Opioidni analgetici u terapiji bola

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Terminologija

- Opioid je termin koji opisuje sve lekove (prirodne ili sintetske), koji se vezuju za opioidne receptore.
- *Opioidi* uključuju lekove koji su agonisti (morfin, fentanil), agonisti-antagonisti (buprenorfin, nalorfin) i antagoniste (nalokson)
- Termin *opijati* označava derivate opijuma (morfin, kodein)
- *Narkotici*, nespecifičan naziv, koji može da se primeni na svaki lek koji uzrokuje san

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OPIOIDI

Morfin

- Morfin je najznačajniji alkaloid dobijen iz opijuma, sasušenog soka koji nastaje zasecanjem čaura tzv. opijumskog maka (*Papaver somniferum var.album)*

- Morfin je tipičan opioidni analgetik i predstavlja referentnu supstancu za čitavu grupu opioida

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Mehanizam dejstva opioida

- Deluju kao agonisti specifičnih G -kuplovanih opioidnih receptora koji se nalaze u delovima CNS-a i kičmene moždine i učestvuju u procesu prenosa i modulacije bola
- Stimulacija opioidnih receptora izazivaju inhibiciju adenil ciklaze i smanjenje sadržaja cAMP-a u ćeliji. Direktnim spajanjem G- proteina sa jonskim kanalom, opioidi pospešuju otvaranje kalijumovih kanala a inhibiraju otvaranje voltažnih kalcijumskih kanala. Ovi membranski efekti smanjuju i ekscitaciju neurona (zbog ulaska kalijuma i hiperpolarizacije) i oslobađanje neurotransmitera

- Ukupan efekat opioida na ćelijskom nivou je inhibitoran

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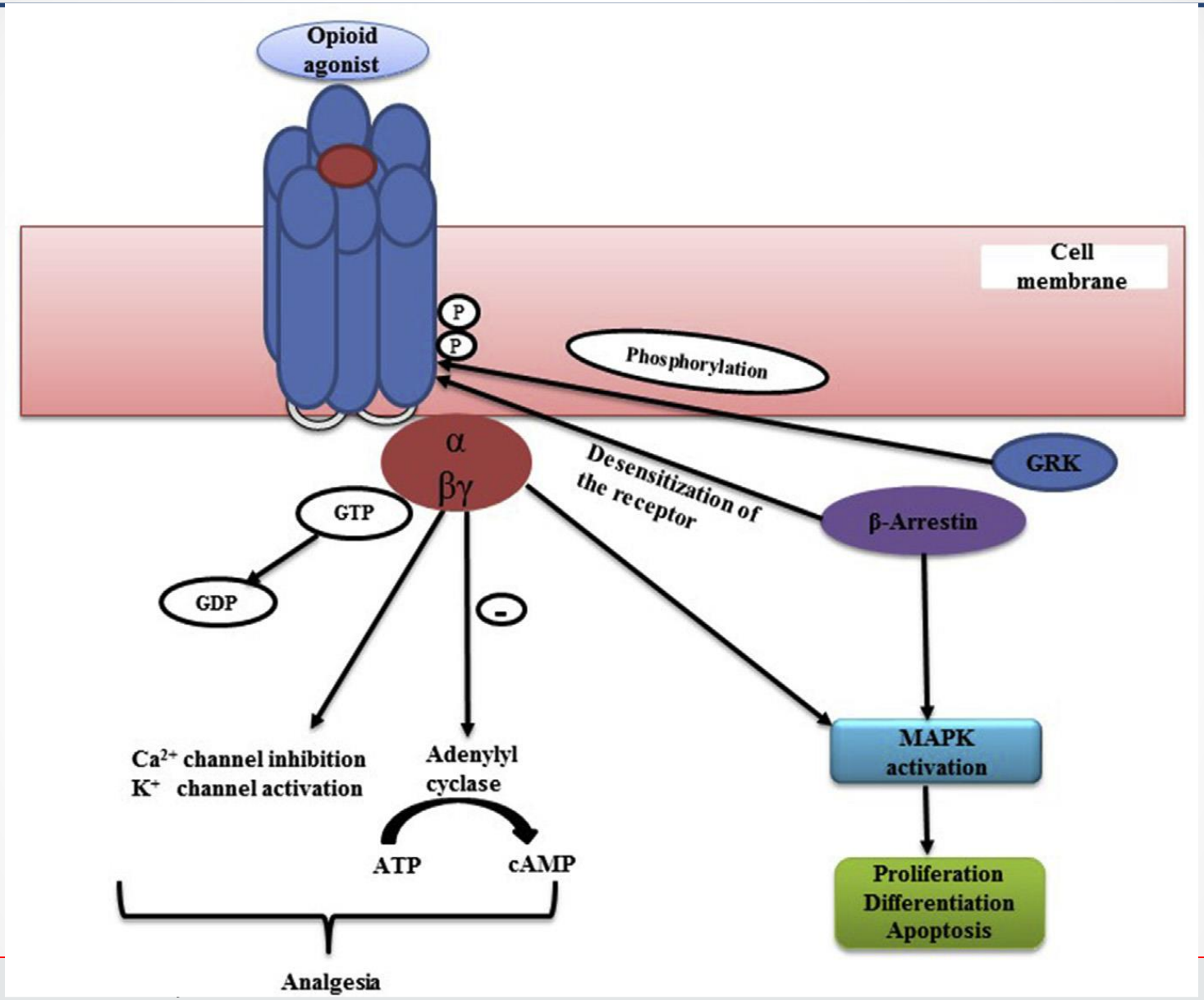

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Opioidni receptori

- Tri tipa opioidnih receptora koji se, na osnovu stare klasifikacije, nazivaju mi(**μ**), kapa(**κ**) i delta (**δ**) receptori, odnosno prema novijoj IUPHAR nomenklaturi iz 2000.godine na **MOP (μ)**, **KOP (κ)** i **DOP (δ)** receptore
- Nociceptin receptor (NOP) - sličan opioidnim, za njega se vezuje endogeni ligand nociceptin, ali nalokson ne može antagonizovati njegova dejstva, pa kao takav nije klasičan opiodni receptor

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Opioidni receptori i farmakološka dejstva

Рецепотор	Ефекти стимулисаног рецептора	
MOP (μ)- ми	супраспинална и спинална аналгезија, седација, зависност, еуфорија, депресија дисања, модулација ослобађања хормона и појединих неуротрансмитера	
KOP (κ)- капа	миоза, спинална аналгезија, седација, дисфорија, повећање ослобађања антидиуретског хормона	
DOP (δ)- делта	спинална аналгезија, модулација ослобађања хормона и појединих неуротрансмитера, смањен мотилитет ГИТ-а	

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Endogeni opioidi ("opiopeptini")

- Biološki aktivni peptidi koji se nalaze u CNS-u i koji ispoljavaju slično dejstvo kao morfin.
- Tri porodice ovih peptida:

✓ ENKEFALINI : met-enkefalin; leu-enkefalin- **delta** rec
✓ DINORFINI: dinorfin A, dinorfin B –**kapa** rec
✓ ENDORFINI: beta-endorfin,endomorfin-1, endomorfin-2 – **mi** rec

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Farmakokinetika opioida

- Dobro se apsorbuju nakon oralne, supkutane i intramuskularne primene
- Kod morfina je oralna doza znatno veća od parenteralne (zbog presistemske eliminacija)
- BI morfina je oko 25% (interindividualne varijacije)
- Bioraspoloživost kodeina i oksikodona je 80-90%
- ravnomerno se raspodeljuju po tkivima i to uglavnom u plućima, jetri, bubrezima i mozgu (dobro prokrvljena tkiva)
- Neki opioidi bolje prolaze kroz HEB (heroin, kodein) dok drugi prolaze slabije
- Lipofilan opioid-fentanil (transdermalni flasteri)
- Deca su posebno osetljiva na morfin
- Svi opijati lako prolaze kroz placentu

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Farmakološka dejstva opioida

- **Analgezija**
- Promena ponašanja (euforija, disforija)
- Depresija disanja
- Nauzeja
- Mioza
- Supresija refleksa kašlja
- Smanjenje motiliteta u GIT-u

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Indikacije za primenu opioida

- Intraoperativna i postoperativna analgezija
- Opšta i regionalna anestezija (fentanil i derivati)
- Suzbijanja bolova različite etiologije (kod opekotina, teških fraktura, infarkta miokarda, šoka, maligniteta)
- Akutni edem pluća (popravlja dispneju i insuficiijenciju leve komore, smanjuje anksioznost)
- Uporni kašalj (kodein, dekstromorfin)
- Dijareja (loperamid, periferni opioid)
- Terapija opoidne zavisnosti (buprenorfin i metadon)

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Kontraindikacije

- Povišen intrakranijalni pritisak (kod povrede glave ili kraniotomije)
- Bronhijalna astma
- Akutno trovanje etanolom (zbog adicije depresornih efekata)
- Emfizem pluća i hronično plućno srce
- Hipotireoidizam i adisonizam
- Konvulzivna stanja
- Kombinacija čistih agonista (morfin) i agonista-antagonista, npr. pentazocina

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Neželjena dejstva

- nauzeja i povraćanje
- depresija disanja
- uporna opstipacija
- retencija urina
- svrab i urtikarija
- Svi opioidi koji deluju preko mi receptora prouzrukuju toleranciju, fizičku i psihičku zavisnost, koji su naročito izraženi kod hronične primene morfina (heroina), tj.postojanja zavisnosti od opijata.

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Tolerancija

- Kod duže primene razvija se tolerancija (sporo) i na željene i neželjene efekte opioida
- Potreba za povećanjem doze kako bi se postigao analgetski efekat kao na početku primene
- Postoji ukrštena tolerancija, ali nije potpuna, što daje mogućnost rotacije opioide i postizanje boljeg odgovora

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Fizička zavisnost

- Posledica neuroadaptivnih mehanizama koji su u vezi sa intracelularnim glasnicima u centralnom i perifernom NS
- 2-3 dana nakon obustave – apstinencijalni sindrom: lakrimacija, midrijaza, rinoreja, bolovi, zevanje, tremor, znojenje, piloerekcija, mučnina, dijareja, anksioznost, nesanica, ubrzanje srčanog rada i disanja

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Adikcija (psihička zavisnost)

- Neodoljiva želja za lekom /drogom i gubitak kontrole nad upotrebom leka
- Poremećaj funkcionisanja u smislu zanemarivanja drugih interesovanja
- Izuzetno retko se razvija kod bolesnika u terminalnoj fazi maligniteta
- Pseudozavisnost (ako bol nije dobro kupirana)

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Analgezija

- **OPIOIDI - Najpotentniji analgetici**
- Mehanizam analgezije obuhvata bar tri faktora:

✓ Povišenje praga za percepciju bola

✓ Promena emocionalne reakcije na bol (morfin deprimira psihičko doživljavanje bola)

✓ Izazivanje sedacije

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Opioidni analgetici

Generic Name	Receptor Effects[1] μ	δ	κ	Approximately Equivalent Dose (mg)	Oral:Parenteral Potency Ratio	Duration of Analgesia (hours)	Maximum Efficacy
Morphine[2]	+++		+	10	Low	4–5	High
Hydromorphone	+++			1.5	Low	4–5	High
Oxymorphone	+++			1.5	Low	3–4	High
Methadone	+++			10	High	4–6	High
Meperidine	+++			60–100	Medium	2–4	High
Fentanyl	+++			0.1	Low	1–1.5	High
Sufentanil	+++	+	+	0.02	Parenteral only	1–1.5	High
Alfentanil	+++			Titrated	Parenteral only	0.25–0.75	High
Remifentanil	+++			Titrated[3]	Parenteral only	0.05[4]	High
Levorphanol	+++			2–3	High	4–5	High
Codeine	±			30–60	High	3–4	Low
Hydrocodone[5]	±			5–10	Medium	4–6	Moderate
Oxycodone[2,6]	++			4.5	Medium	3–4	Mod-High
Pentazocine	±		+	30–50	Medium	3–4	Moderate
Nalbuphine	−−		++	10	Parenteral only	3–6	High
Buprenorphine	±	−−	−−	0.3	Low	4–8	High
Butorphanol	±		+++	2	Parenteral only	3–4	High

Katzung BG. Basic and Clinical Pharmacology. 12th ed., McGrawHill Lange, Boston, 2012

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Opioidi sa jakim analgetskim dejstvom

- Agonisti opioidnih receptora: morfin, metadon, meperidin, oksikodon, levorfanol, fentanil, sufentanil, alfentanil, remifentanil
- Mešoviti- agonisti-antagonisti: pentazocin, nalbufin (slabiji analgetici od punih agonista)
- Parcijalni agonisti (buprenorfin)
- **Morfin je zlatni standard** za jake akutne i hronične bolove

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Opioidi sa blagim do umerenim analgetskim dejstvom

- Kodein
- Dihidrokodein
- Hidrokodon
- Propoksifen
- Tramadol
- Primenjuju se uglavnom za kupiranje slabih bolova (često u kombinaciji sa paracetamolom ili ASA)

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Opioidni antagonisti

- Najvažniji su N-supstituisani derivati morfina: nalokson i naltrekson
- Kod predoziranja opioidima
- Vezuju se za OP receptore mi tipa i kompetitivnim mehanizmom antagonizuju depresivne efekte opioida na mi receptorima.
- Nalokson i naltrekson kompletno i skoro dramatično otklanjaju sve efekte opioida u toku 1-2 minuta (normalizovanje disanja, dolazak svesti, normalizovanje širine zenica, normalizovanje crevne peristaltike)

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Način primene opioida

- Put primene: per os, i.m, i.v. (u bolusu ili u kontinuiranoj infuziji), transdermalno, sublingvalno (sufentanil), subarahnoidalno, periduralno, intratekalno

- Način davanja: intermitantno, promptno, u bolus dozama, kontinuirane infuzije.- značajno za brzinu apsorpcije, dužinu dejstva i pojavu neželjenih efekata

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Terapija akutnog bola

- Počinje se sa minimalnim dozama slabijih analgetika, a zatim se prelazi na potentnije, kratkodelujuće opioide, ili se kombinuju
- Analgetike primenjivati u tačno određenim doznim intervalima, jer se bol lakše kupira u inicijalnoj fazi, nego kada dostigne visok intezitet

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Postoperativni bol

- Akutan bol koji treba kupirati
- Bolesnik koji ima bolove, zauzima „antalgični“ položaj, uz smanjenje pokreta, smanjenje ekskurzije disanja i refleksa kašlja
- Posledice su venska staza, uz povećan rizik od tromboze, zaostajanje sekreta u traheobronhijalnom stablu, uz rizik od hipostatske pneumonije
- U „nultom“ danu efekat intraoperativno primenjenih opioida traje još 6-8 časova nakon operacije
- Nakon tog vremena davati analgetike na svakih 6 časova, i narednog (prvog postoperativnog) dana, a zatim ih davati po potrebi

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Preventivna analgezija („preemptive“ analgesia)

- Noviji pristup kontroli bola
- Prevencija bola primenom analgetika kada se očekuje bolno stanje
- U premedikaciji, čime se redukuje potreba za intraoparativnom i postoperativnom analgezijom

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Analgezija koju kontroliše pacijent (PCA- patient controled analgesia)

- Samo za svesne bolesnike koji su spremni da saradjuju
- Prema intezitetu bola, pacijenti sami podešavaju brzinu kontinuirane infuzije opioida

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Opioidi sa ultrakratkim dejstvom- Remifentanil

- Kratak poluživot
- U kontinuiranoj infuziji, preko infuzionih pumpi
- Dejstvo prestaje odmah nakon isključenja infuzije
- Bezbedan za primenu u JIL-u, jer nema neželjenih efekata

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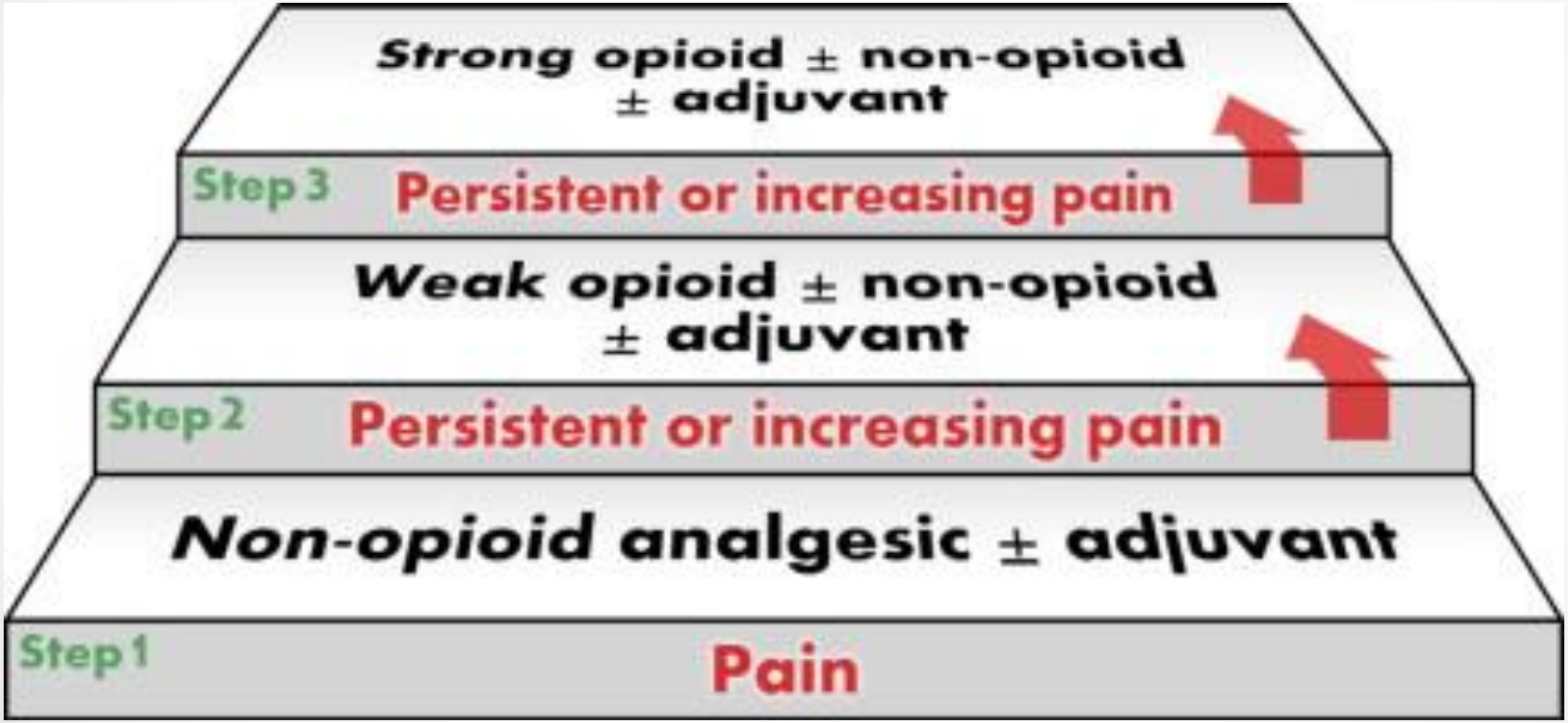
Terapija hroničnog bola

World Health Organization analgesic ladder



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Terapija hroničnog bola

- Ne-opoidni analgetici su lekovi izbora u lečenju hroničnog ne-kancerskog bola
- Proceniti odnos **korist/rizik** od uvodjenja opioida
- Individualni pristup i pažljiva titracija doze opioida
- Kod upotrebe opoida, treba koristiti najmanju moguću efektivnu dozu

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Ekvivalentne doze opioida

Analgetik	Per os doza	Parenteralna doza	Rektalna doza	Učestalost doziranja-svakih
Tramadol	150mg	100mg	150mg	4h
Kodein	200mg	120mg		4h
Oksikodon	10-15mg			4h
Levorfanol	4mg	2mg		6h
Metadon	20mg	10mg		6-8h
Hidromorfon	4mg	2mg	3mg	4h
Morfin sulfat rastvor	20-30mg			4h
Morfin sulfat SR caps	60-90mg			12h
Morfin hlorid		10mg		4h
Tapentadol SR	50-250mg			12h

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Problemi kod primene opioida tolerancija i hiperalgezija

CrossMark

Postoperative pain management and opioids 3

Perioperative opioid analgesia—when is enough too much? A review of opioid-induced tolerance and hyperalgesia

Lesley A Colvin, Fiona Bull, Tim G Hales

Lancet 2019; 393: 1558–68

See Editorial page 1478

See Comment page 1483

This is the third in a Series of three papers about postoperative pain management and opioids

Division of Population Health and Genomics, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK (Prof L A Colvin FRCA); and Institute for Academic Anaesthesia, Division of Systems Medicine, School of Medicine, Ninewells Hospital,

Opioids are a mainstay of acute pain management but can have many adverse effects, contributing to problematic long-term use. Opioid tolerance (increased dose needed for analgesia) and opioid-induced hyperalgesia (paradoxical increase in pain with opioid administration) can contribute to both poorly controlled pain and dose escalation. Hyperalgesia is particularly problematic as further opioid prescribing is largely futile. The mechanisms of opioid tolerance and hyperalgesia are complex, involving μ opioid receptor signalling pathways that offer opportunities for novel analgesic alternatives. The intracellular scaffold protein β-arrestin-2 is implicated in tolerance, hyperalgesia, and other opioid side-effects. Development of agonists biased against recruitment of β-arrestin-2 could provide analgesic efficacy with fewer side-effects. Alternative approaches include inhibition of peripheral μ opioid receptors and blockade of downstream signalling mechanisms, such as the non-receptor tyrosine kinase Src or N-methyl-D-aspartate receptors. Furthermore, it is prudent to use multimodal analgesic regimens to reduce reliance on opioids during the perioperative period. In the third paper in this Series we focus on clinical and mechanism-based understanding of tolerance and opioid-induced hyperalgesia, and discuss current and future strategies for pain management.

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Nove mogućnosti u primeni opioida

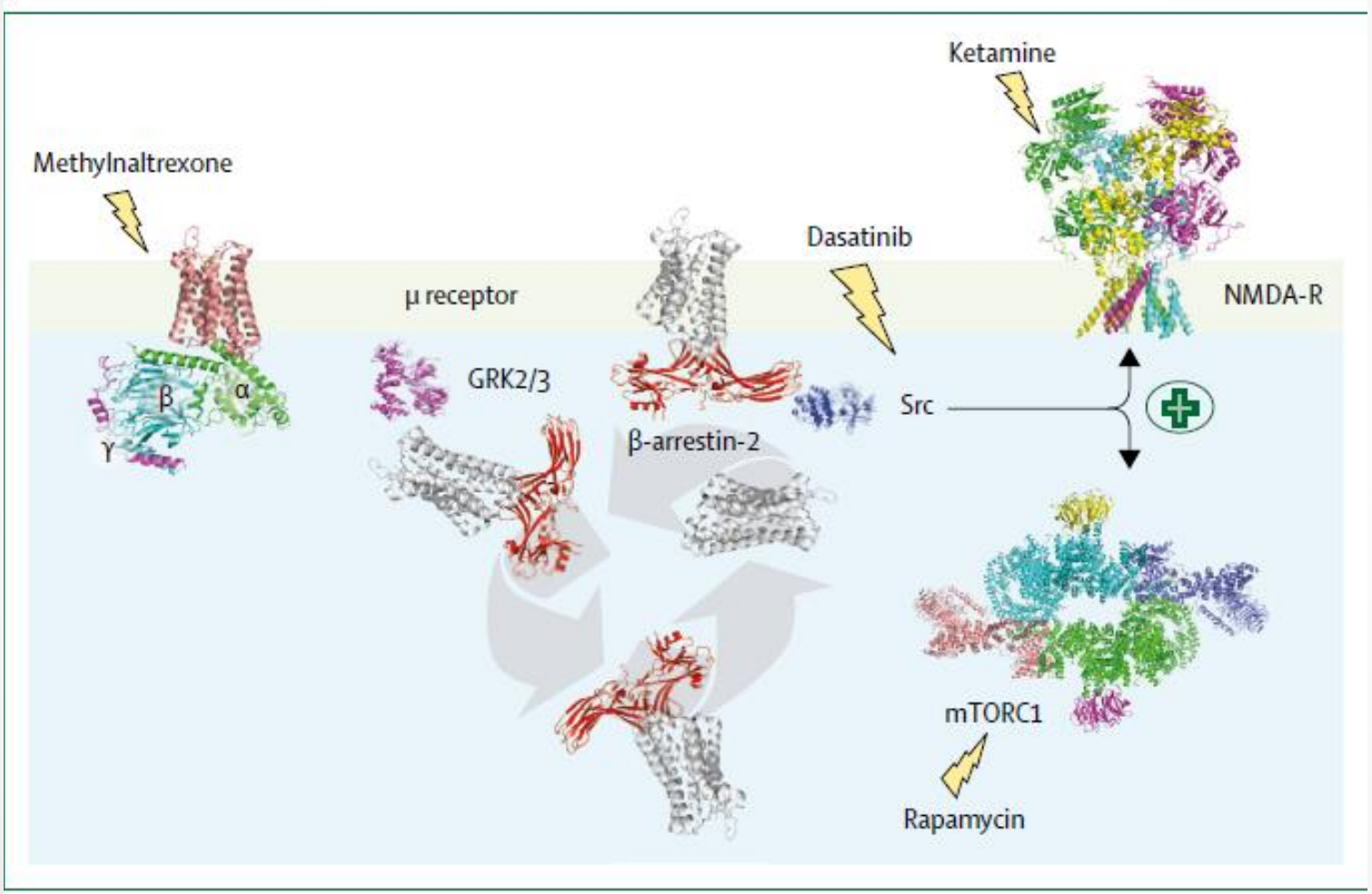

Figure 2: Available drugs that reduce opioid tolerance and/or hyperalgesia in preclinical studies through proteins in the μ receptor signalling pathway

"*This project has been funded with support from the European Commission. This publication reflects the views only of the author, and the Commission cannot be held responsible for any use which may be made of the information contained therein*"

Kontrola propisivanja opioida !!!

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