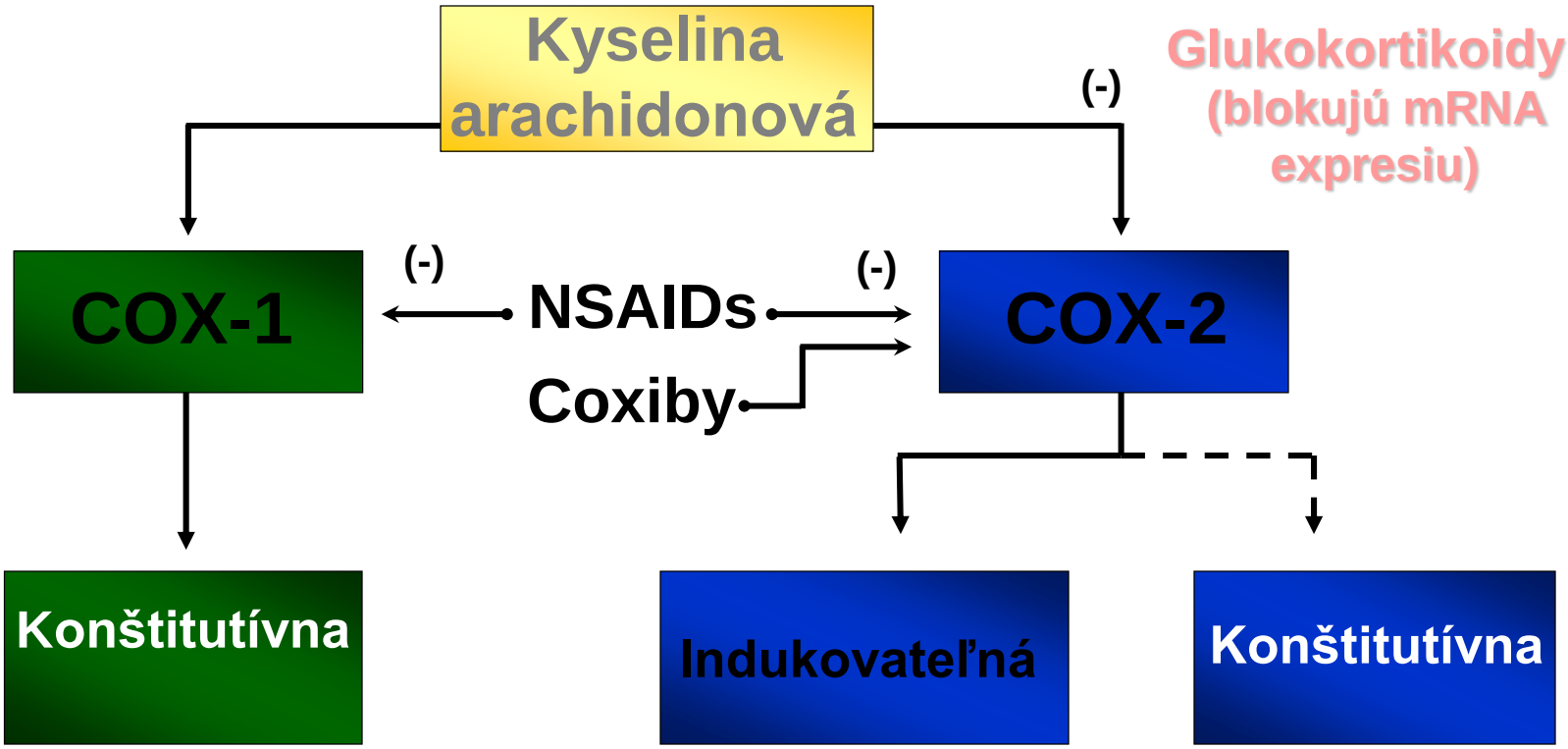
Cyklooxygenáza



- cytoprotekcia slizníc GIT
- obličky – renálny prietok
- agregácia trombocytov

- zápal
- bolesť
- horúčka

Cyklooxygenáza



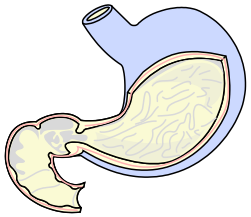
- cytoprotekcia slizníc GIT
- obličky – renálny prietok
- agregácia trombocytov

- zápal
- bolesť
- horúčka

- mozog, miecha
- obličky
- ováriá, uterus
- kosti ...

Nežiaduce účinky NSAIDs

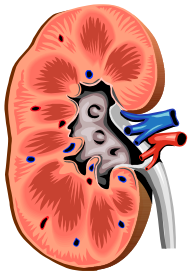
GIT (COX-1) najmä pri dlhodobom užívaní



menej časté v liečbe akútnej POB

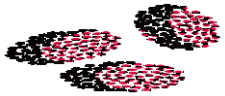
- Dyspepsia (všetky liekové formy)
- Anémia – Erózie, GI krvácanie
- Vredy – krvácanie / perforácia

Renálne (COX-1, COX-2)



- ↑ reabsorpcia Na, ↓ GF (?)
- Hypertenzia, edémy, srdcové zlyhanie
- RI – akútna / chronická
- Rizikoví pacienti - aj v poop.období

Anti-Trombocytárne (COX-1)



- zvyšujú krvné straty (koxiby nie)

Pľúcne (COX-1, COX-2)

- 10% astmatikov = aspirín senzitívni

Opatrenia

- včasné zaradenie PPI resp. antacíd do liečby,
- vhodná galenická forma – enterosolventné, acidorezistentné, mikropeletové alebo retardované formy (vstrebávanie až v tenkom čreve)
- effervescentné formy - uvoľňovaním CO_2 zvyšujú prekrvenie sliznice žalúdka, čím sa urýchľuje nie len vstrebávanie, ale aj nástup účinku.
- stupeň poškodenia GIT závisí najmä od plazmatickej hladiny NSA v plazme – **ide teda o systémový efekt**, a gastrotoxicita sa môže prejaviť **aj po parenterálnom a rektálnom podaní NSA**

Delenie NSAIDs

1. selektívne COX-1 inhibítory

(ASA v nízkych dávkach < 325 mg)

2. neselektívne COX inhibítory

(diklofenak, ibuprofen, ketoprofen, piroxikam...)

3. preferenčné COX-2 inhibítory

(meloxikam, nimesulid, etodolak)

4. selektívne COX-2 inhibítory – „COXIBY“

Parenterálne formy: Almiral 75 mg inj.

Neodolpasse inf.

Ketonal inj., Ibuprofen inf

NSAIDs - farmakológia

- Slabé kyseliny, lipofilné molekuly
- Dobrá absorpcia z GIT
- Silná väzba na plazmatické bielkoviny –

(↓ albumín = vyššia voľná/účinná koncentrácia)

- Analgetická dávka < antiflogistická dávka
- **Stropový efekt !** – max. 1,5-2 násobok odporúčanej terapeutickej dávky
- Nekombinovať medzi sebou

NSAIDs v liečbe akútnej bolesti

- **Step down**
- **multimodálna (balansovaná) analgézia**

Princíp: **1+1=3** (Rawal, 2003)

často ↓ spotrebu opiátov (p.o., p.e., epid.) o **40%**

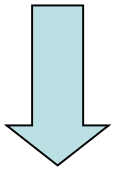
↑ kvalitu analgézie

(priekaznosť EBM – úroveň A,B)

- rôzne liekové formy (p.o., i.m., i.v., supp.)
- bolusovo / kontinuálne (PCA) + slabé opioidy
- preemptívne pôsobenie
- cena

NSA prax – 30 miliónov pac.

- Populácia starne – ↑ výskyt OA, RA, vertebrogénne ochorenia
- Dobrá účinnosť
- Pestrá paleta liekových foriem
- Dostupnosť aj bez Rp



boom coxibov

COX-2 selektívne inhibítory

- Celecoxib (molekula r. 2002) – p.o liečba OA a RA
- Rofecoxib VIGOR (2000) ROF/NAP

  APROVe (2004) 2x vyššie riziko KV príhod

30.9.2004
celosvetovo stiahnutý

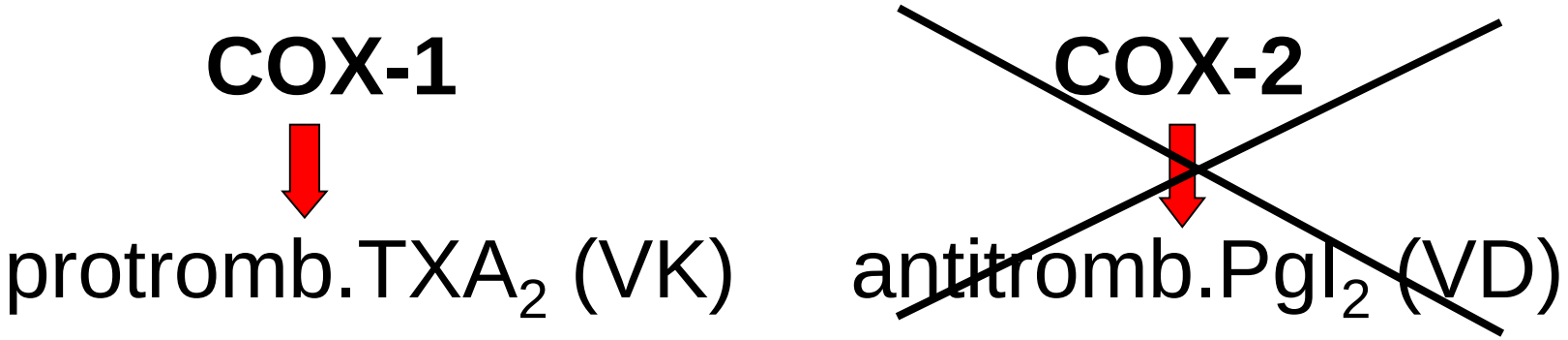
- Etoricoxib, valdecoxib, parecoxib, lumiracoxib
- Nimesulid – Fínsko, Španielsko *(hepatotoxicita)*

EMEA 2002-2004 Európske prehodnocovanie prínosov/rizika

Osud koxibov

- **rofecoxib**
  - štúdia VIGOR….2001: 4x viac IM > naproxen
  - štúdia APROVe - FAP, po 18 mes; 2x vyššie riziko trombotických príhod (IM, CMP) vs. placebo
- **valdecoxib**
  - jar 2005 – kožné NÚ, ? kardiotoxicita - stiahnutý
- **etoricoxib**
  - v ČR nikdy neuvedený – štúdia MEDAL
- **parecoxib**
  - jediný parenterálny koxib, krátkodobá aplikácia
- **celecoxib**
  - posledný „mohykán“; ? selektivita

KI – EMEA (www.emea.eu.int.)



- KI pre ICHS (NYHA III-IV) a NCMP
- KI pre etoricoxib – a. hypertenzia
- Pozor u pac. s **RF** pre ochorenie srdca
- Aktívny vred
- Nenahrádzajú ASA v prevencii och. KVS

Rýchlosť nástupu účinku

- **Liekové formy**
  - efervescentné tablety, beta-cyklodextrin piroxicam
- **Stereoizoméry**
  - dexketoprofen, dexibuprofen
- **Soli**
  - dexketoprofen tromethamol, ibuprofen arginat, ibuprofen lysinat, diclofenac K+
- **Kombinácie**
  - + kofein (paracetamol, ibuprofen)
  - + bikarbonát (paracetamol)
  - + guaifenesin

Coxibs vs nsNSAIDs in Postop Pain

(summary of key messages of APM:SE 4th edition 2015)

- Blood loss and bleeding complications:
  - nsNSAIDs > placebo (Level I)
  - Coxibs = placebo (Level I)
  - Coxibs < nsNSAIDs (Level II)
- GI ulceration short-term (5-7 days):
  - nsNSAIDs >> placebo (Level II)
  - Coxibs = placebo (Level I)
  - Coxibs << nsNSAIDs (Level II)
- Bronchospasm in aspirin sensitive asthma
  - Coxibs = placebo (Level I)
  - nsNSAIDs > Coxibs (Level I)
- Acute kidney injury
  - Coxibs = placebo (Level III-2)
  - Coxibs < nsNSAIDs (Level III-2)
- Cardiovascular complications short-term (5-7 days)
  - Parecoxib/celecoxib = placebo (Level I)

EFIC kongres, 2019

Eur J Pain. 2016 Aug;20(7):1025-43. doi: 10.1002/ejp.842. Epub 2016 Mar 15.

Preoperative preemptive drug administration for acute postoperative pain: A systematic review and meta-analysis.

Nir RR[1,2], Nahman-Averbuch H[1,2], Moont R[1,2], Sprecher E[1,2], Yarnitsky D[1,2].

Author information

1 Department of Neurology, Rambam Health Care Campus, Haifa, Israel.

2 Laboratory of Clinical Neurophysiology, The Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel.

A significant reduction in postoperative analgesic consumption was observed using preoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs; 95% CI, 0.61 to 0.14; 31 comparisons), chiefly by the COX-2 inhibitors class (95% CI, 0.95 to 0.33; 13 comparisons).

Preferenčné COX-2 inhibítory

- Rýchlosť nástupu účinku
  - nimesulid…… do 30 min (t-max=1-3 h)
  - meloxikam……. do 90 min (t-max=4-11 h)
- Biologický polčas
  - nimesulid……..4-6 hod…….2x denně
  - meloxicam……15-20 hod …1x denně

……. použitie u akútnych vs. chronických bolestí

Ako v praxi - NSA

- preferovať koxiby – parecoxib 40 mg i.v.
  (už pri úvode do CA)
- prechod na celecoxib p.os. (ak sa dá)
- ak riziko GIT komplikácií – pridaj PPI
- sú KI u renálne kompromitovaných,

(hypovolémia, hypotenzia, nefrotoxické lieky)

- dôležitá súčasť multimodálnej analgézie

Paracetamol

- nemá antiflogistický efekt !

Analgetický účinok je centrálny – aktivácia descendentných serotoninergných dráh, prostredníctvom svojich aktívnych metabolitov (p-aminophenolu) pravdepodobne ovplyvňuje aj kanabinoidné receptory.

Antipyretický efekt - inhibíciou COX-2 (hipocampus)

- analgetická dávka > ako antipyretická

  1g 0,5g

- maximálna denná dávka - 4g krátkodobo

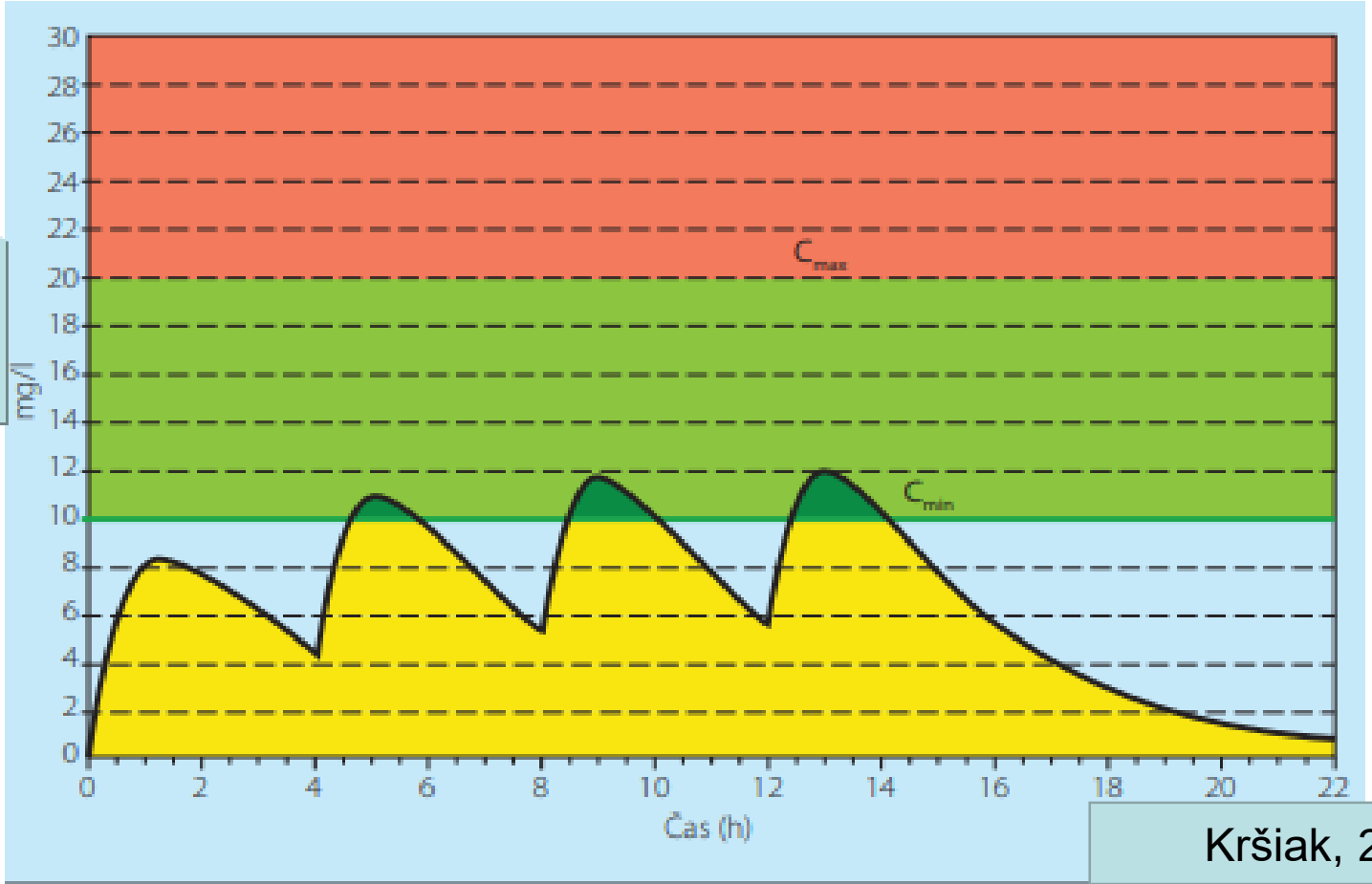
  - 2g dlhodobo

- patrí medzi najbezpečnejšie analgetiká (polymorbídni, geriatrickí ...)

Farmakokinetika

10-15mg/kg teda >50 kg 1 tbl (500 mg) nestačí
1,0g – max. jednotlivá dávka

85 kg
1,0g/6h
p.os.



Kršiak, 2012

Hepatotoxicita

Analýza takmer 800 publikácií (4g/deň)

- 30 tisíc pacientov

- ALT zvýšené u 0,4 % liečených, nikdy nedošlo k zlyhaniu pečene

- 4 g denne – alkoholici (1–3 nápoje denne):

po 4 d =ALT, po 10 d ↑ALT

- 4g denne 14 d u 18 dobrovoľníkov:

prechodne ↑ALT asi u 1/3 osôb

Ako v praxi - paracetamol

- Ak dávka 1g neúčinná – kombinuj
- s NSA/koxibmi, s metamizolom
- so slabými/silnými opioidmi
- súčasť mnohých kombinovaných preparátov

- Zrýchlenie nástupu účinku
- nalačno (vstrebávanie v TČ), + prokinetiká
- šumivé tablety, tbl so zvýšeným rozpúšťaním

Metamizol

- analgetické, antipyretické a spazmolytické účinky
- **inhibícia COX** – veľmi slabo neselektívne inhibuje COX-1/COX-2, ale je to účinok tak slabý, že v podmienkach zápalu je klinicky nevýznamný,
- inhibuje pravdepodobne predovšetkým **COX-3** v CNS, čím znižuje hladinu PgE2 a tým i senzitivitu a excitabilitu nociceptorov na účinky mediátorov bolesti.
- aktivácia **endokanabinoidového** systému – aktívne metabolity metamizolu sú agonistami kanabinoidných reptorov typu 1, ktoré sú súčasťou DIS
- aktiváciou **endogénneho opioidového** systému

Metamizol - indikácie

- **nociceptívna viscerálna** bolesť brucha a hrudníka, ktoré sú spojené so spazmom dutých orgánov alebo ich distenziou.
- **neuropatická** – kontinuálna pálivá bolesť - nádorovej i nenádorovej etiológie.
- nemigrenózne **bolesti hlavy**

- vhodne sa kombinuje s paracetamolom, NSA, opioidmi.

Opioidy - výhody

- veľmi účinné analgetiká v liečbe silnej akútnej i chronickej bolesti, ...

... ale niektoré opioidy sú horšie ...

Meperidín - nie je lepší ako morfín alebo hydromorfón v liečbe bolesti pri renálnej kolike (L II)

- je spojený s vyšším rizikom delíria v pooperačnom období v porovnaní s inými opioidmi (LIII)

V manažmente POB sú niektoré opioidy lepšie u niektorých pacientov (LII)

Opioidy - nevýhody

- Zhoršenie ventilácie
- Nauzea, zvracanie
- Obstipácia
- Retencia moča
- Sedácia
- Imunosupresia, endokrinné zmeny
- Onkologickí pacienti?

... predlžujú pobyt v nemocnici a zvyšujú náklady na liečbu

... sú na dávke závislé (L I)

Multimodálna analgézia

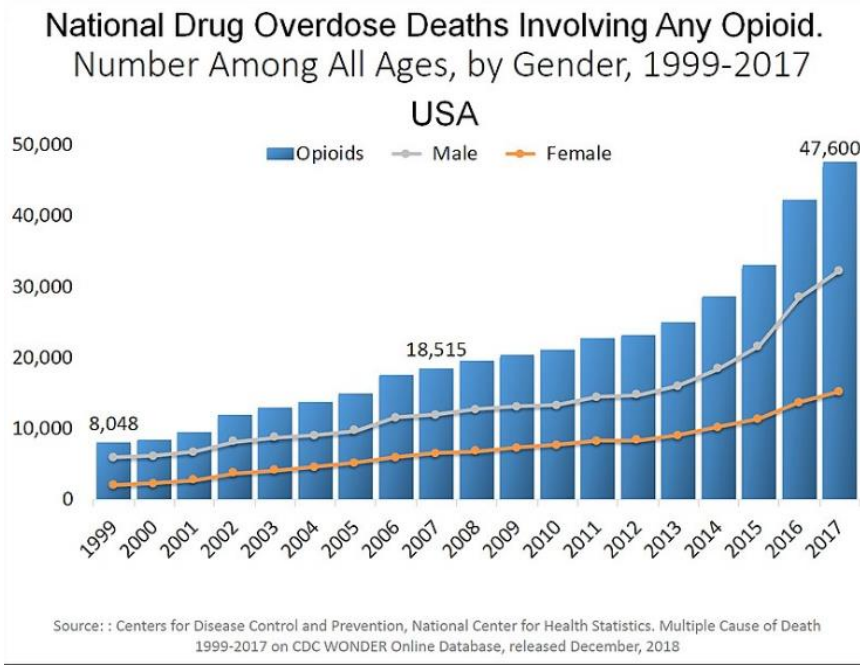
- Je účinnejšia – pri znížení dávky opioidov a aj NÚ (L II)

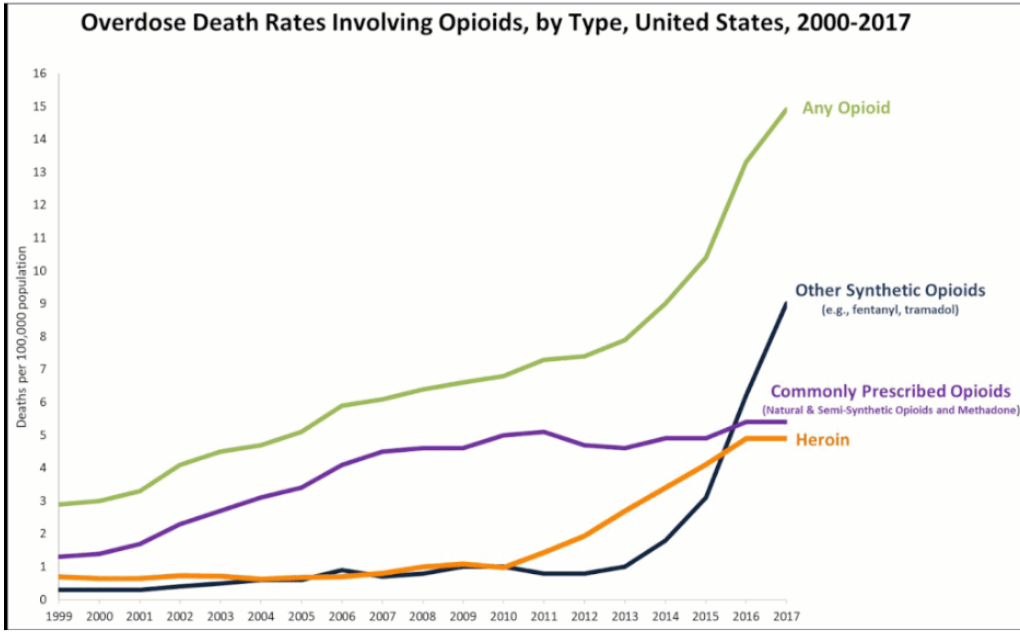
- Panel expertov : APS, ASRAaPM, ASA

Chou et al., J Pain, 2016, 17:131-57

- Kombinácia - rôznych analgetík, analgetických techník a nefarmakologických postupov (L I, QoE – H)

Opioidná kríza v USA





Anesthesiology. 2016 Apr;124(4):837-45. doi: 10.1097/ALN.0000000000001034.

Variations in the Use of Perioperative Multimodal Analgesic Therapy.

Ladha KS[1], Patorno E, Huybrechts KF, Liu J, Rathmell JP, Bateman BT.

Author information

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Abstract

BACKGROUND: Practice guidelines for perioperative pain management recommend that multimodal analgesic therapy should be used for all postsurgical patients. However, the proportion of patients who actually receive this evidence-based approach is unknown. The objective of this study was to describe hospital-level patterns in the utilization of perioperative multimodal analgesia.

METHODS: Data for the study were obtained from the Premier Research Database. Patients undergoing below-knee amputation, open lobectomy, total knee arthroplasty, and open colectomy between 2007 and 2014 were included in the analysis. Patients were considered to have multimodal therapy if they received one or more nonopioid analgesic therapies. Mixed-effects logistic regression models were used to estimate the hospital-specific frequency of multimodal therapy use while adjusting for the case mix of patients and hospital characteristics and accounting for random variation.

RESULTS: The cohort consisted of 799,449 patients who underwent a procedure at 1 of 315 hospitals. The mean probability of receiving multimodal therapy was 90.4%, with 95% of the hospitals having a predicted probability between 42.6 and 99.2%. A secondary analysis examined whether patients received two or more nonopioid analgesics, which gave an average predicted probability of 54.2%, with 95% of the hospitals having a predicted probability between 9.3 and 93.2%.

CONCLUSIONS: In this large nationwide sample of surgical admissions in the United States, the authors observed tremendous variation in the utilization of multimodal therapy not accounted for by patient or hospital characteristics. Efforts should be made to identify why there are variations in the use of multimodal analgesic therapy and to promote its adoption in appropriate patients.

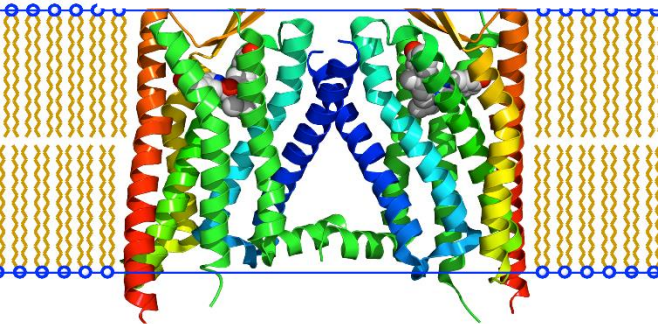
Ladha, 2016 USA

- 4 operácie - kolektómia (22%), TKA (71%),
  - lobektómia (3%), amputácie pod kolenom (4%)
- takmer všetci pac. dostali opioidy (97%)
- iba 2/3 pac. dostali paracetamol (66%)
- málo využívané neopioidné analgetiká:
  - NSA 15-57%, koxiby 1-2%
  - gabapentín 4-36%
  - ketamín 2-5%
- veľmí nízke využitie regionálnych analgetických techník:
  - amputácie 3%
  - kolektómie 6%
  - lobektómie 27%
  - TKA 14%

Opioidné receptory

OP

EC – N terminálny koniec



IC – C terminálny koniec

G proteín

cAMP, K^+kanál, Ca^+kanál

signálne dráhy – progresia

mí, kappa, delta, ORL-1

Lokalizácia:

- **CNS**, PNS, GIT, KVS, UGS
- na bunkách IS (imunomodulačný efekt)
- na nádorových bb.

Opioidy

- Slabé - tramadol, kodeín, tapentadol
- Silné - fentanyl a deriváty (su-, remi-, al-)
  - morfín
  - hydromorfon, oxykodon
  - buprenorfín
  - piritramid
  - nalbufín
  - petidín, dipidolor

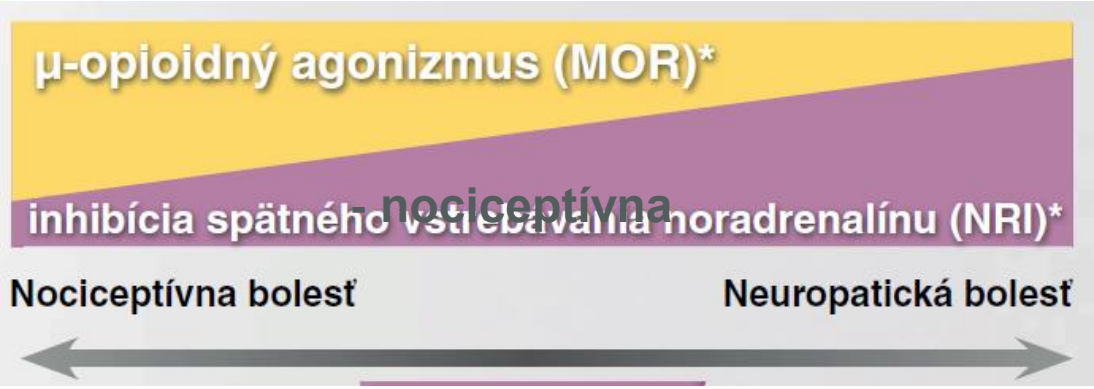
Opioidy

- Typické: pôsobiace na OR
- Atypické: pôsobiace na OR + iné receptory

MOR-NRI a bolesť nociceptívnej alebo neuropatickej etiológie

Experimentálne testy potvrdili významnejšiu úlohu:

- μ-komponentov v **nociceptívnej** bolesti
- NRI-komponentov **neuropatickej** bolesti



Akútna bolesť - **nociceptívna**
Chronická bolesť - **neuropatická**

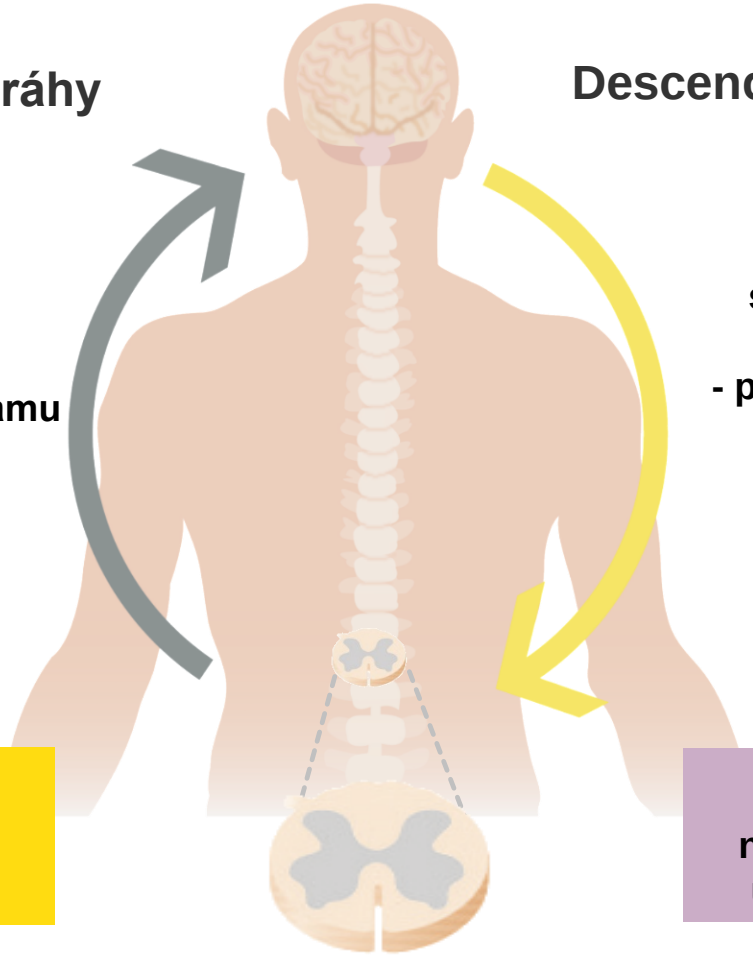
Duálny mechanizmus účinku

Ascendentné dráhy

Aktivácia μ-opioidných receptorov - inhibícia prenosu bolestivého signálu do talamu

Descendentné dráhy

Potlačenie spätného vstrebávania noradrenalínu - posilnenie descendentnej inhibície bolesti



MOR
μ-opioid receptor agonista

NRI
noradrenaline re-uptake inhibitor

Súčasná aktivácia oboch systémov vedie k synergickému analgetickému účinku

Referencie: Tzschentke, TM. et al. Drugs of Today 2009, 45 (7): 483-496

Opioidy

- Typické: pôsobiace na OR
- Atypické: pôsobiace na OR + iné receptory

- tramadol - 40% μ-agonista
  - 60% SSNRI + nepriamy α2 agonista (NMDA, 5-HT2C, N a M receptorov)
- sila: 1/10-1/6 morfínu
- výborná biologická dostupnosť (70-100%)

Atypické opioidy

- tapentadol - 40% parciálny μ agonista
  - 60% NRI
- tbl IR aj SR

- buprenorfín - parciálny μ agonista
  - κ antagonista
  - δ antagonista

Opioidy

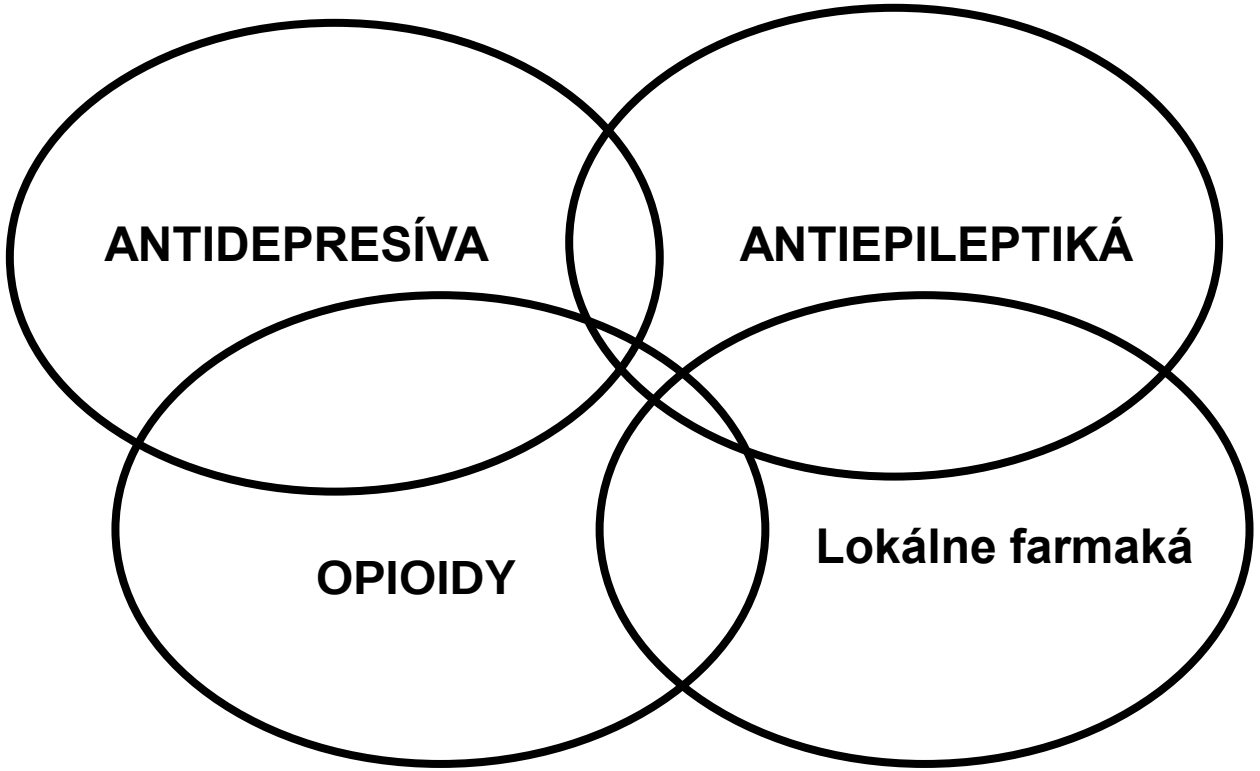
- nalbufín - μ antagonista
  - κ agonista

- stropový efekt – denná dávka 30 mg
- 15mg=10 mg MO
- max. jednorazová dávka: 20 mg
- pôrodnícka analgézia - skôr cez κ receptory
  - prechod placentou

- remifentanil – 2x> FNL, esterová väzba – hydrolýza
  neaktívne metabolity

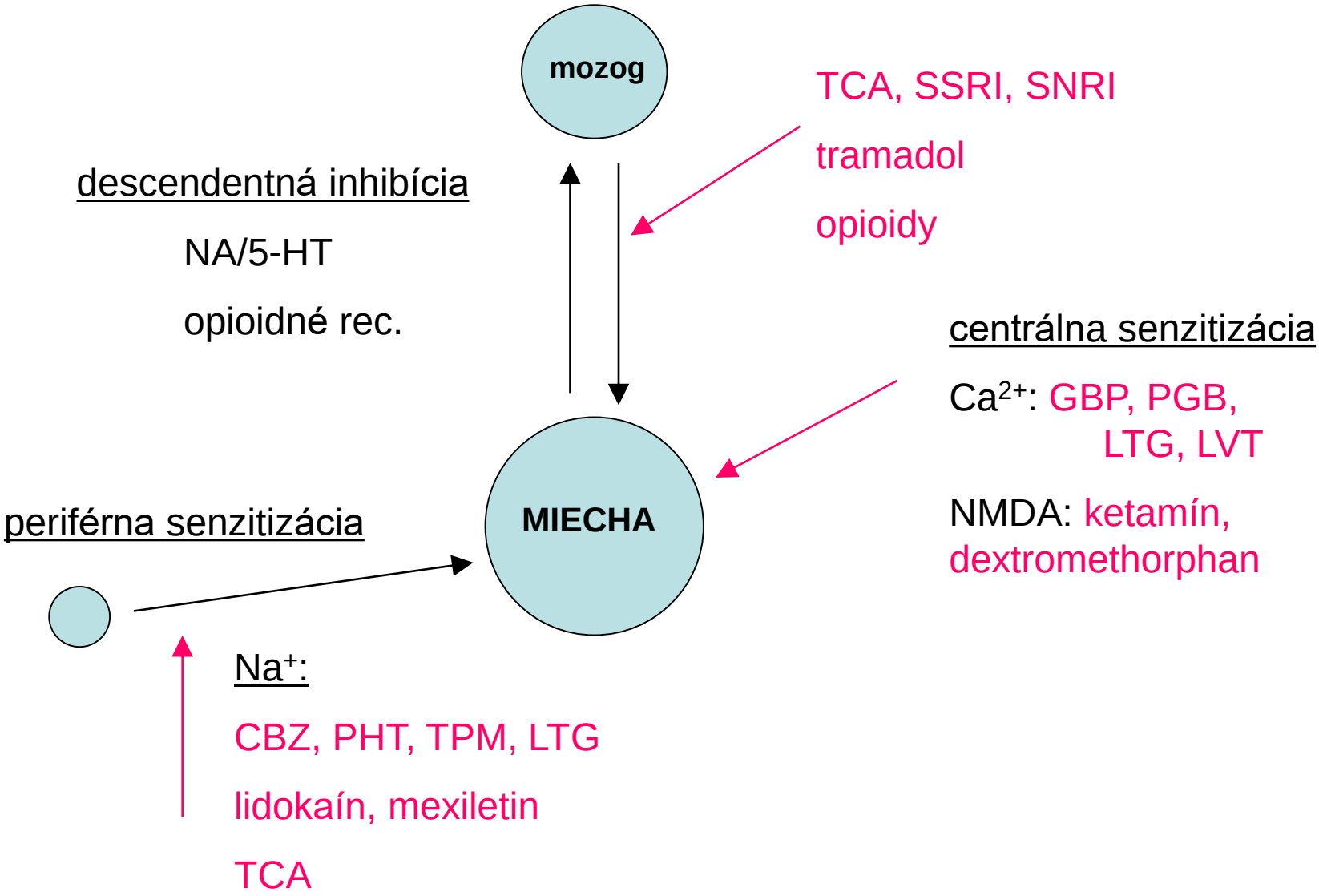
PEDA: bolus 20-30 ug, lock out 2-3 min, až do konca 2DP
kont. 0,1 ug/kg/min

Adjuvantné analgetiká liečba neuropatickej bolesti



- TCA (amitriptylin) $\rightarrow\rightarrow\rightarrow$ SNRI (venlafaxín, duloxetín)
  DNRI (bupropion)
- CBZ, PHT $\rightarrow\rightarrow\rightarrow$ gabapentín, pregabalín
- Morfin $\rightarrow\rightarrow\rightarrow$ oxykodon, tramadol

Mechanismy účinku liečiv v terapii neuropatickej bolesti

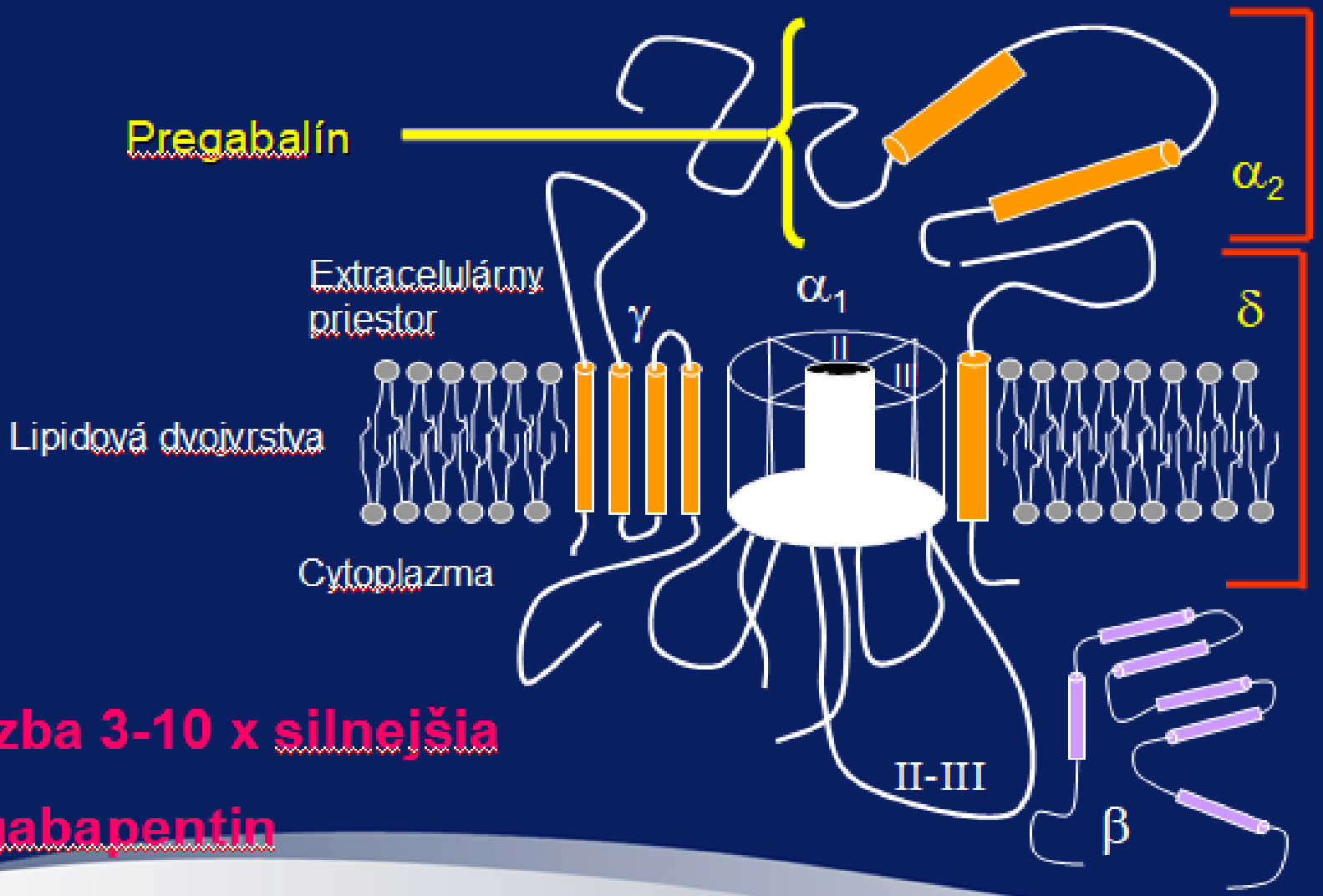


podľa Beydoun 2003

Klasifikácia farmák k liečbe neuropatickej bolesti

- membrány – stabilizujúce liečivá
  - antiepileptiká
    - carbamazepin, fenytoin, valproát
  - antiarytmiká
    - lidocain, mexiletin
- ↑ inhibície v ZRM
  - antiepileptiká
    - clonazepam, gabapentin
  - antidepresíva
    - amitriptylín, imipramín, fluoxetín
  - GABA-B agonisty…..baclofen

Pregabalín sa viaže na α_2-δ podjednotku napäťovo riadených Ca kanálov

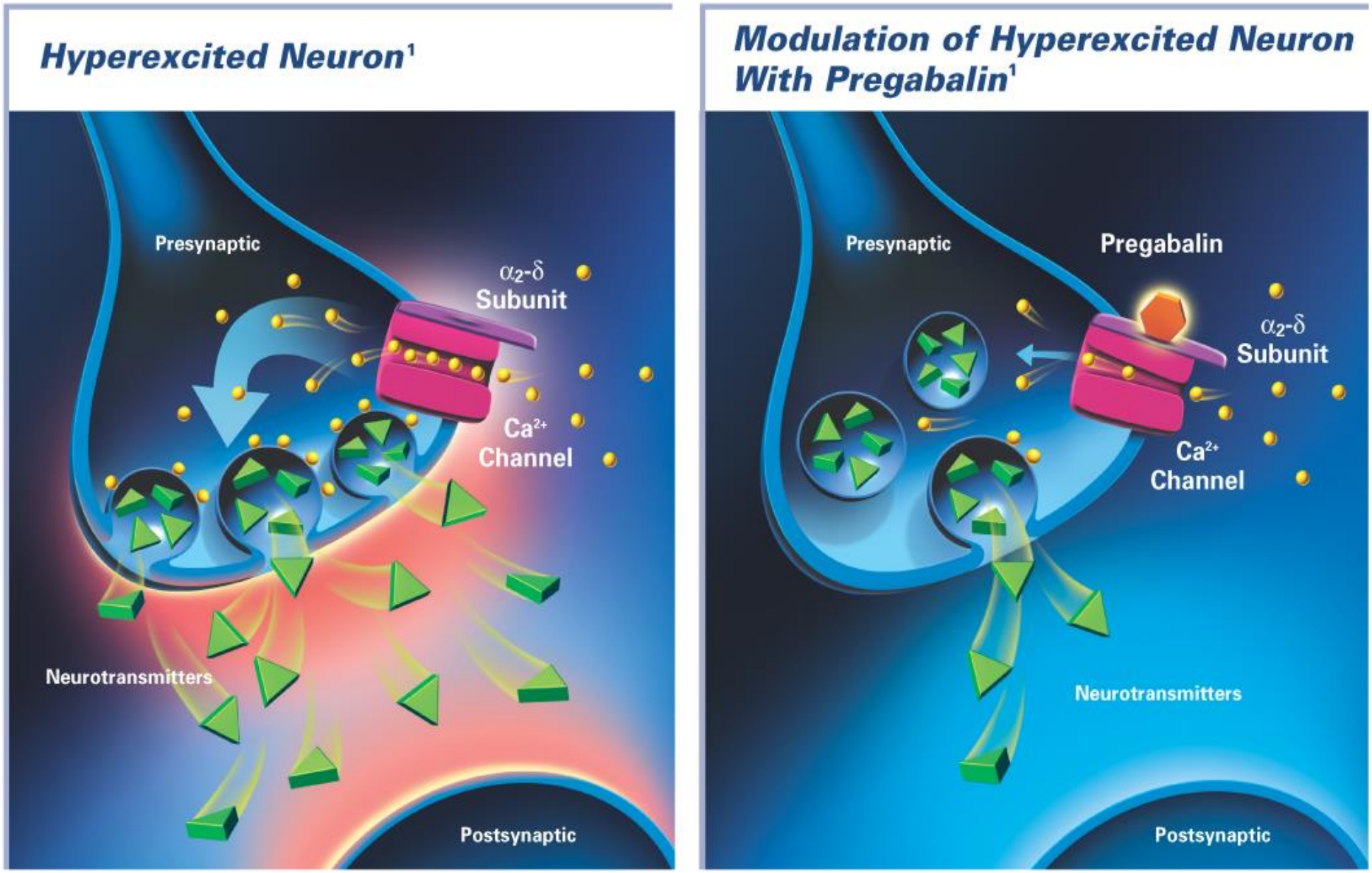


vazba 3-10 x silnejšia

> gabapentin

Arikkath and Campbell. Curr Opin Neurobiol. 2003;(3):298-307.

Pregabalín moduluje hyperexcitované neuróny



Br J Anaesth. 2015 Jan;114(1):10-31. doi: 10.1093/bja/aeu293. Epub 2014 Sep 10.

Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis.

Mishriky BM[1], Waldron NH[1], Habib AS[2].

Author information

1 Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA.

2 Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA habib001@dm.duke.edu.

Abstract

We performed this systematic review to assess the analgesic efficacy of perioperative pregabalin. Subgroup analyses and meta-regression were performed to assess the impact of individual dose and frequency of pregabalin administration on analgesic efficacy. We included 55 studies. When all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 h compared with placebo {mean difference [95% confidence interval (CI)]=-0.38 (-0.57, -0.20), -0.47 (-0.76, -0.18), and -8.27 mg morphine equivalents (-10.08, -6.47), respectively}. Patients receiving pregabalin had less postoperative nausea and vomiting and pruritus compared with placebo [relative risk (RR) (95% CI)=0.62 (0.48, 0.80) and 0.49 (0.34, 0.70), respectively]. Sedation, dizziness, and visual disturbance were more common with pregabalin compared with placebo [RR (95% CI)=1.46 (1.08, 1.98), 1.33 (1.07, 1.64), and 3.52 (2.05, 6.04), respectively]. All doses of pregabalin tested (≤75, 100-150, and 300 mg) resulted in opioid sparing at 24 h after surgery. There were no significant differences in acute pain outcomes with pregabalin 100-300 mg between single preoperative dosing regimens and those including additional doses repeated after surgery. Data were insufficient to reach conclusions regarding persistent pain, but limited data available from two studies suggested that pregabalin might be effective for the reduction of neuropathic pain. In conclusion, this review suggests that pregabalin improves postoperative analgesia compared with placebo at the expense of increased sedation and visual disturbances.

Ako v praxi - pregabalín

- kedy - 90-120 min pre operáciou
- dávka – rutinne 150 mg, resp.
  - 75 mg u starých
  - 300 mg u „big and robust“
- pokračovať po operácii ak zvýšené riziko neuropatickej bolesti
- najlepšie dáta: TKA, spinálna chirurgia, mastektómia?, prostatektómia

Ketamín

- nekompetitívny antagonista NMDA receptorov

+ ďalších cca 35 receptorov a kanálov – AMPA, GABA, N, M, kainátové, Na+, K+, SSRI...

+ protizápalový účinok (cez IL6...)

+ LS, MK .....

- len somatická analgézia
- cesta podania: i.v.,

S+ ketamín: p.os. 2-3mg/kg (↓ biodostupnosť)

intranazálne 10 mg (0,1ml roztoku) (71% biodostup.)

0,5 mg/kg – rýchly efekt (ďalší deň)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Rapid Antidepressant Effects of Ketamine in Major Depression

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

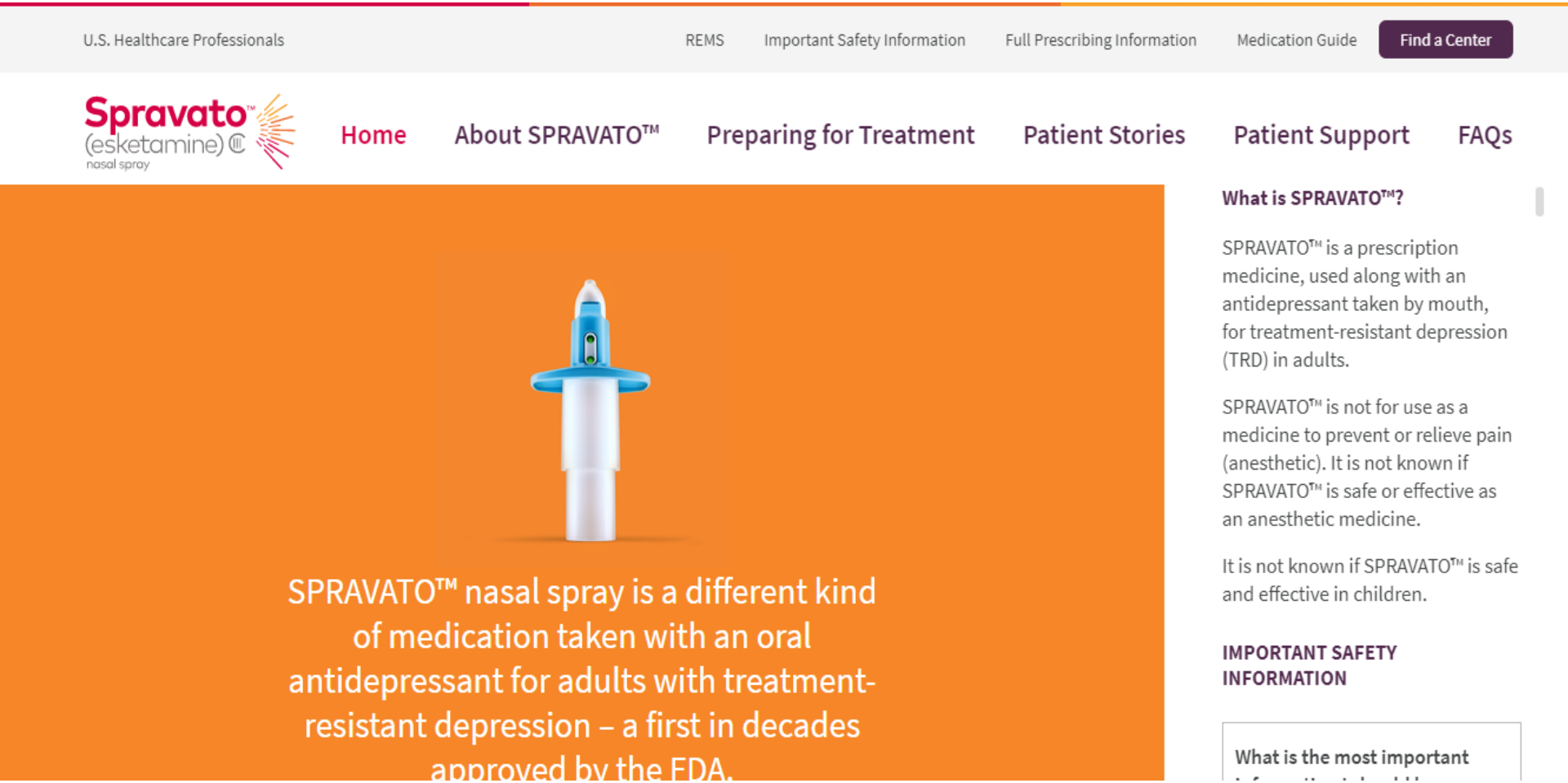
Sponsor:

National Institute of Mental Health (NIMH)

Information provided by (Responsible Party):

National Institutes of Health Clinical Center (CC) (National Institute of Mental Health (NIMH))

SPRAVATO spray – prevencia suicídia



Can J Anaesth. 2011 Oct;58(10):911-23. doi: 10.1007/s12630-011-9560-0. Epub 2011 Jul 20.

A systematic review of intravenous ketamine for postoperative analgesia.

Laskowski K[1], Stirling A, McKay WP, Lim HJ.

Author information

1 Department of Anesthesiology, Perioperative Medicine and Pain Management, College of Medicine, University of Saskatchewan, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada. kevin.laskowski@usask.ca

Abstract

PURPOSE: Perioperative intravenous ketamine may be a useful addition in pain management regimens. Previous systematic reviews have included all methods of ketamine administration, and heterogeneity between studies has been substantial. This study addresses this issue by narrowing the inclusion criteria, using a random effects model, and performing subgroup analysis to determine the specific types of patients, surgery, and clinical indications which may benefit from perioperative ketamine administration.

SOURCE: We included published studies from 1966 to 2010 which were randomized, double-blinded, and placebo-controlled using intravenous ketamine (bolus or infusion) to decrease postoperative pain. Studies using any form of regional anesthesia were excluded. No limitation was placed on the ketamine dose, patient age, or language of publication.

PRINCIPAL FINDINGS: Ninety-one comparisons in seventy studies involving 4,701 patients met the inclusion criteria (2,652 in ketamine groups and 2,049 in placebo groups). Forty-seven of these studies were appropriate for evaluation in the core meta-analysis, and the remaining 23 studies were used to corroborate the results. A reduction in total opioid consumption and an increase in the time to first analgesic were observed across all studies ($P < 0.001$). The greatest efficacy was found for thoracic, upper abdominal, and major orthopedic surgical subgroups. Despite using less opioid, 25 out of 32 treatment groups (78%) experienced less pain than the placebo groups at some point postoperatively when ketamine was efficacious. This finding implies an improved quality of pain control in addition to decreased opioid consumption. Hallucinations and nightmares were more common with ketamine but sedation was not. When ketamine was efficacious for pain, postoperative nausea and vomiting was less frequent in the ketamine group. The dose-dependent role of ketamine analgesia could not be determined.

CONCLUSION: Intravenous ketamine is an effective adjunct for postoperative analgesia. Particular benefit was observed in painful procedures, including upper abdominal, thoracic, and major orthopedic surgeries. The analgesic effect of ketamine was independent of the type of intraoperative opioid administered, timing of ketamine administration, and ketamine dose.

Ako v praxi - ketamín

- Odporúčané dávky:
- kontinuálne 0,1mg/kg/hod
- psychomimetické účinky raritné (ak, + midazolam)

- Vhodné najmä u:
- opioid tolerantných pacientov
- neuropatickej bolesti

- Vhodný pre prevenciu chronickej pooperačnej bolesti a fantómovej bolesti

Anesthesiology. 2012 Jun;116(6):1312-22. doi: 10.1097/ALN.0b013e31825681cb.

Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials.

Blaudszun G[1], Lysakowski C, Elia N, Tramèr MR.

Author information

1 Division of Anesthesiology, Geneva University Hospitals, Geneva, Switzerland. gregoire.blaudszun@hcuge.ch

Abstract

BACKGROUND: Systemic α2 agonists are believed to reduce pain and opioid requirements after surgery, thus decreasing the incidence of opioid-related adverse effects, including hyperalgesia.

METHODS: The authors searched for randomized placebo-controlled trials testing systemic α2 agonists administrated in surgical patients and reporting on postoperative cumulative opioid consumption and/or pain intensity. Meta-analyses were performed when data from 5 or more trials and/or 100 or more patients could be combined.

RESULTS: Thirty studies (1,792 patients, 933 received clonidine or dexmedetomidine) were included. There was evidence of postoperative morphine-sparing at 24 h: the weighted mean difference was -4.1 mg (95% confidence interval, -6.0 to -2.2) with clonidine and -14.5 mg (-22.1 to -6.8) with dexmedetomidine. There was also evidence of a decrease in pain intensity at 24 h: the weighted mean difference was -0.7 cm (-1.2 to -0.1) on a 10-cm visual analog scale with clonidine and -0.6 cm (-0.9 to -0.2) with dexmedetomidine. The incidence of early nausea was decreased with both (number needed to treat, approximately nine). Clonidine increased the risk of intraoperative (number needed to harm, approximately nine) and postoperative hypotension (number needed to harm, 20). Dexmedetomidine increased the risk of postoperative bradycardia (number needed to harm, three). Recovery times were not prolonged. No trial reported on chronic pain or hyperalgesia.

CONCLUSIONS: Perioperative systemic α2 agonists decrease postoperative opioid consumption, pain intensity, and nausea. Recovery times are not prolonged. Common adverse effects are bradycardia and arterial hypotension. The impact of α2 agonists on chronic pain or hyperalgesia remains unclear because valid data are lacking.

Dis Colon Rectum. 2012 Nov;55(11):1183-94. doi: 10.1097/DCR.0b013e318259bcd8.

Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials.

Sun Y[1], Li T, Wang N, Yun Y, Gan TJ.

Author information

1 Department of Anesthesiology, TongRen Hospital, Capital Medical University, Beijing 100730, [corrected] China. sun00017@gmail.com

Erratum in
Dis Colon Rectum. 2013 Feb;52(2):271.

Abstract

BACKGROUND: Postoperative pain management remains a significant challenge after abdominal surgery.

OBJECTIVE: The aim of this meta-analysis was to evaluate the efficacy of systemic lidocaine for postoperative pain management and recovery after abdominal surgery.

DATA SOURCE: Data were derived from Medline (1966-2010), CINAHL, The Cochrane Central Register of Controlled Trials, and Scopus.

STUDY SELECTION: Randomized controlled trials of systemic administration of lidocaine for postoperative analgesia and recovery after abdominal surgery in adults, ie, >18 years, were considered.

INTERVENTIONS: Combined data were analyzed with use of a random-effects model.

MAIN OUTCOMES MEASURES: Data on opioid consumption, postoperative pain intensity, opioid-related side effects, time to first flatus, time to first bowel movement, and length of hospital stay were extracted.

RESULTS: Twenty-one trials comparing systemic lidocaine with placebo or blank control for postoperative analgesia and recovery after abdominal surgery were included in this meta-analysis. Weighted mean difference for cumulative analgesic opioid (morphine) consumption 48 hours after surgery was -7.04 mg (95% CI: -10.40, -3.68, I2= 46.1%).Systemic lidocaine also significantly reduced postoperative pain intensity(visual analog scale, 0-100 mm) 6 hours after surgery at rest (weighted mean difference: -8.07 mm (95% CI: -14.69, -1.49); I2 = 90.6%) and during activity (weighted mean difference: -10.56 mm (95% CI: -16.89, -4.23), I2 = 82%). The time to first flatus and bowel movement was significantly shortened with lidocaine intervention by 6.92 hours (95% CI: -9.21, -4.63, I2 = 62.8%) and 11.74 hours (95% CI:-16.97, -6.51, I2 = 0). Moreover, systemic lidocaine also reduced hospital length of stay following the open procedure (weighted mean

Dis Colon Rectum. 2012 Nov;55(11):1183-94. doi: 10.1097/DCR.0b013e318259bcd8.

Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials.

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Dis Colon Rectum. 2013 Feb;52(2):271.

Abstract

BACKGROUND: Postoperative pain management remains a significant challenge after abdominal surgery.

OBJECTIVE: The aim of this meta-analysis was to evaluate the efficacy of systemic lidocaine for postoperative pain management and

CONCLUSION: Perioperative systemic lidocaine may be a useful adjunct for postoperative pain management by decreasing postoperative pain intensity, reducing opioid consumption, facilitating GI function, and shortening length of hospital stay.

abdominal surgery in adults, ie, > 18 years, were considered.

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BJA
British Journal of Anaesthesia

Systemic lidocaine fails to improve postoperative morphine consumption, postoperative recovery and quality of life in patients undergoing posterior spinal arthrodesis. A double-blind, randomized, placebo-controlled trial

G. Dewinter[1,*], P. Moens[2], S. Fieuws[3], B. Vanaudenaerde[4], M. Van de Velde[1,5], S. Rex[1,5]

Handling editor: Lesley Colvin

Open Archive PlumX Metrics

DOI: https://doi.org/10.1093/bja/aex038

Br J Anaesth. 2013 Feb;110(2):191-200. doi: 10.1093/bja/aes431. Epub 2012 Dec 5.

Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis.

Waldron NH[1], Jones CA, Gan TJ, Allen TK, Habib AS.

Author information

1 Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA.

Abstract

BACKGROUND: The analgesic efficacy and adverse effects of a single perioperative dose of dexamethasone are unclear. We performed a systematic review to evaluate the impact of a single i.v. dose of dexamethasone on postoperative pain and explore adverse events associated with this treatment.

METHODS: MEDLINE, EMBASE, CINAHL, and the Cochrane Register were searched for randomized, controlled studies that compared dexamethasone vs placebo or an antiemetic in adult patients undergoing general anaesthesia and reported pain outcomes.

RESULTS: Forty-five studies involving 5796 patients receiving dexamethasone 1.25-20 mg were included. Patients receiving dexamethasone had lower pain scores at 2 h {mean difference (MD) -0.49 [95% confidence interval (CI): -0.83, -0.15]} and 24 h [MD -0.48 (95% CI: -0.62, -0.35)] after surgery. Dexamethasone-treated patients used less opioids at 2 h [MD -0.87 mg morphine equivalents (95% CI: -1.40 to -0.33)] and 24 h [MD -2.33 mg morphine equivalents (95% CI: -4.39, -0.26)], required less rescue analgesia for intolerable pain [relative risk 0.80 (95% CI: 0.69, 0.93)], had longer time to first dose of analgesic [MD 12.06 min (95% CI: 0.80, 23.32)], and shorter stays in the post-anaesthesia care unit [MD -5.32 min (95% CI: -10.49 to -0.15)]. There was no dose-response with regard to the opioid-sparing effect. There was no increase in infection or delayed wound healing with dexamethasone, but blood glucose levels were higher at 24 h [MD 0.39 mmol litre(-1) (95% CI: 0.04, 0.74)].

CONCLUSIONS: A single i.v. perioperative dose of dexamethasone had small but statistically significant analgesic benefits.

PMID: 23220857 PMCID: PMC3544008 DOI: 10.1093/bja/aes431

[Indexed for MEDLINE] Free PMC Article

Systematic Reviews

BMC

Syst Rev. 2017; 6: 92.

Published online 2017 Apr 27. doi: 10.1186/s13643-017-0485-8

PMCID: PMC5406982

PMID: 28449696

Perioperative adjuvant corticosteroids for post-operative analgesia in elective knee surgery – A systematic review

Hasan Raza Mohammad,[1] Marialena Trivella,[2] Thomas W. Hamilton,[1] Louise Strickland,[1] David Murray,[1] and Hemant Pandit[1,3]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Practical Conclusions: Multimodal Analgesia

EFIC, 2019

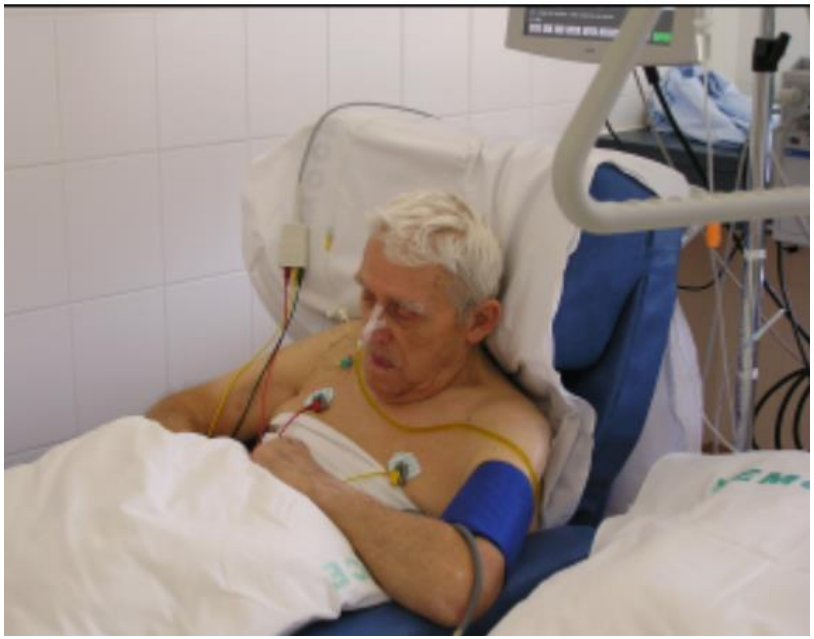
- It remains unclear, which combinations of how many compounds should be used?
- In practical terms current routine use for systemic analgesia should include:
  - Paracetamol
  - Parecoxib/Celecoxib (if no renal contraindications)
  - Pregabalin (one single preoperative dose)
- In selected patients
  - Low-dose ketamine (opioid-tolerant, neuropathic pain, prevention)
  - Systemic local anaesthetics (major surgery, in particular abdominal surgery without epidural analgesia)
  - Alpha-2 agonists (agitation?, withdrawal?)

Schug et al. Acute Pain Management. Scientific Evidence 4th edition ANZCA&FPMANZCA

Cieľ liečby POB

„ Importantly, the goal of any pain therapy should be it´s ability to improve perioperative outcome and ambulation rather than achieve a specific pain score.“

JP Joshi, H Kehlet 2013



Perioperačná analgézia a imunitný systém pacienta

Jana Šimonová
I.KAIM UN LP a UPJŠ-LF Košice

CEEA
30. november 2019, Košice

Úvod

- Chirurgická liečba + Adjuvantná onkologická liečba
  Neoadjuvantná onkologická liečba

- Perioperačné obdobie – stresová reakcia organizmu na chirurgický výkon – významne ovplyvňuje funkciu imunitného systému

Nádorová disseminácia

- - schopnosť NB migrovať, uhniezdiť sa a proliferovať
  - schopnosť IS tieto NB rozpoznať a eliminovať

... faktory, ktoré negatívne ovplyvnia funkciu IS, môžu mať zásadný vplyv na priebeh ochorenia.

(Neeman, Ben-Eliyahu, 2013)

1. Stresová reakcia na operačný výkon, bolesť
2. Perioperačné poškodenie tkanív
   (DAMPs → cytokíny...)
3. Podchladenie
4. Liečebné postupy - transfúzna liečba
   - anestetiká/**analgetiká**

(Levins, Buggy, 2015)

- Literárne údaje + výsledky výskumov + panelové diskusie expertov roky 2016 a 2017

Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article 01/2019 RAPM

- Retrospektívne epidemiologické štúdie naznačujú ....

...rôzne spôsoby vedenia anestézie a pooperačnej analgézie rôznou mierou ovplyvňujú riziko recidívy nádorového ochorenia

(Chen a Miao, 2013)

- Prospektívne štúdie (zamerané na dlhodobé prežívanie)

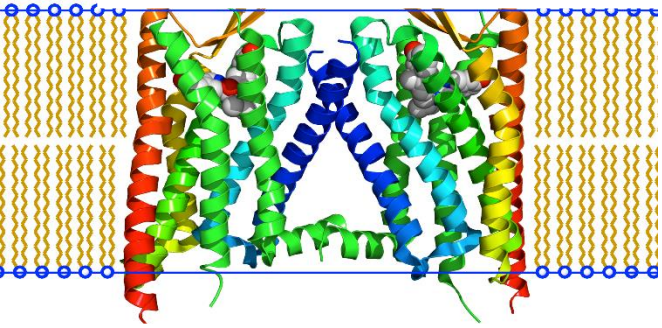
prinesú podklady pre zmenu liečebnej stratégie (Byrne et al., 2016)

- In vitro, in vivo a klinické štúdie ... OPIOIDY – zásadný faktor, ktorý negatívne ovplyvňuje diseminácii u nádorového ochorenia – ich mnohoúrovňovým vplyvom na metastatickú kaskádu

Opioidné receptory

OP

EC – N terminálny koniec



IC – C terminálny koniec

G proteín

↓ cAMP, K^+kanál, Ca^+kanál
signálne dráhy – progresia

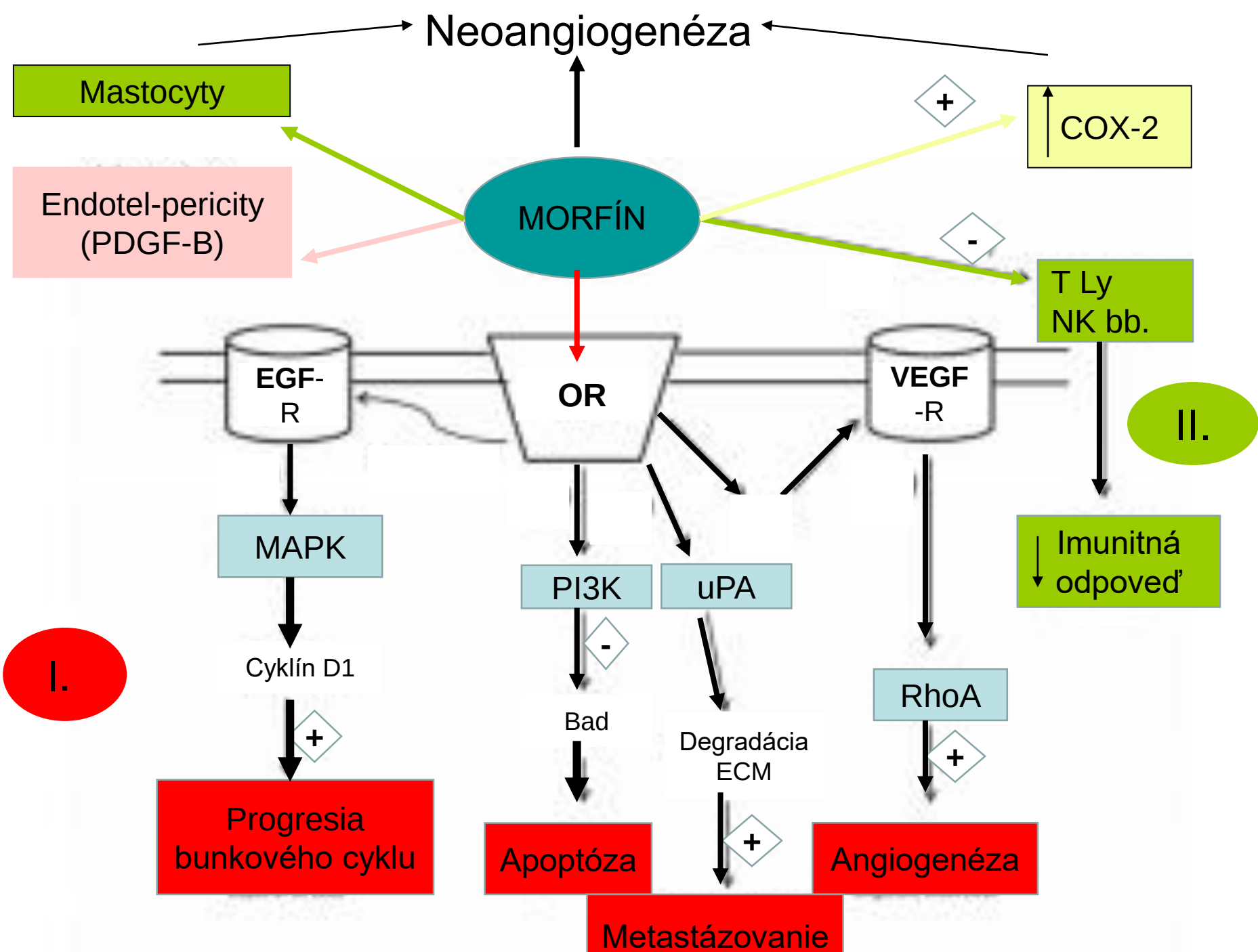
mí, kappa, delta, ORL-1

Lokalizácia:

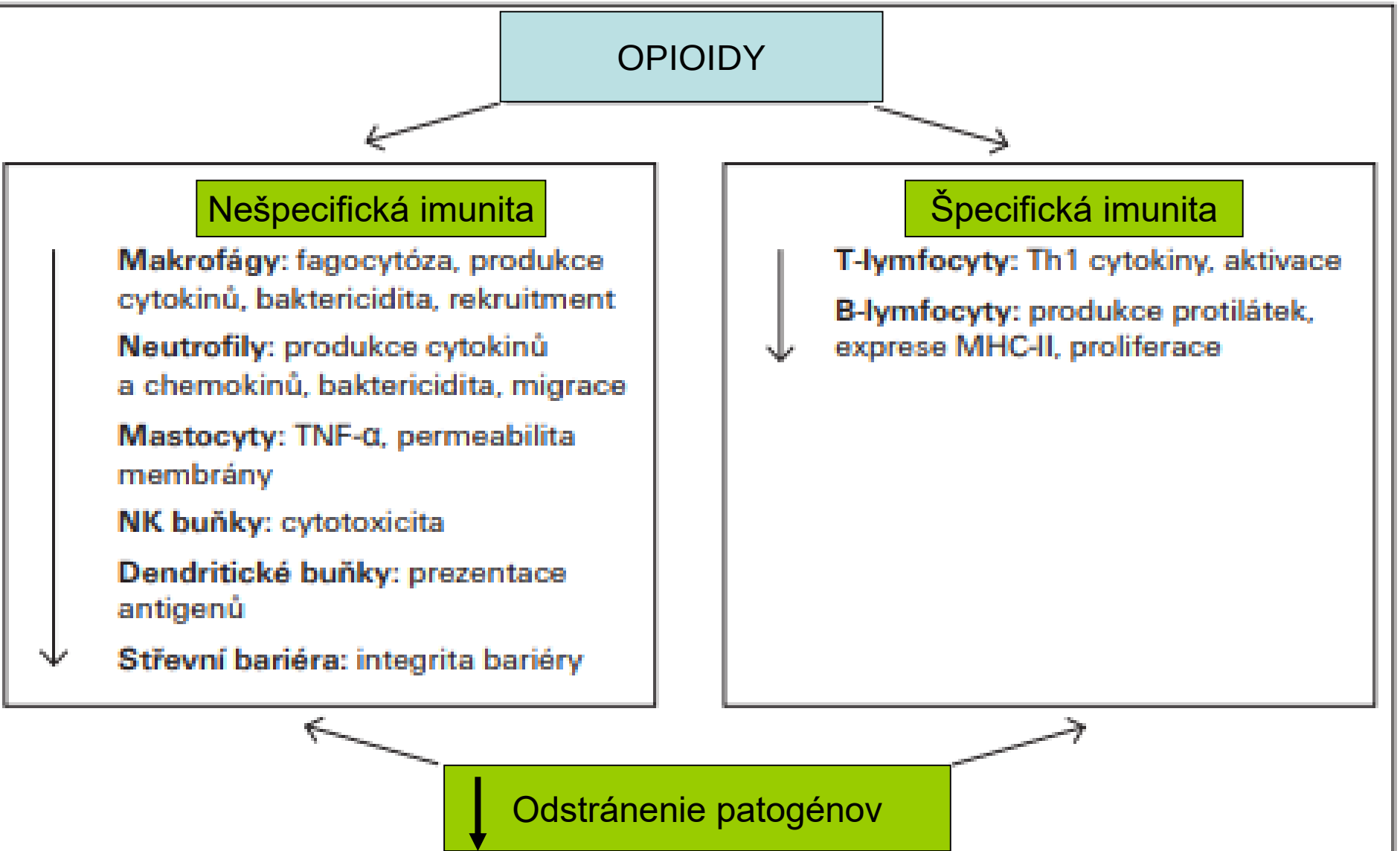
- **CNS**, PNS, GIT, KVS, UGS
- na bunkách IS (imunomodulačný efekt)
- na nádorových bb.:

  Ca pľúc (Singleton et al., 2014)
  Kolorektálny Ca (Nylund et al., 2008)

Nadmerná expresia OR nádorovými bb. –
negatívny vplyv
na progresiu primárneho TU a MTS
(Zhang et al., 2015)


Neoangiogenéza
Mastocyty
Endotel-pericity
(PDGF-B)
MORFÍN
+
COX-2
-
T Ly
NK bb.
EGF-
R
OR
VEGF
-R
II.
MAPK
PI3K
uPA
Imunitná
odpoveď
I.
Cyklín D1
-
RhoA
+
Bad
Degradácia
ECM
+
Progresia
bunkového cyklu
Apoptóza
Angiogenéza
Metastázovanie

Periférny mechanizmus – OR na bunkách IS



Imunomodulačné pôsobenie OP

- efekt na IS – komplexný – ovplyvní ho:

  1. druh opioidu – molekulárna štruktúra

MO, FNL, kodein, metadon – najviac imunosupresívne

tramadol, hydromorfon, oxykodon, hydro-)

buprenorfín – aj imunostimulačne (Martucci, 2004)

  2. dávka

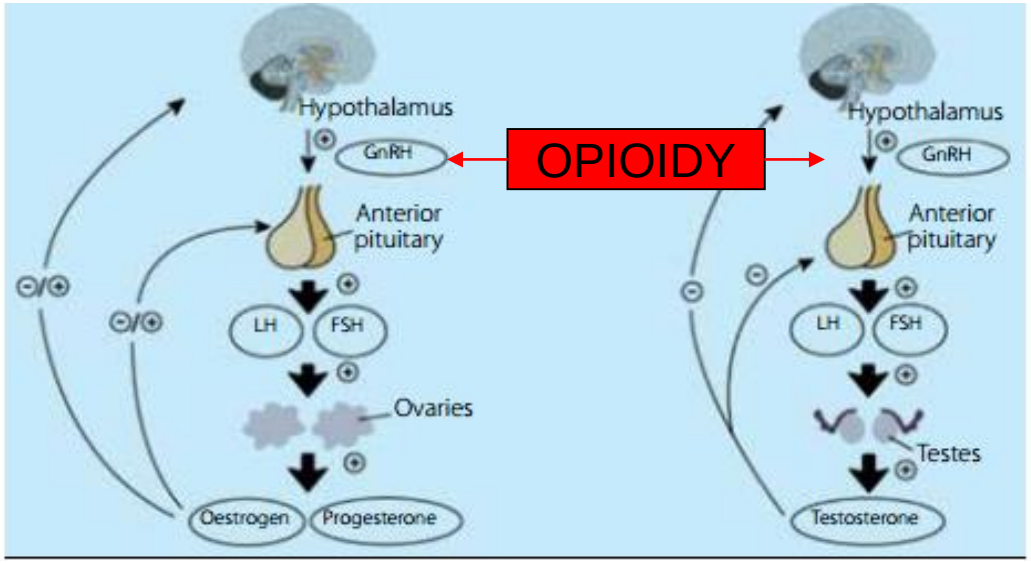
  3. dĺžka podávania a spôsob podávania (Yokota, 2000)

- **Výsledok – negatívne ale i pozitívne ovplyvnenie IS**

(Liang, 2016)

III. Pôsobenie opioidov v CNS

1. Interakcie neuroendokrinné (H-H-NO)- skôr dlhodobé užívanie



2. VNS – tonus sympatika

   - akútne podanie

1. Ovplyvnenie osi H-H-NO

- ACTH – kortikoidy - ↓ cytotoxicity NK bb (Vuong, 2010)

jeden z hlavných pilierov protinádorovej imunity

(YangQ, 2006)

1. rozlíšia bunky cudzie
2. odstraňujú ich bez potreby predchádzajúcej senzitizácie

NK bb.:

významná úloha v inhibícii rastu primárneho TU aj MTS

2. Ovplyvnenie VNS

- VNS inervuje - primárne (slezina, tymus)
  - sekundárne (LU, payerove plaky) LO

- Aktivácia SYMP → KA - ↓ proliferáciu Ly, proliferáciu NK bb. aktivitu Mak ↑ VEGF IL_6

- Aktivácia α-adren rec. - supresia NK bb.
- Aktivácia ß-adren.rec. - supresia Ly (Neeman, 2012)

NSA – blokátory COX-2

- ASP - ↓riziko kolorektálneho Ca
- Kolorektálny Ca - ↑expresia COX-2 (epitelové/endotelové bb)
  (staging – frekventné MTS,↓ prežívanie)
- Ca prsníka
- Ca pľúc (70-90%)

Summary: strong recommendation for use
weak to average evidence

Kortikoidy

- supresia NK buniek
- ↑ odolnosť nádorových bb. voči apoptóze

- 5 ročné sledovanie pacientov (Singh et al., 2014)

dexametazón (4-10 mg) vs. placebo

pred kolektómiou

pred nemalobunkovým Ca pľúc

= „disease-free survival“

↑ frekvencia vzdialených MTS

nesignifikantne ↑ „cancer-specific“ mortalitu

Summary: conflicting weak recommedations for and aginst use

Ketamín – antagonista NMDA

- interakcie s OR, muskarínovými receptormi, Ca kanály...
- protizápalové účinky – Neu, makrofágy
- sedatívne účinky
- Forget et al.: ketamín a klonidín podaný pred OP – signifikantne ↓ výskyt pľúcnych MTS
- Beilin et al.: 0,15 mg/kg i.v. : ↓ IL-6 a TNFα

Summary: weak evidence ketamín vs FNL - ↓ pľúcne MTS

0,05-0,1mg/kg i.v., kont. 0,25mg/kg/hod

LA - i.v. lidokain

- **Analgetické** + antihyperalgické účinky

(inhibuje: VGSC, K^+, Ca^{2+} , glycínergný systém, NMDA)

- **Protizápalové** účinky

adhezivitu a migráciu Leu ↓„priming“ T a B Ly

IL-1ß, IL-6, IL-8

Pg, TX, LT, histamínu z mastocytov

- **AntiMTS** účinky?

- bb. so silným MTS potenciálom – hyperexcitované BM

expresia VGSC (Nav 1,5) + down reg. VGKC,

TRPV6 Ca^{2+} (migrácia) - prsník, prostata, ovárium, HČ

- apoptotický efekt amid LA – NSCLC, karcinóm ŠŽ

LA - i.v. lidokain

- Summary: in vitro štúdie - strong evidence

  protektívny efekt LA

  málo predklinických a klinických štúdií

- Sľubné dáta zo štúdií na zvieratách + ↓riziko

  weak recommendation

- 1-3mg/kg tečie 20-30 minút
- 0,5-2mg/kg/hod kontinuálne

Alfa-2 agonisti - dexmedetomidín

- Protizápalové účinky ↓ cytokínov ← LPS
- Pronádorové účinky?

- nádorové bb. pankreasu a prsníka - ↑ expresia α_2 rec.
- in vitro/in vivo štúdie - proliferácia, migrácia a invázia bb. Ca prsníka po expozícii DEX

- Summary: in vitro štúdie – bunkové štúdie

Nervové bloky

- Retrospektívne štúdie – rôzne závery
- Štúdie: priamy efekt RA – angiogenézu (hladiny VEGF)

  GA/opioidy vs TIVA/PVB

- Summary: weak evidence (z retrospekt. analýz)

  RA môže ↓ riziko MTS

  Conflicting weak recommendation for and against use, weak evidence

Neuraxiálne blokády (humánne štúdie)

- RCTs - Ca ovária, Ca cervicis uteri - ak EA:
  - Ca pažeráka, Ca žalúdka - ak hrudná EA:
  1. signifikantne lepšia funkcia NK bb.
  2. ↓ hladiny proinflamatórnych cytokínov
- Ale nie u pacientov s Ca prostaty, hoci:
  - ak EA: ↓ hladiny IL-17 (angiogenéza)

Summary: 5 RCTs – small-to-moderate protective role
EA na funkciu IS a zápalovú odpoveď
strong evidence, weak for using

Ďalšie štúdie: ...ako sa toto jasne pozitívne ovplyvnenie IS premietne do lepšieho prežívania pacientov.....

Záver

- Incidencia MTS a recidívy TU po kuratívnej OP –
  multifaktoriálna etiológia, ale
  perioperačné obdobie toto môže signifikantne ovplyvniť

- Onkologickí pacienti podstupujú aj neonkochirurgické op., ...

- Nie je možné na základe dostupných výsledkov vydať jasné odporúčania pre zmenu klinickej praxe ....

  ... ale isté smery výskumu sú vytýčené!

Ďakujem za pozornosť