Smärtfysiologi och farmakologisk smärtlindring

Farmakologisk smärtlindring

Nervtråd

- Olika nervtrådar förmedlar information
  - Motoriska impulser –
    - tjocka myeliniserade – snabba nervfibrer
      - A-alfa-fibrer
  - Akut smärtimpulser –
    - myeliniserade – snabba nervfibrer
      - A-delta-fibrer
  - Molande dov smärta/obehag
    - Tunna icke myeliniserade nervfibrer
      - C-fibrer
        - » Autonoma funktioner förmedlas ofta av C-fibrer

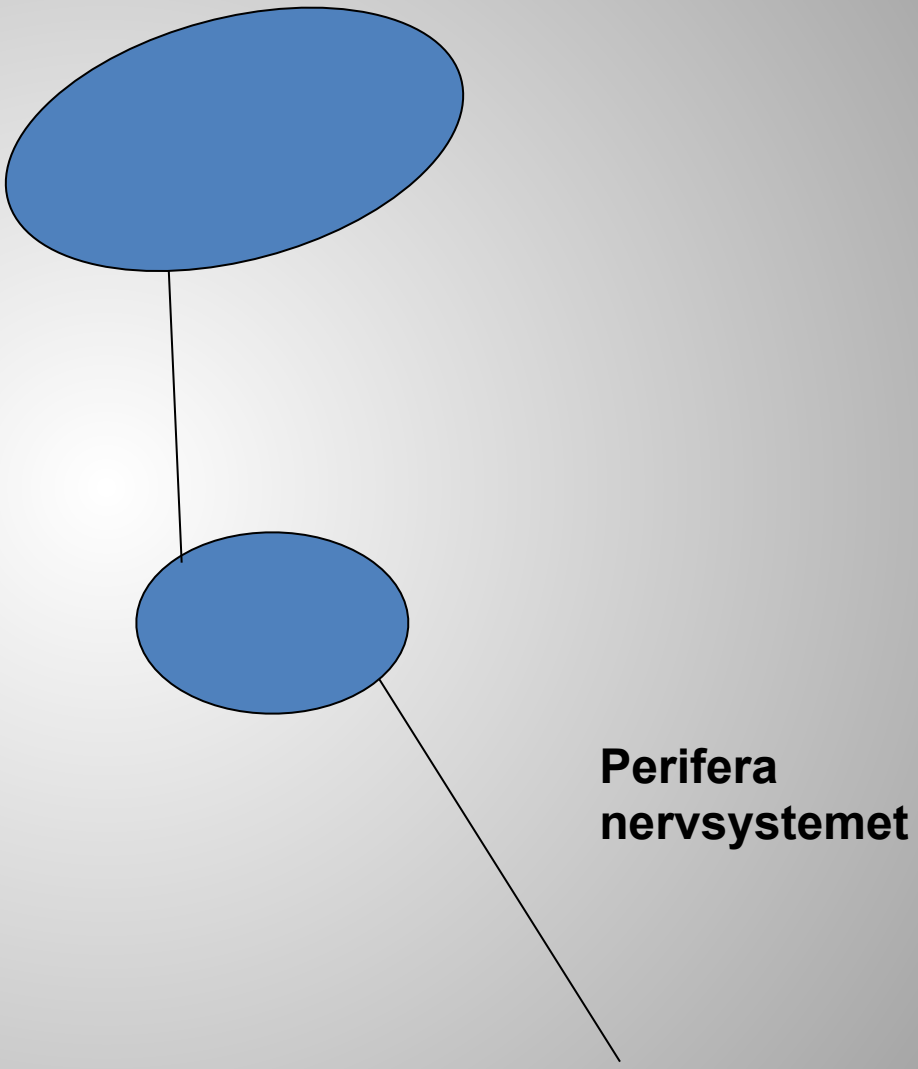
Centrala Nervsystemet

Hjärna

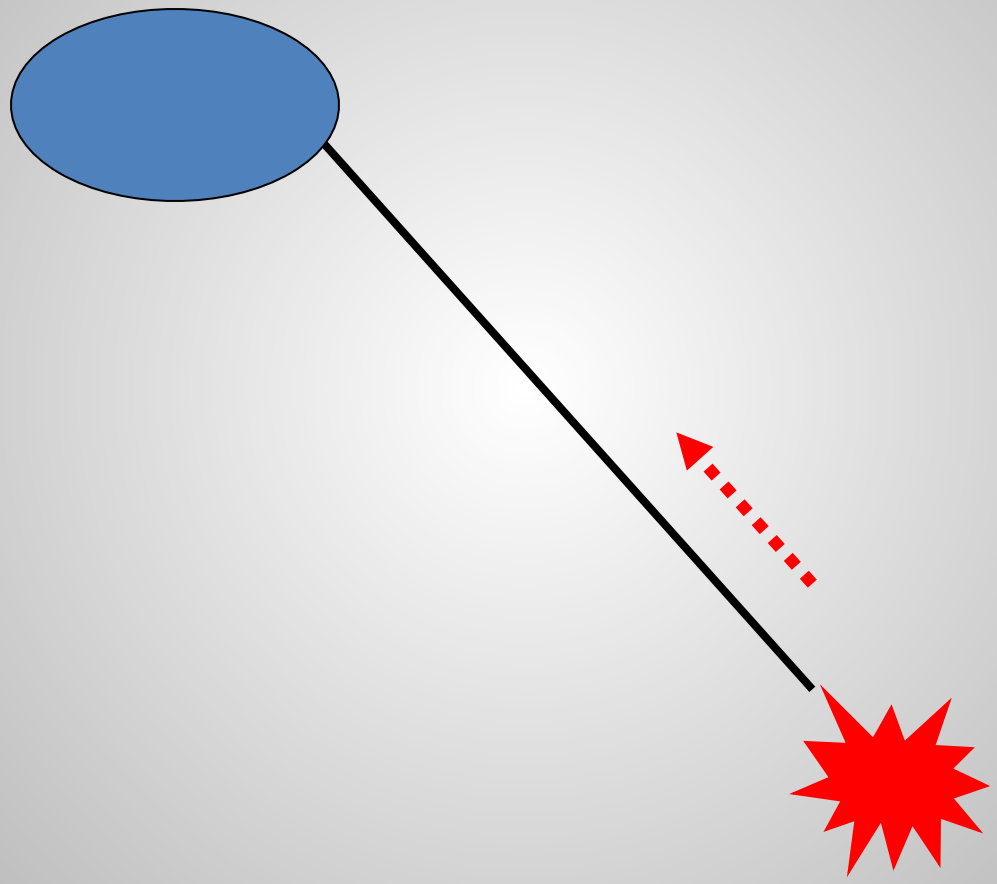
Centrala kärnor

Ryggmärg

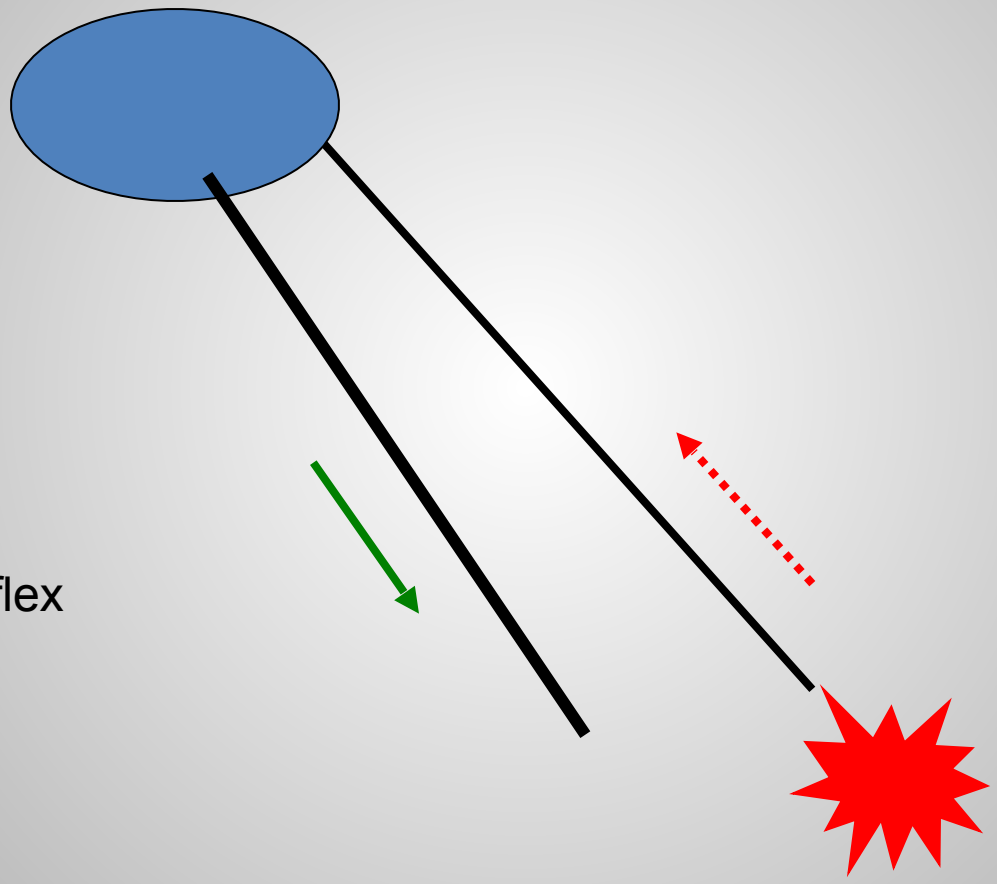
Bakhorn

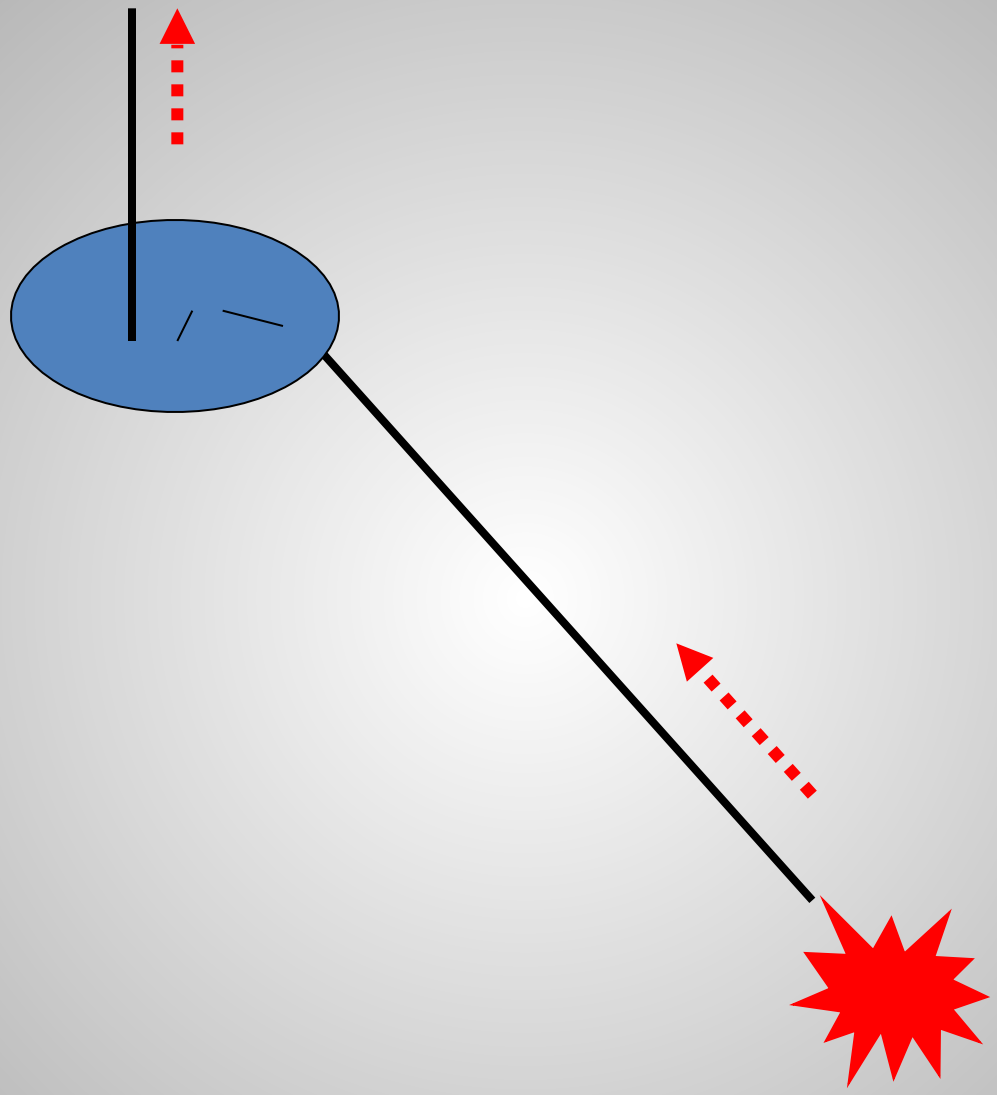


Perifera nervsystemet



Skyddsreflex





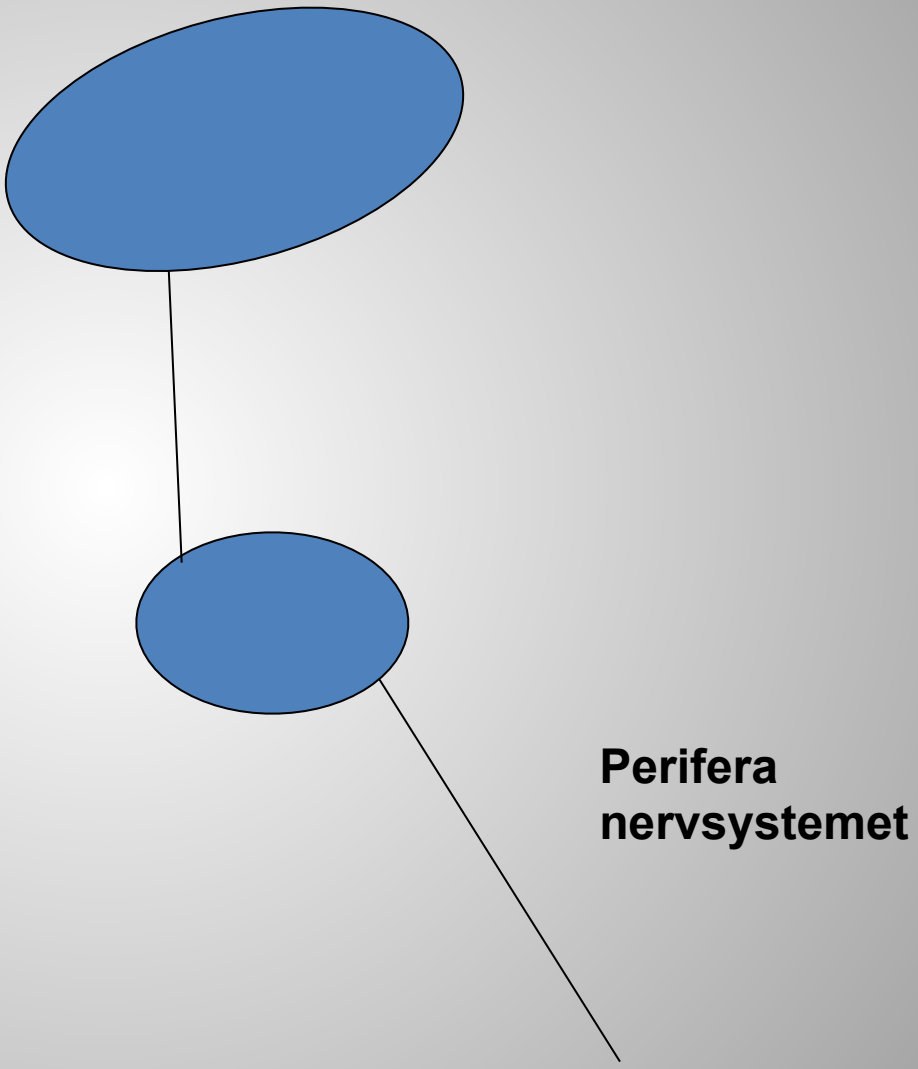
Centrala Nervsystemet

Hjärna

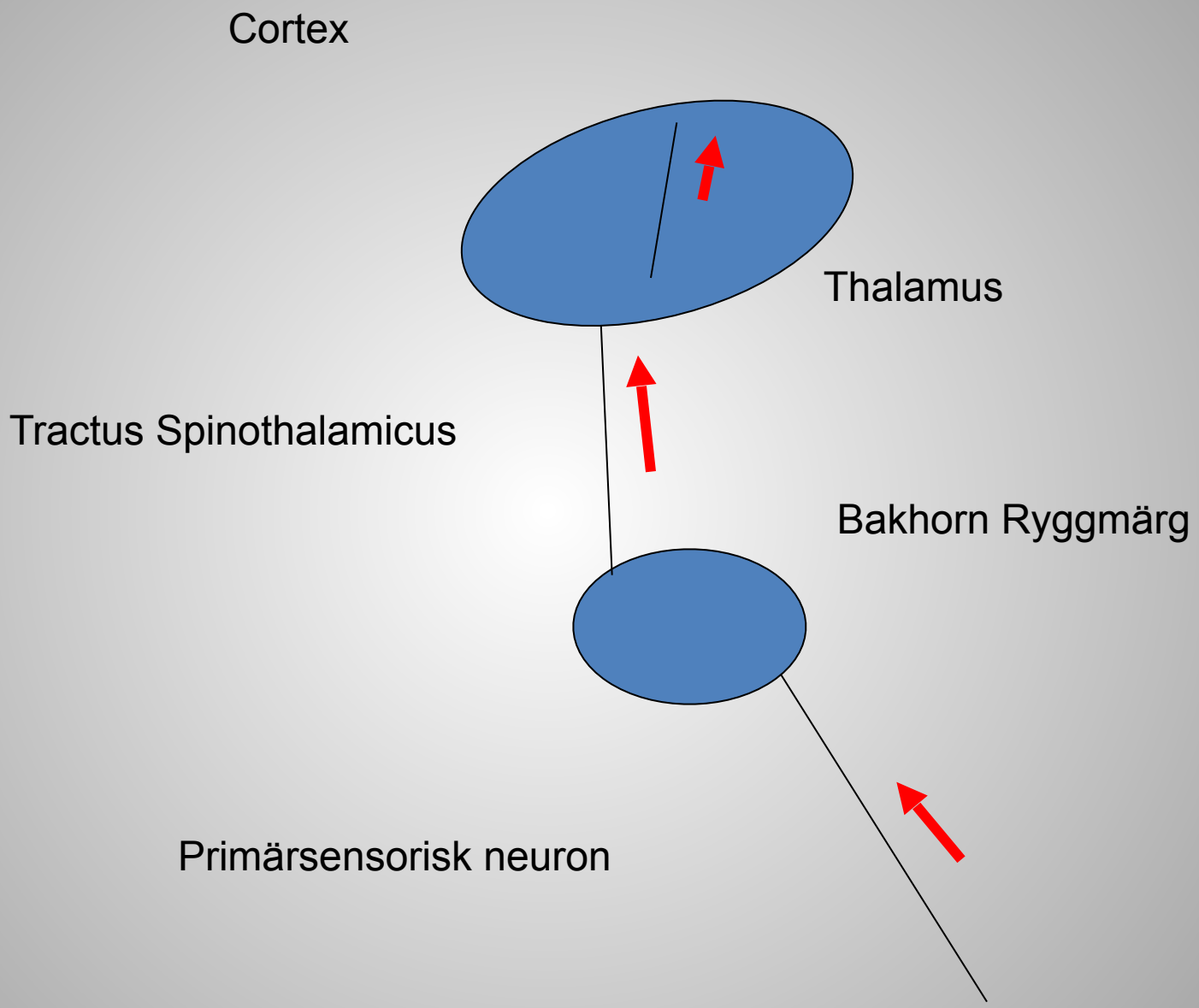
Centrala kärnor

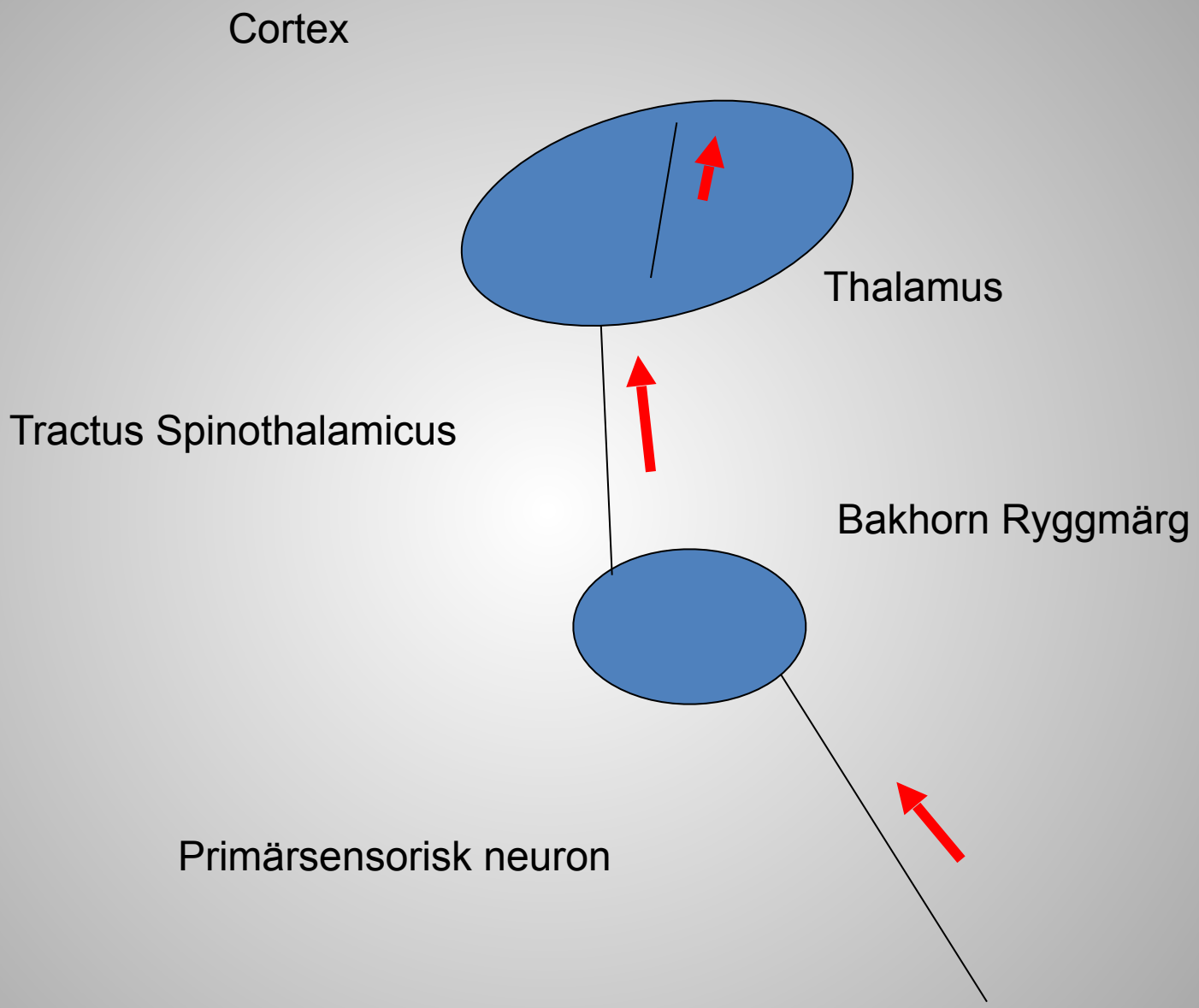
Ryggmärg

Bakhorn

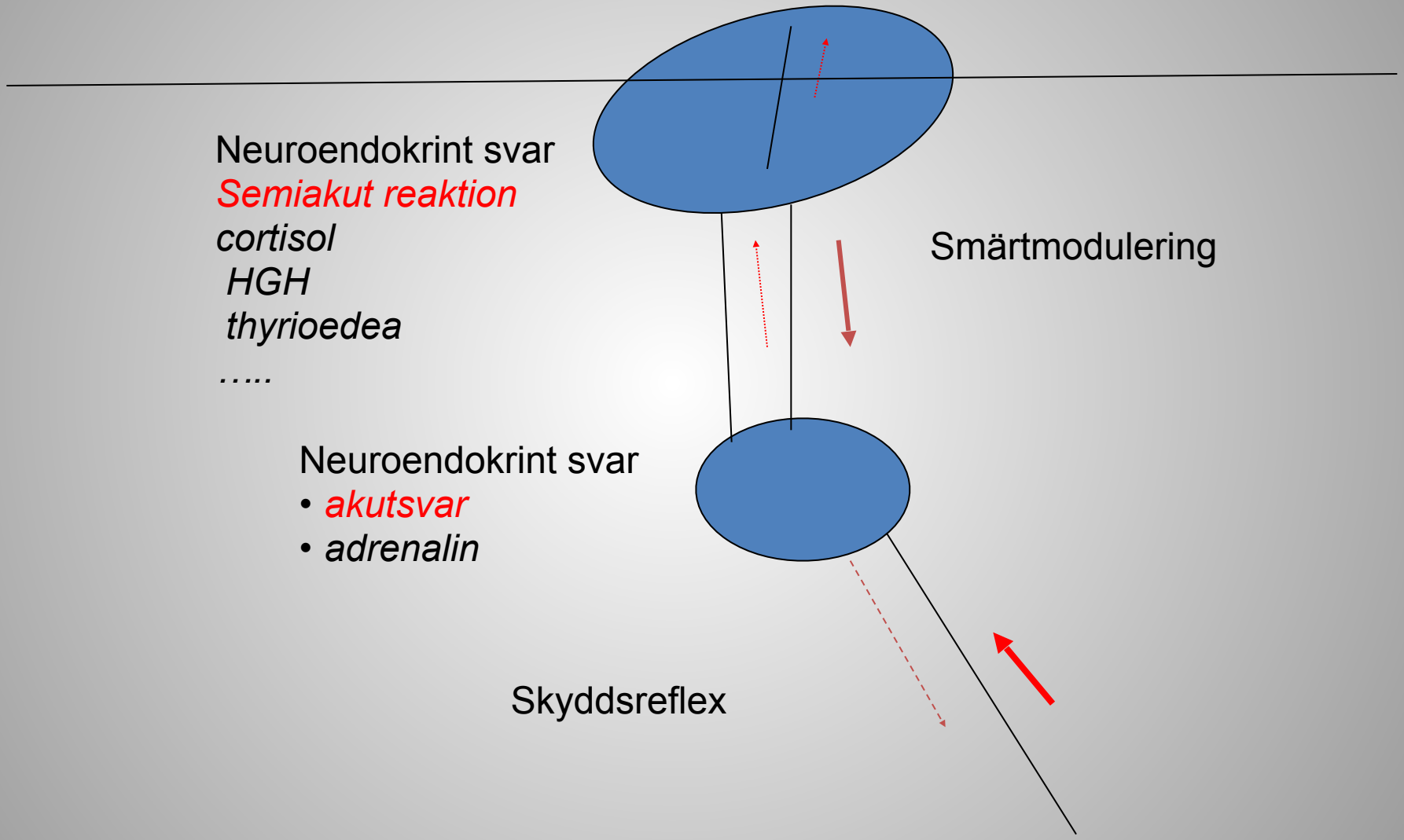


Perifera nervsystemet


Cortex
Thalamus
Tractus Spinothalamicus
Bakhorn Ryggmärg
Primärsensorisk neuron


Cortex
Thalamus
Tractus Spinothalamicus
Bakhorn Ryggmärg
Primärsensorisk neuron

Smärtupplevelse



Neuroendokrint svar
Semiakut reaktion
cortisol
HGH
thyrioedea
…..

Smärtmodulering

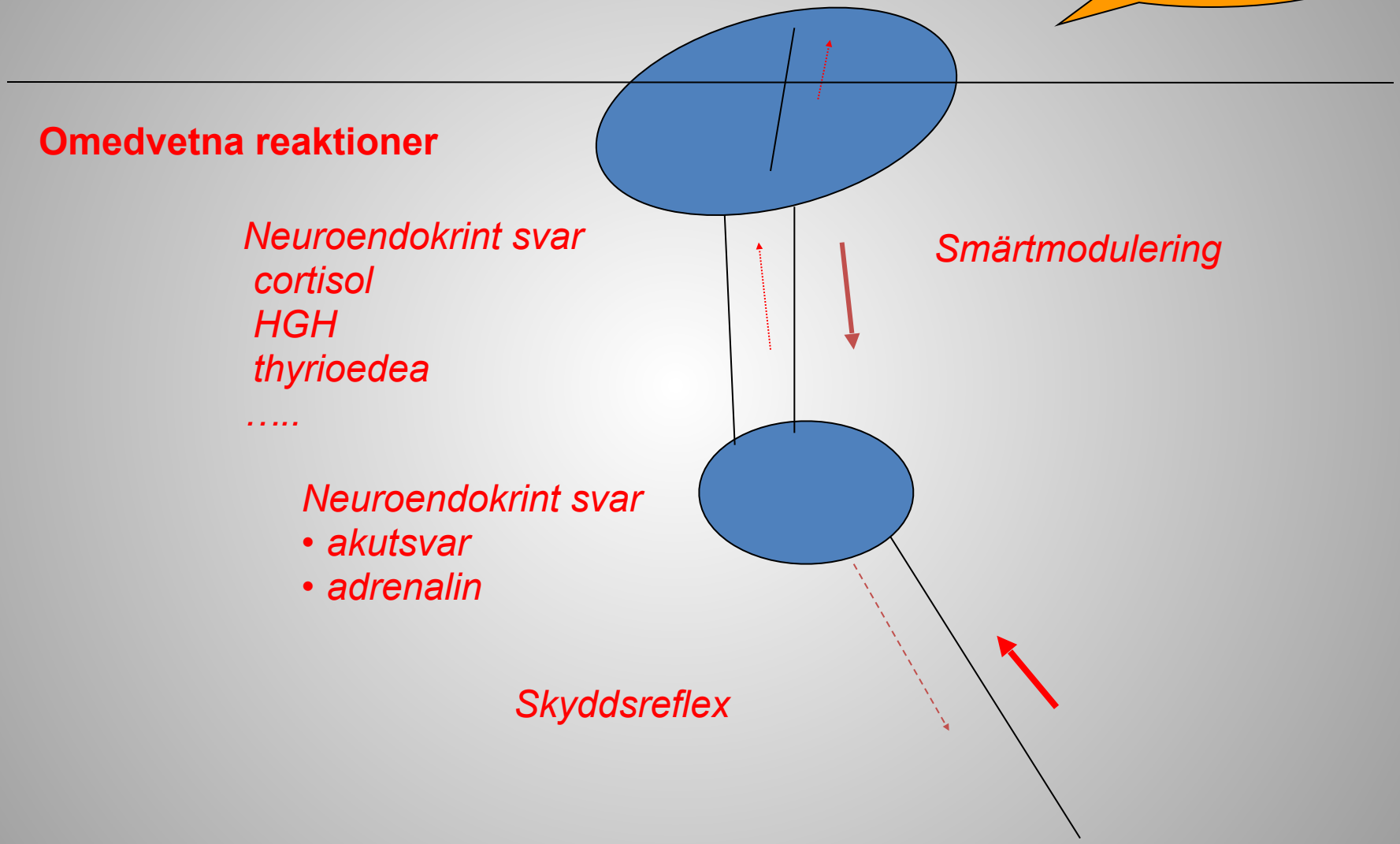
Neuroendokrint svar
- *akutsvar*
- *adrenalin*

Skyddsreflex

Medvetna reaktioner

Smärtupplevelse

Aj, det gör ont



Omedvetna reaktioner

Neuroendokrint svar
cortisol
HGH
thyrioedea
…..

Smärtmodulering

Neuroendokrint svar
- *akutsvar*
- *adrenalin*

Skyddsreflex

Smärtbehandling

icke farmakologisk

- fysikalisk terapi
- kyla
- TNS
- akupunktur
- suggestion/ avslappning

farmakologisk

- Perifert verkande: -Paracetamol, NSAID, ASA, betapred
- Lokalanestesi: -Blockader
- Centralt verkande:
  - anestesi
  - opioider

Perifert aktiva analgetika

- paracetamol
- acetylsalicylsyra
- NSAID’s/Coxibe
- lokalanestesimedel

- steroider

NSAIDs

Perifera effekter

- **hämmar cyklocygenas**
- **COX-I och COX-II**
  - **effekt på lipoxygenas**
  - **effekter på tromboxansyntetas**

NSAIDs

Perifera effekter

- **hämmar cyklocygenas**
  - **effekt på lipoxygenas**

Centrala effekter

- **ökar endorfinaktiviteten**

NSAIDs

Perifera effekter

- **hämmar cyklocygenas**
  - **effekt på lipoxygenas**

Centrala effekter

- **ökar endorfinaktiviteten**
- **påverkar serotoninomsättningen**

NSAIDs

Perifera effekter

- **hämmar cyklocygenas**
  - **effekt på lipoxygenas**

Centrala effekter

- **ökar endorfinaktiviteten**
- **påverkar serotoninomsättningen**
- **hämmar-blockerar NMDA effekter**

NSAIDs

Perifera effekter

- **hämmar cyklocygenas**
  - **effekt på lipoxygenas**

Centrala effekter

- **ökar endorfinaktiviteten**
- **påverkar serotoninomsättningen**
- **hämmar NMDA effekter**
  - **minskar NO bildningen**
  - **minskar cfos bildningen**

Centralt verkande analgetika

- **opiater**
- ? ***morfinliknande läkemedel***
  - ketamin - NMDA blockerande läkemedel
  - noradrenalin upptaghämmare
  - serotoninåterupptagshämmare
  - *lustgas*

Centralt verkande analgetika

- opiater - morfinliknande läkemedel
- **NMDA blockerande läkemedel**
  - ? ***ketamin***
  - ? ***ketobemidon***
- noradrenalin upptaghämmare
- serotoninåterupptagshämmare
- *lustgas*

Centralt verkande analgetika

- opiater - morfinliknande läkemedel
- NMDA blockerande läkemedel - ketamin
- **noradrenalin upptaghämmare**
- **serotoninåterupptagshämmare**
- ***lustgas***

Centralt verkande analgetika

- opiater - morfinliknande läkemedel
- ketamin - NMDA blockerande läkemedel
- noradrenalin upptaghämmare
- serotoninåterupptagshämmare
- ***lustgas***

Opiatreceptorer -smärthämmande effekter

my/kappa receptor effekter

- morfin
- fentanyl
- …..
- ketobemidon
- tramadol
- …..

Opiater
- morfinliknande läkemedel

- morfin
- Ketobemidon - Ketogan
- petidin

- fentanyl
- alfentanil
- remifentanil

Opiater
- morfinliknande läkemedel

- kodein
- **oxycodon (oxynorm/oxicontin)**
- tramadol
- buprenorfin
- pentazocin
- *dolcontin*

glutamat/aspartat -
exitatoriska aminosyrer
- NMDA-receptorn

“NMDA” receptor

antagonistisk effekt/er

- ketamin
- ketobemidon
- gabapentin
- pregabalin

Läkemedelsverket allmänt kring läkemedelsval

- god effekt
- gynnsamt biverkningsspektrum
- enkel farmakokinetik
- god dokumentation
- långvarig erfarenhet

Per oral morfinbehandling

- morfin
- metadon
- temgesic
- **Oxynorm/ oxicontin**

- kodein
  - Tramadol
    - Tapentadol

Analgetika under op.

- Fentanyl
- Alfentanil
- Remifentanil
- Ketamin
- ….

Analgetika *”vardags kinetik”*

	Anslagstid (min)	*Duration (min)*
Fentanyl **1μg/kg**	3 - 5	45 - 60
Alfentanil (rapifen)	1 - 2	30 - 45
remifentanyl (ultiva)	1 - 2	3 - 5
Ketamin **0.3 mg/kg**	2 - 4	Ca 20

Opiater

- **Iv. per kg** anpassa efter;
  - effekt
  - patient
  - ”trauma”

Perifert verkande analgetika

- **Per oralt ”tablett”**
  - **Rektalt**
- **Intravenöst**
- **……**

Perifert verkande analgetika

Paracetamol

- 20 **-30 mg/kg**
- **Max effekt**
- **Maxdos**
- **Sämre resorption rektalt**
- **Dyrt intravenöst**

Perifert verkande analgetika

- **NSAID's**
  - **Preparat**
  - **Dos**
  - **Administrationsväg**

Perifert verkande analgetika

- **NSAID's**
  - **Anslagstid 25 – 45 minuter!!!**
  - **Per oralt i stort samma effekt som intravenöst**
  - **Peroralt "bättre" resorption än rektalt**

Perifert verkande analgetika NSAID’s

- **”klassiska”**
- Dokumenterad kliniks effekt
- Lång erfarenhet
- Billiga

- **”selektiva COX-II”**
- Relativt effekt?
- Bieffekter vid kort behandling – en dos??
- Riskfritt med ökad dos???

Treatment of acute pain

McQuay H & Moore A BMJ 1997; 314:1531-1535

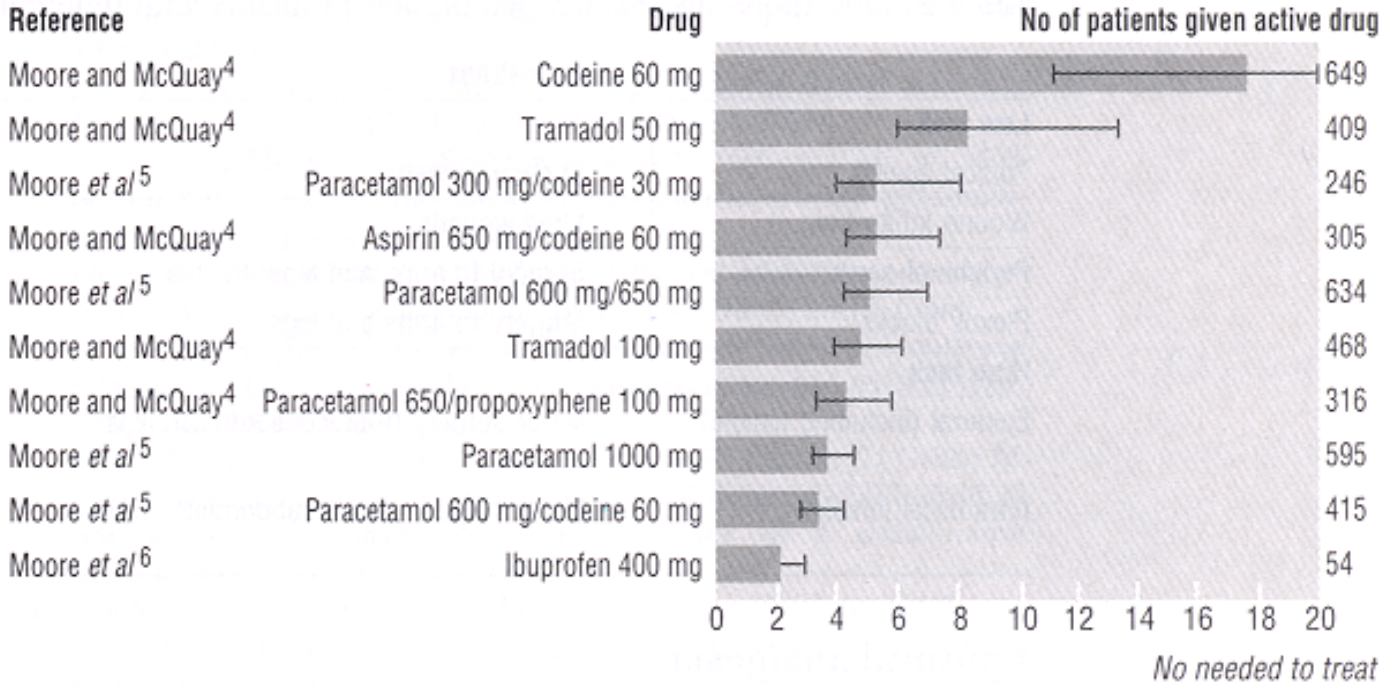


Fig 3 Effectiveness of oral analgesics. Horizontal lines show 95% confidence intervals

Smärtbehandling

McQuay et al BMJ 1997

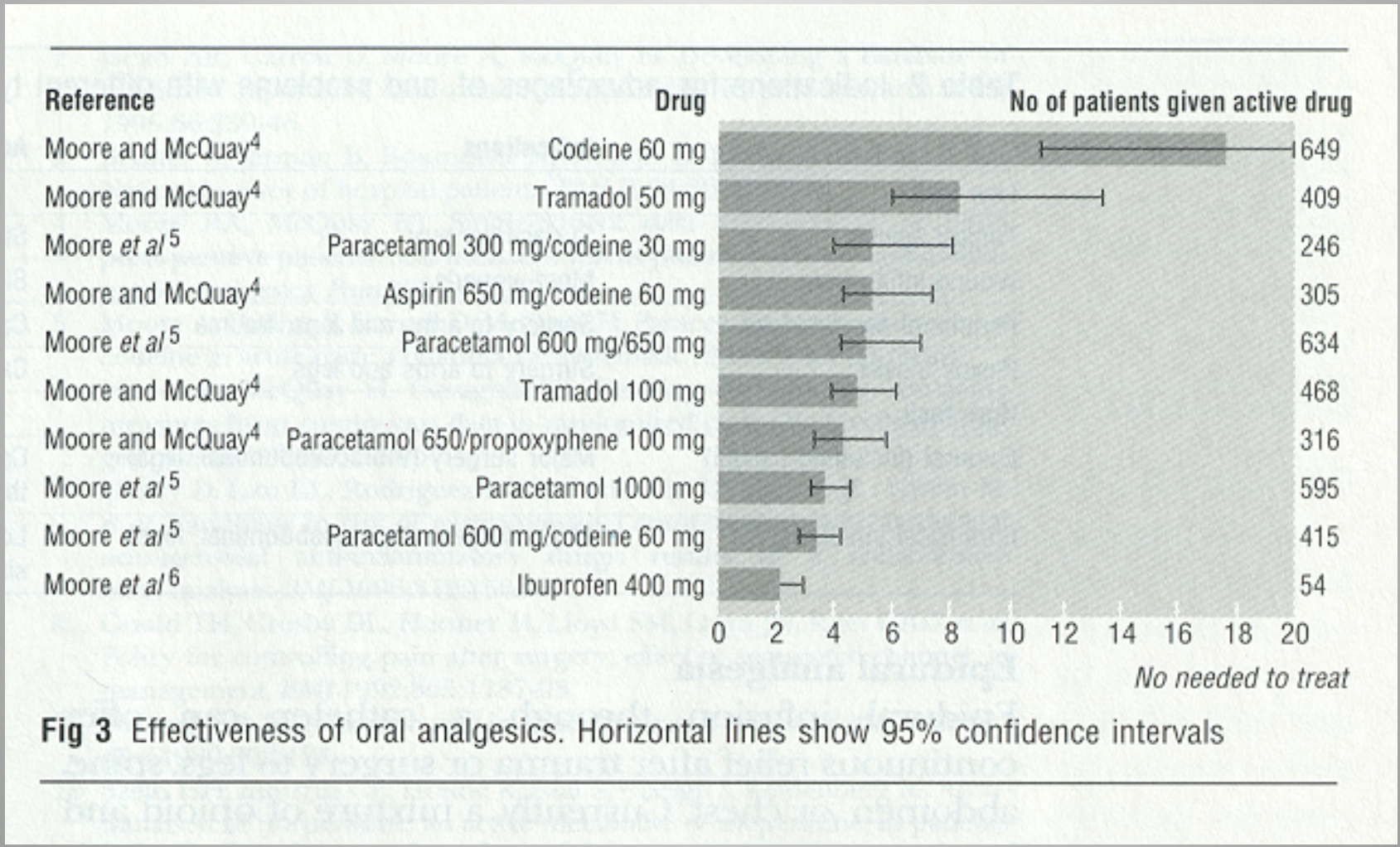
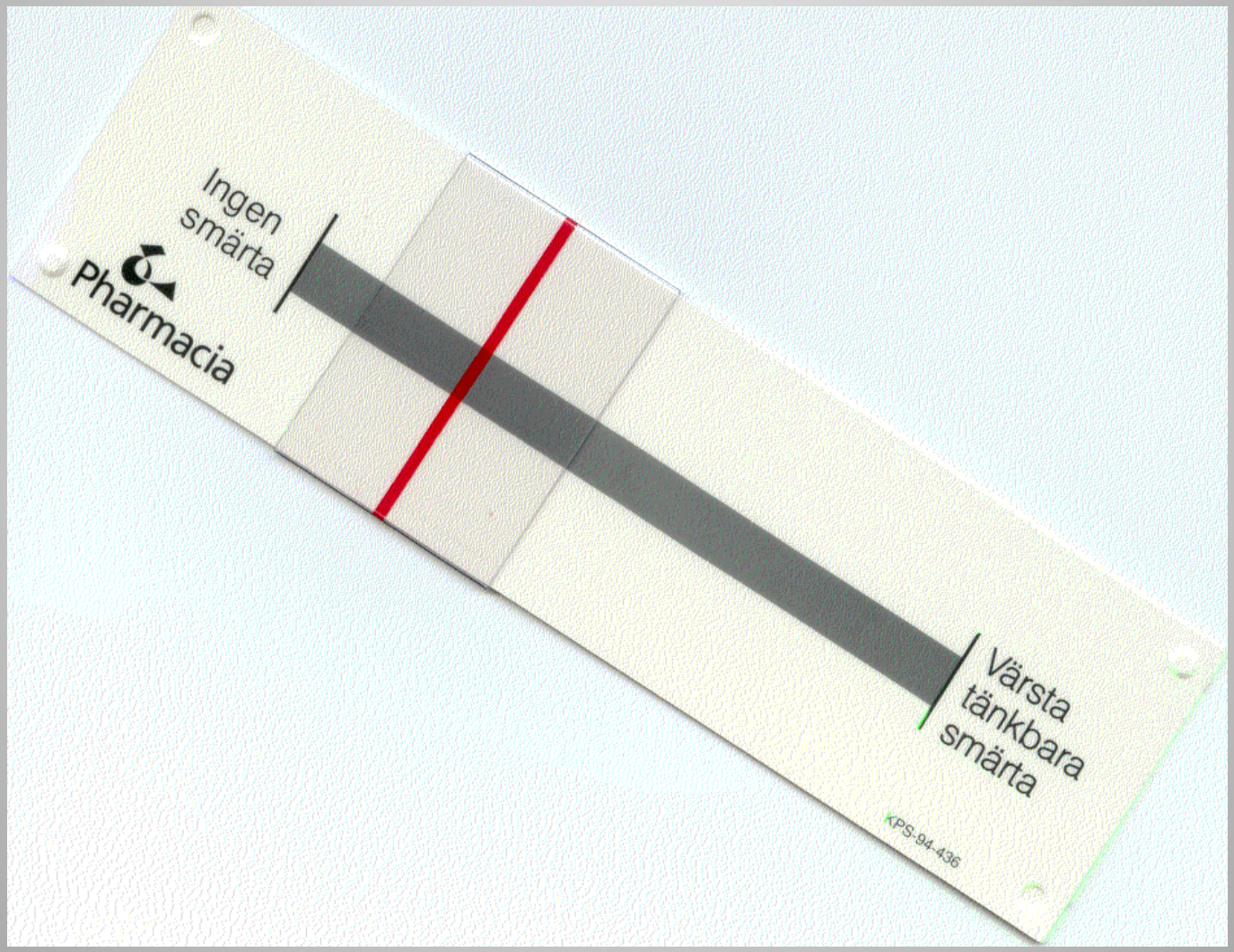


Fig 3 Effectiveness of oral analgesics. Horizontal lines show 95% confidence intervals

Att “mäta” smärta



Användbarhet för Paracetamol/ NSAID's

	akut	**subakut**	**"kronisk"**
nocioceptiv	++	+	+
neurogen	-	(+)	(+)
psykogen	-	-	-

Smärtbehandling

icke farmakologisk

- fysikalisk terapi
- kyla
- TNS
- akupunktur
- suggestion/ avslappning

farmakologisk

- centralt verkande
- lokalanestesi - blockader
- perifert verkande

"max doser" opiater

- **inga maxdoser**
- **dosera efter effekt**

- **påverkad andningsdrive**
- **illamående**
- **yrsel/matthet**
- **gallkolik**

Opiater - ”svaga” - morfinliknande läkemedel

- kodein
- tramadol
- buprenorfin
  - Pentazocin
- Tapentadol (Palexia)

glutamat/aspartat -

exitatoriska aminosyrer

- NMDA-receptorn

- **antagonistisk effekt**
  - **ketamin**
  - *ketobemidon*
  - *dextropropoxyfen*
  - *gabapentin*
  - *pregabalin*

”max doser” lokalanestetika

- **tydliga *högst rekommenderade dos* som ej bör överskridas**

- **risk för system påverkan**
  - **hjärta**
  - **CNS**
- **methemogobinemi (Citanest)**

”max doser” lokalanestetika

- **tydliga *högst rekommenderade dos* som ej bör överskridas**

- **risk för system påverkan**
  - **hjärta**
  - **CNS**
- **methemogobinemi (Citanest)**

”max doser” paracetamol

- **tydlig maxdos som ej bör överskridas**
  1 gr x 4
- **startdos hos naiv patient**
  20 - 30 mg/kg

- **risk för leverpåverkan**

"max doser" NSAID's

- **tydliga maxdoser *som ej skall överskridas***
- **dosreduktion med stigande ålder och sjukdom**
- ***voltaren 150 mg /24 t***

- påverkan på koagulationen
- gastrit - erosion i ventrikeln - blödning
- allergiska reaktioner
- vätskeretention via tubulär påverkan
  - hjärtsvikt
  - hypertoni
  - njurpåverkan

Graviditet och amning, NSAID's

- **kan hämmar kontraktionerna av uterus**
- **kan ge pulmonell hypertension hos det nyfödda barnet genom påverkan på ductus arteriosus**
- **kan medföra koagulations rubbning hos modern och barnet**

Bilkörning, NSAID’s

- Vid behandling med NSAID’s kan reaktionsförmågan nedsättas. Detta bör beaktas då skärpt uppmärksamhet krävs, t.ex. bilkörning
  - är dock **ej** märkt med **”varningstriangel”**

Perifert verkande analgetika

- **NSAID's**
  - **Anslagstid 25 – 45 minuter!!!**
  - **Per oralt i stort samma effekt som intravenöst**
  - **Peroralt "bättre" resorption än rektalt**

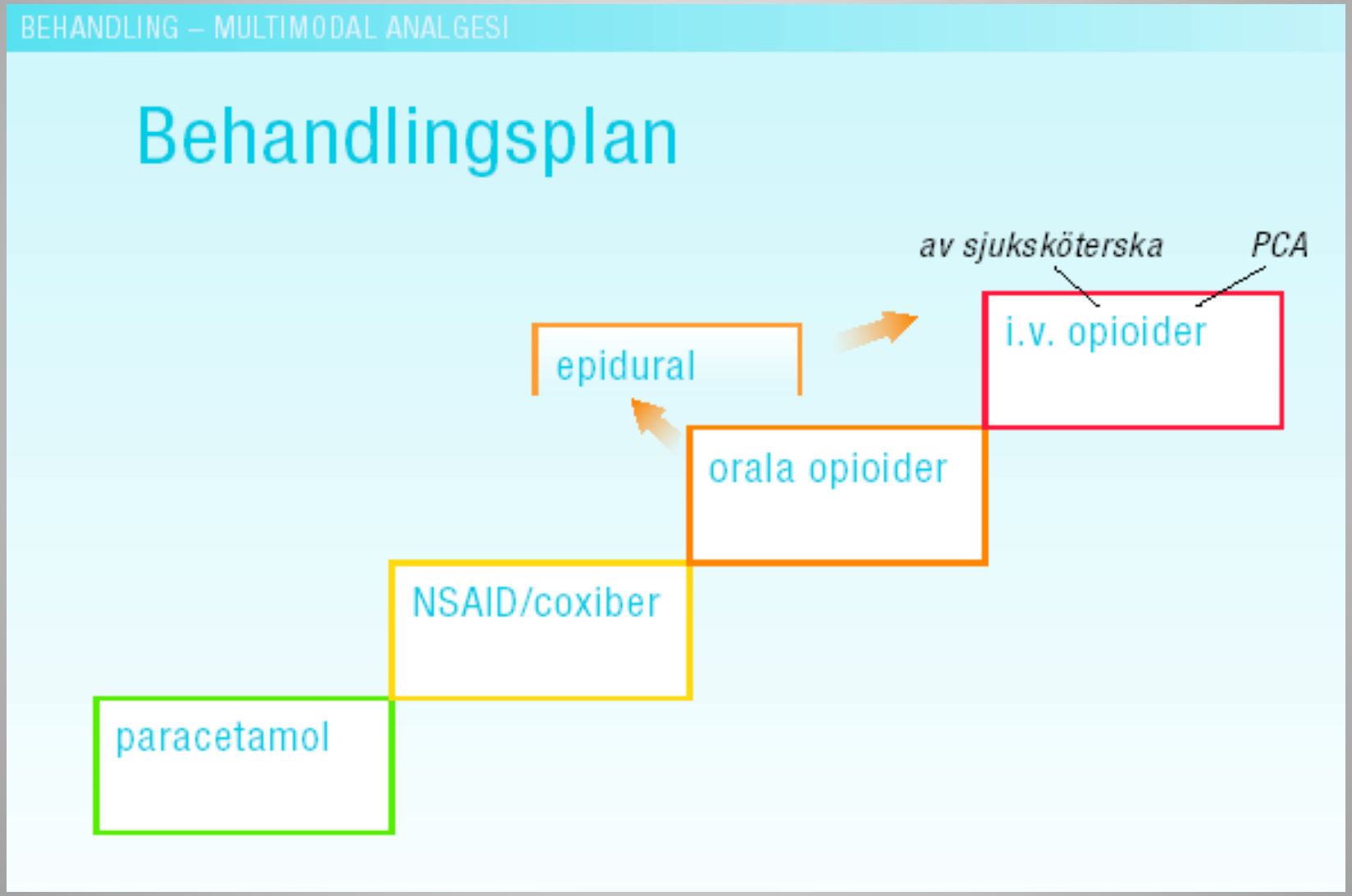
…hur gör *"jag"* …

- Tydlig plan,
- ordination till varje enskild patient
- **VAS**

Smärtbehandling

Ketogan
VAS > 6-8
Oxicontin
VAS > 6
t. Oxynorm/tramadol
VAS > 5
t. Paracetamol / t. NSAID
lokalanestesi i sårområdet alt blockad
xylocain före & marcain efter

En enkel & strikt behandlingsplan..



Acetylsalicylsyra

- Verkningsmekanism
  - Övervägande perifert verkande,
    - Hämnig/blocker av bildandet av prostaglandiner, leukotriener och tromboxan
- Biverkningar
  - Mag besvär, gastrit, ulcus
  - Ökad blödningsbenägenhet
    - Överdosering kan leda till alvarig intoxikation
- Preparat
  - ASA
    - Tabletter, brustabletter, Suppositorier, mixture

Nonsteroidala antiinflammatoriska medel NSAID

- Verkningsmekanism
  - Övervägande perifert verkande,
    - Hämnig/blocker av bildandet av prostaglandiner, leukotriener och tromboxan
- Biverkningar
  - Mag besvär, gastrit, ulcus
  - Ökad blödningsbenägenhet
    - Överdosering kan leda till njurpåverkan, leverpåverkan, vätskeretention, hjärtsvikt
- Preparat
  - NSAID
    - Tabletter, brustabletter, Suppositorier, mixture och intravenösa beredningar

Selektiva COX-II-hämmare **Coxiber**

- Verkningsmekanism
  - Övervägande perifert verkande,
    - Hämnig/blocker av bildandet av prostaglandiner, leukotriener utan nämnvärd påverkan på tromboxanbildningen
- Biverkningar
  - Mag besvär, gastrit, ulcus
    - Misstänks kunna öka risken för kardiovaskulära events, AMI, stroke etc.
- Preparat
    - Tabletter, brustabletter, Suppositorier, mixture

Morfinpreprat

- Verkningsmekanism
  - Företrädesvis centrala effekter inom hjärna och ryggmärg, effekter på opiatreceptorerna
- Biverkningar
  - Rikligt med bieffekter
    - Gastrointestinala
      - Illamående, förlångsammad GI-passage
      - Andningspåverkan respiratorisk depression
      - Allmän sedering
      - Urinretention
      - Gallkolik
      - …..
- Preparat
  - morfinanaloger
    - Tabletter, mixture, plåster och intravenös beredningar

NMDA-blockerare

- Verkningsmekanism
  - Blockerar/hämmar NMDA transmissionen
  - Biverkningar
    - Hallucinationer, mardrömmar,
    - Sympatikusstimulering
- Preperat
  - Ketamin
    - injektionsberedning

Valet av läkemedel styrs av biverkningsprofilen

1. **Parcetamol**
2. **Lokalbedövning**
    1. Coxib
3. Opiat

- Svagt analgetika
- Minimalt med biverkningar
- Dosberoende effekt
- Få biverkningar
- Potent läkemedel
- ”en del biverkningar”,
  - minimal risk vid korttidsbehandling

- Potent,
  - *–end of line therapy*
  - *–Biverkningar*
  - *–Biverkningar*
  - *–Biverkningar*
  - *–Tillvänjning/beroende*
  - *–……..*

Smärtbehandling

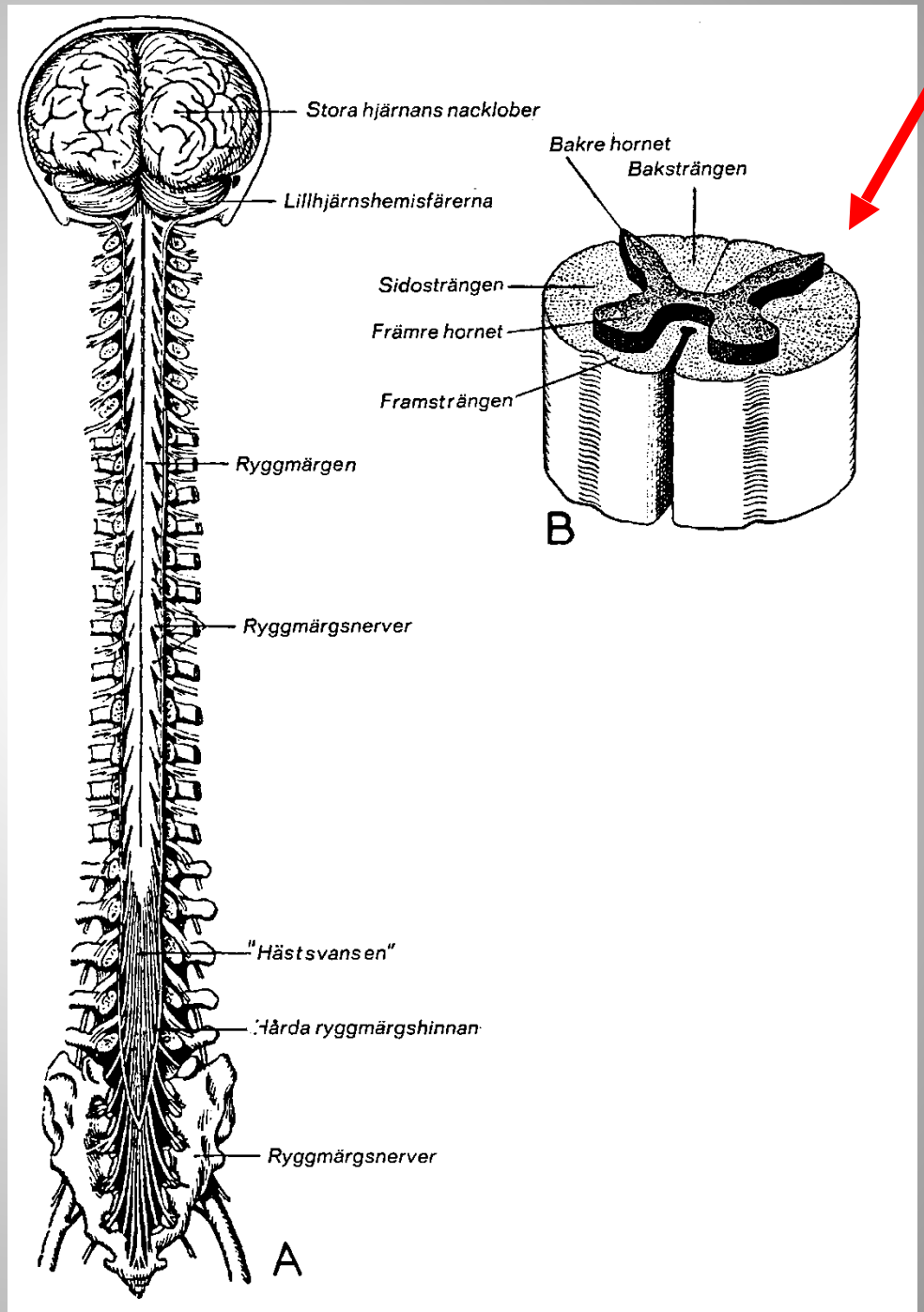
icke farmakologisk

- fysikalisk terapi
- kyla
- TNS
- akupunktur
- suggestion/ avslappning

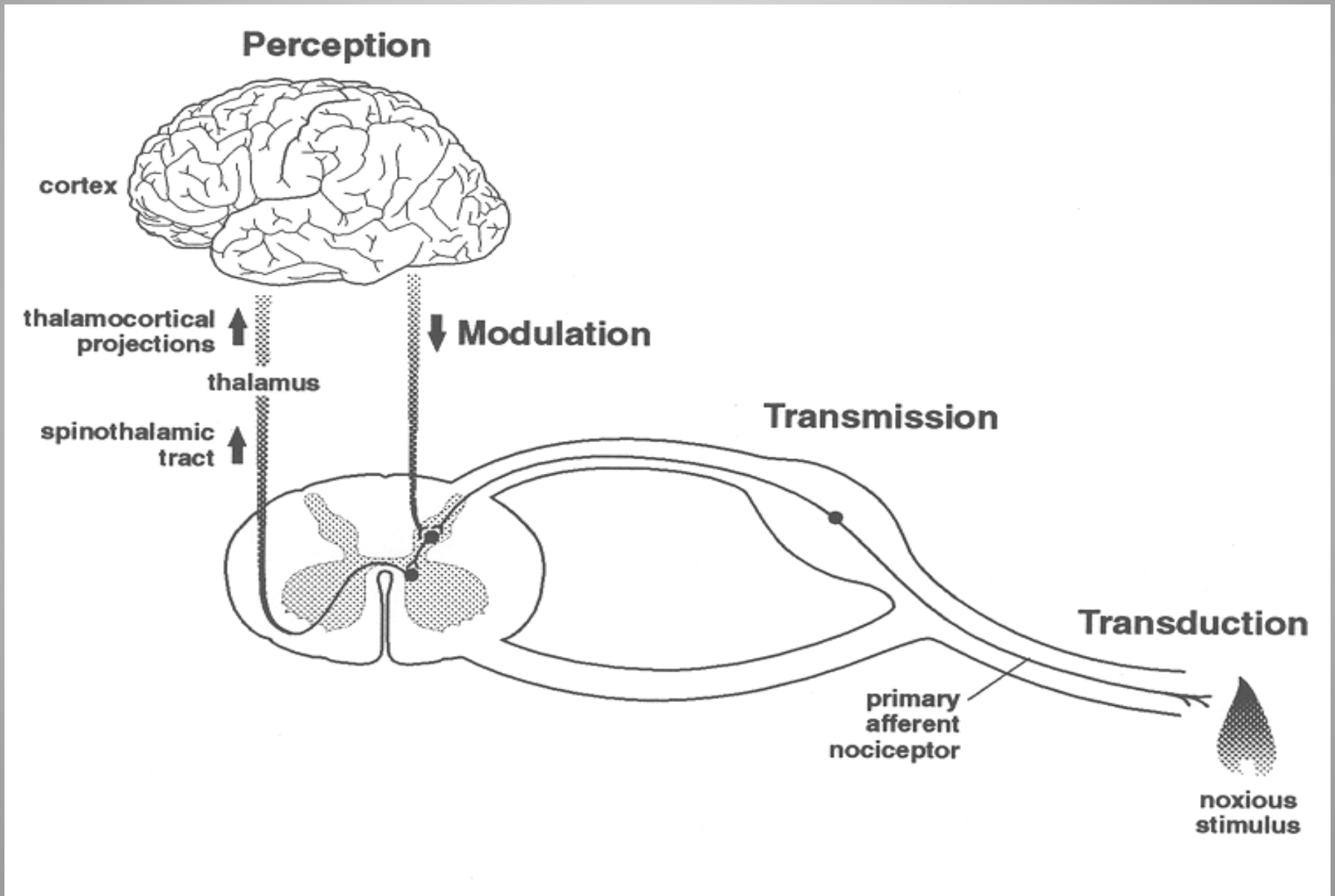
farmakologisk

- perifert verkande
- lokalanestesi - blockader
- centralt verkande
  - anestesi

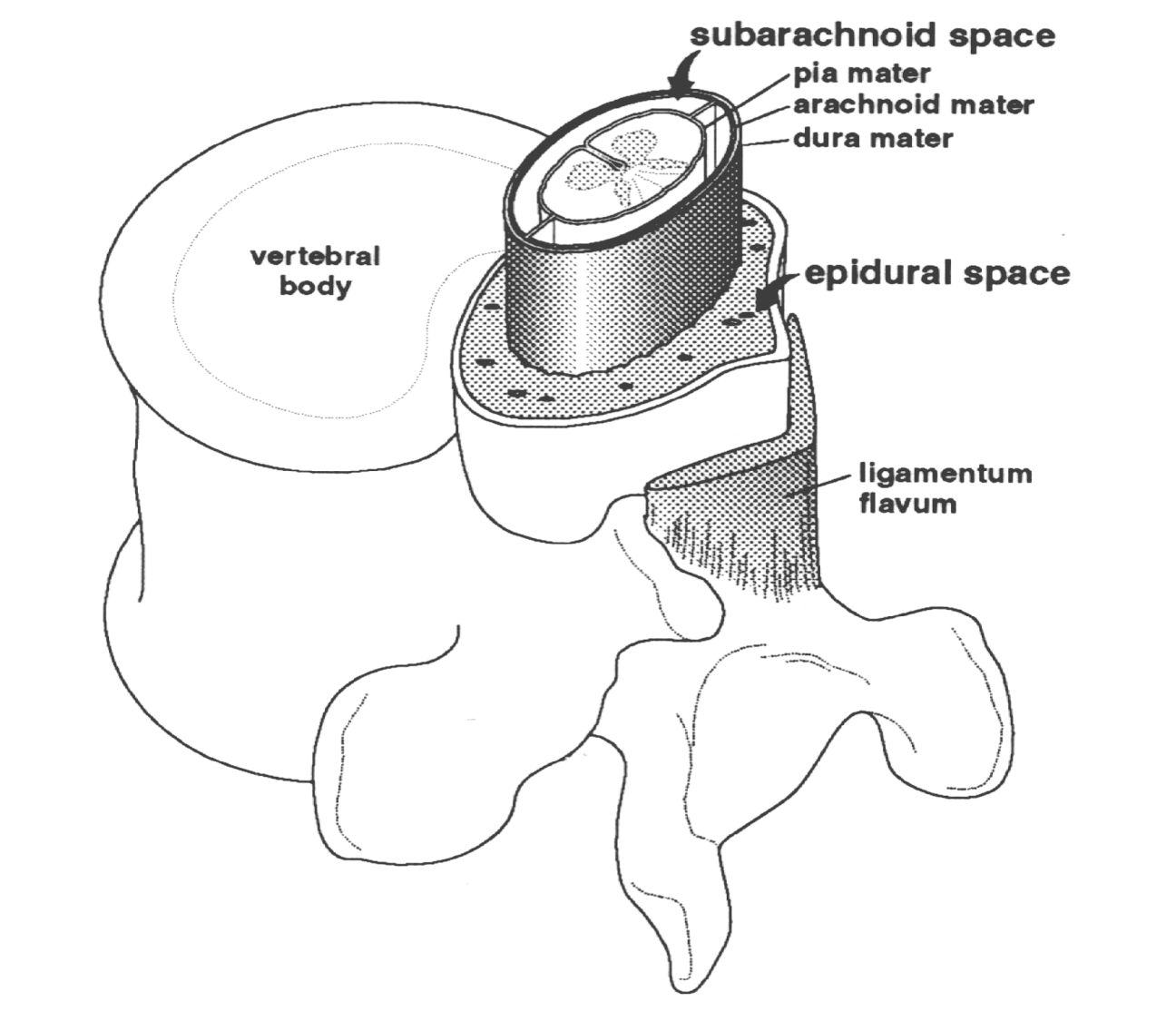
Centrala blockader



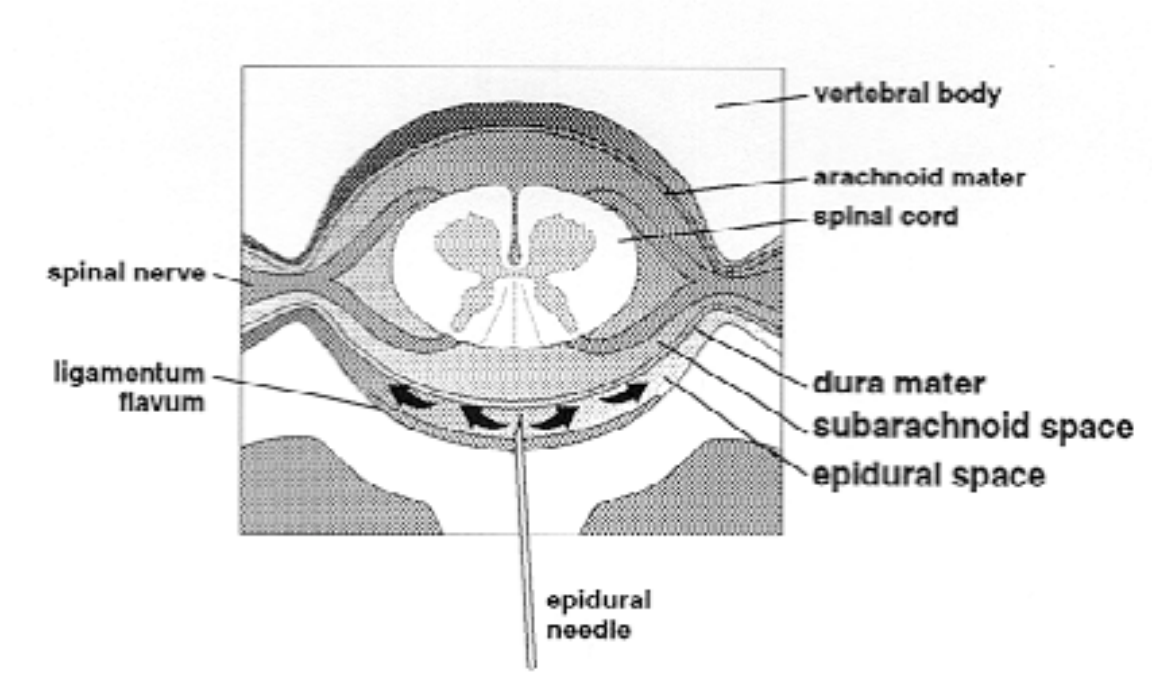
Epiduralbedövning



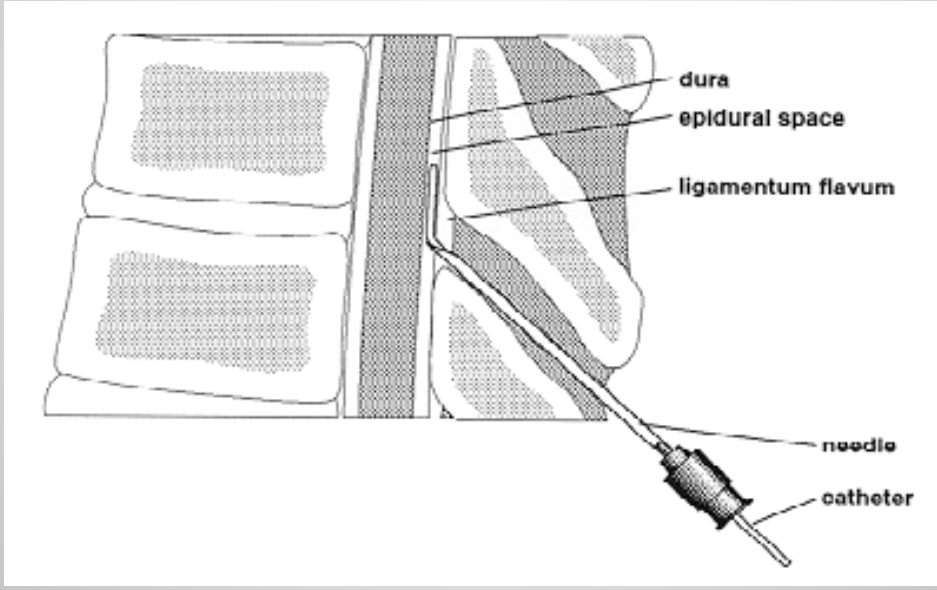
Anatomin


subarachnoid space
pia mater
arachnoid mater
dura mater
vertebral body
epidural space
ligamentum flavum

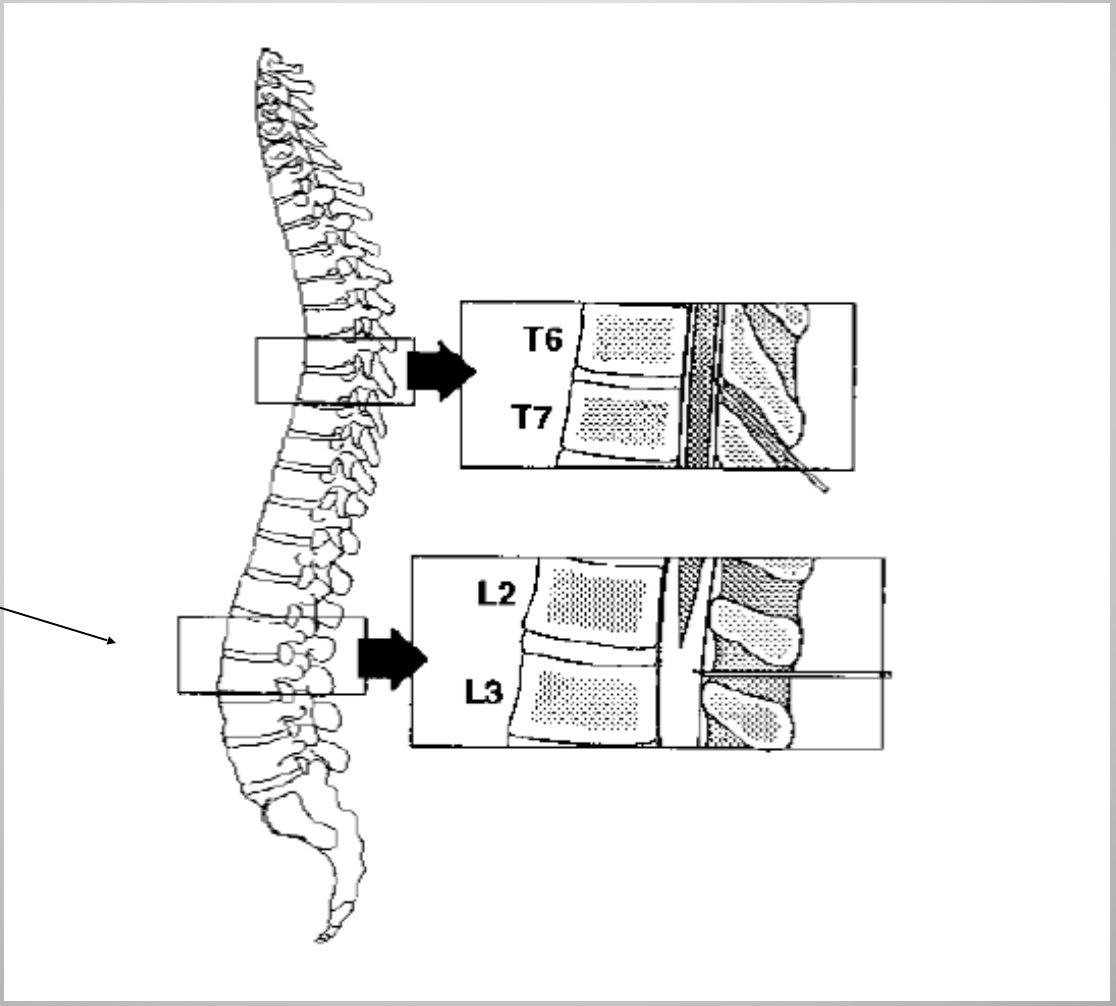
Utbredning


vertebral body
arachnoid mater
spinal cord
spinal nerve
ligamentum flavum
dura mater
subarachnoid space
epidural space
epidural needle

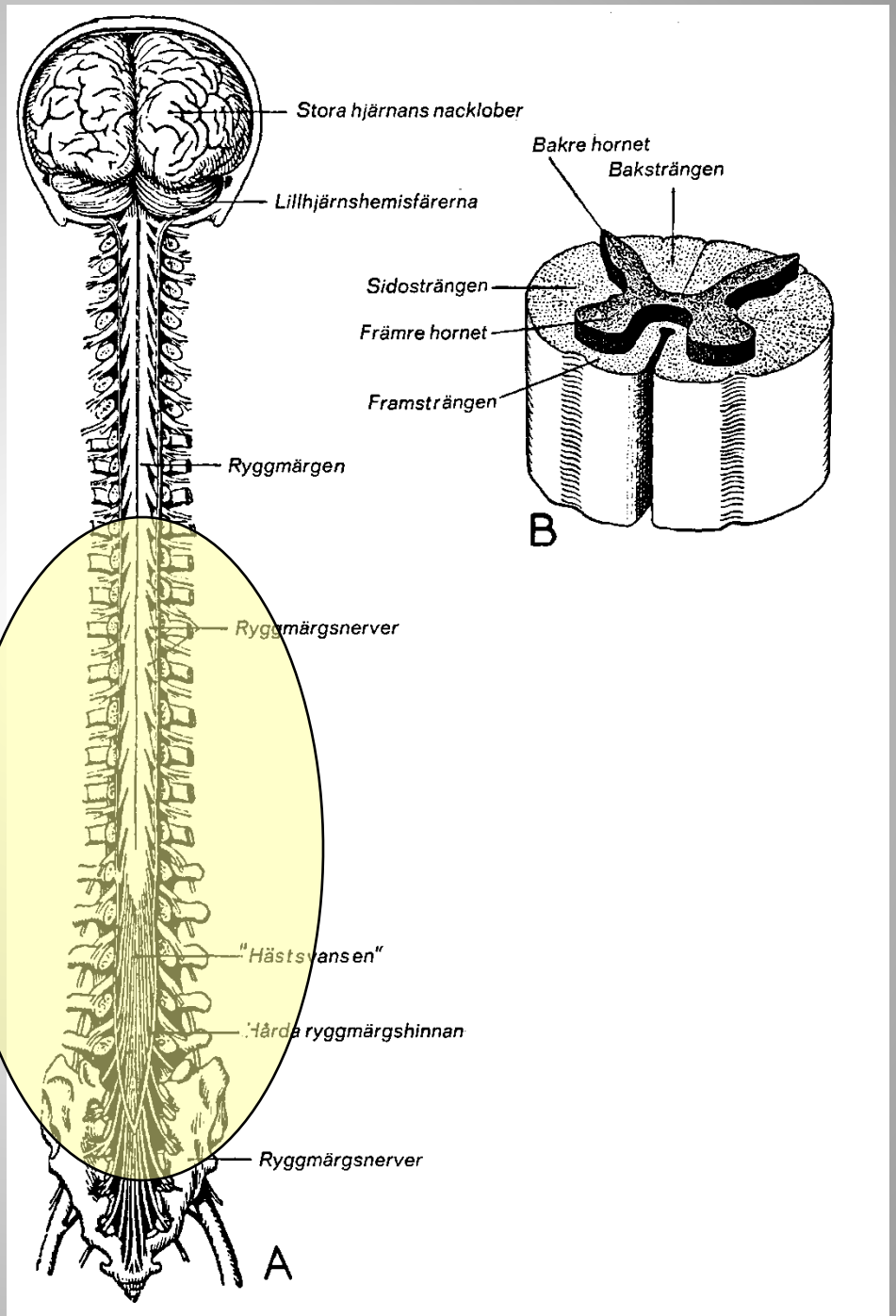
Rätt teknik



Rätt nivå



..***<u>omkringliggande vävnader</u>***,
tarmar, hinnor, urinvägar, …..



Kontraindikationer

- Blödningsrubbning
- Infektioner
  - Motvilja
  - Neurologisk sjukdom

Övervakning

- Vakenhet
- Puls
- Blodtryck
- Andning
- Motorik
  - Blåsfunktion

Smärtupplevelsen

Läkemedlen

- **Snabbverkande**
  - Xylokain
  - Carbocain
    - Citanest
- **Långverkande**
- Marcain
- Narop
- Chirocaine

Marcain

injektionsvätska, lösning **2,5 mg/ml** och **5 mg/ml**

Farmakodynamik

- Marcain innehåller bupivakain, som är ett långverkande lokalanestetikum av amidtyp.
- Bupivakain blockerar impulsledningen i nervfibrerna reversibelt genom att hämma transporten av natriumjoner genom nervmembranet.
- Liknande effekter kan även ses på excitatoriska membran i hjärna och hjärtmuskel.

Marcain

- Koncentrationen styr kvaliteten av blockad, ju högre koncentration desto mer uttalad motorblockad
  - Ju lägre koncentration desto ”lättare blockad” och mindre motorpåverkan
- Volymen styr utbredningen, hur stort område som bedövas, hur många dermatom som blir blockerade
- Kombination mellan lokalbedövning (Marcian) och opiat (Sufenta) ger en potentiering, additiv effekt med avseende på smärtlindringen

Marcain

Farmakokinetik

- Leveremetabolsim och njurutsöndring

Högsta rekommenderade doser

- Den högsta rekommenderade dosen vid ett och samma tillfälle beräknas efter värdet 2 mg/kg kroppsvikt och är för vuxna högst 150 mg inom en fyratimmarsperiod.

Marcain

Mycket vanliga (>1/10)	***Allmänna*: Illamående.** ***Cirk*: Hypotension.**
Vanliga (1/10-1/100)	***Cirk*: Bradykardi, hypertension.** ***CNS*: Parestesi, yrsel.** ***GI*: Kräkningar.** ***Urogenital*: Urinretention.**
Mindre vanliga (1/100-1/1000)	***CNS*: Symtom på CNS-toxicitet. (konvulsioner, cirkumoral parestesi, domningskänsla i tungan, hyperakusi, synstörningar, medvetandeförlust, tremor, berusningskänsla, tinnitus, dysartri).**
Sällsynta (<1/1000)	***Allmänna*: Allergiska reaktioner, i allvarligaste fall anafylaktisk chock.** ***CNS*: Neuropati, perifera nervskador, araknoidit, pares, paraplegi.** ***Ögon*: Dubbelseende.** ***Cirk*: Hjärtstillestånd, hjärtarytmier.** ***Luftvägar*: Andningsdepression.**

Marcain

- **Klinisk användning**
- Vid *epiduralblockad* (för kejsarsnitt): Marcain 5 mg/ml 15-30 ml (75-150 mg bupivakainhydroklorid).

- Vid *kontinuerlig epiduralanestesi* i form av intermittenta bolusdoser ges:
  - **initialt Marcain 2,5 mg/ml 20 ml (50 mg bupivakainhydroklorid)**
  - **därefter Marcain 2,5 mg/ml 6-16 ml (15-40 mg bupivakainhydroklorid) var 4-6 timme**
    - **beroende på önskat antal bedövade segment och patientens ålder.**

Sufenta

- Sufenta 50 mikrogram/ml injektionsvätska, lösning
- Sufenta 5 mikrogram/ml injektionsvätska, lösning

- **Farmakodynamiska egenskaper**
- Opioidanestetika,
- Sufenta är ett potent narkotiskt analgetikum för epiduralt bruk.
- Sufenta innehåller som verksam substans sufentanil som är kemiskt besläktat med fentanyl.

Sufenta

- **Terapeutiska indikationer**
- För postoperativ behandling av smärta efter allmänkirurgi, thorax- och ortopediska operationer samt kejsarsnitt.
- Som analgetisk tilläggsmedel till bupivacain under värkarbete och förlossning.

Sufenta

- Sufentanil kan ge andningsdepression som kan kvarstå eller uppträda under den postoperativa perioden.
- Skärpt övervakning bör ske under minst två timmar efter varje dos.

Sufenta

- **Biverkningar**
- Den vanligaste biverkan är sedation som inträffar hos ca 30% av patienterna.
- Vanliga
- (>1/100)
- *Allmänna:* Huvudvärk. Yrsel.
- *Cirk.:* Övergående blodtrycksfall. Bradykardi.
- *CNS:* Sedation. Feber. Andningsdepression. Apné. Muskelryckningar.
- *GI:* Illamående/kräkningar.
- *Muskuloskel.:* Muskelrigiditet
- *Urogenital:* Urinretention. Urininkontinens.
- *Ögon:* Mios.
- *Övriga:* Klåda.
- Sällsynta
- (<1/1000)
- *Allmänna:* Allergisk reaktion (såsom anafylaxi, bronkospasm, urtikaria).
- *Cirk.:* Asystoli.
- *Luftvägar:* Laryngospasm.

Profil

	Anslagstid (min)	Duration (timmar)	Max dos (mg/kg)
Marcain	Ca 10	2	2
Narop	Ca 10	2	2
Chriocaine	Ca 10	2	2

Blanding till bolus

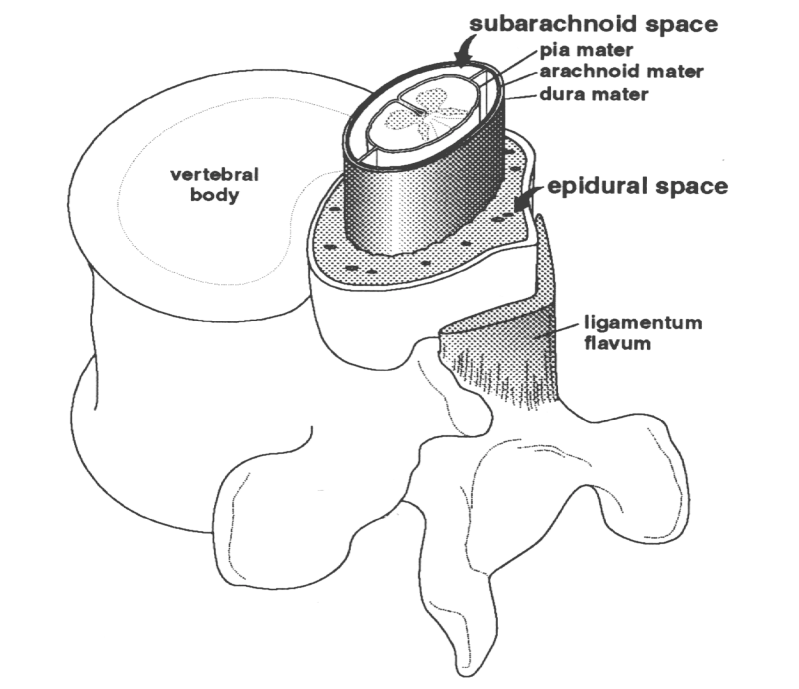
- Marcain 0.625 el. 1,25 mg/ml
- Sufenta 0,5 - 1 µg/ml
  - Adrenail 0,5-1 µg/ml
- **Bolus om 6 – 8 ml**

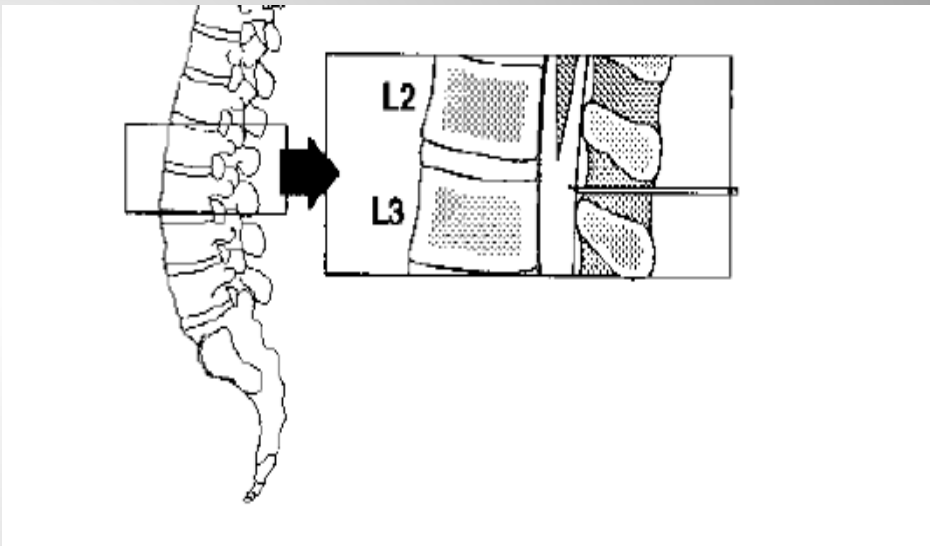
  - *Sufentanil 0,5 µg/ml, 0,75 µg/ml samt 1 µg/ml i kombination med bupivacain 0,625 mg/ml och adrenalin 1,25 µg/ml vid förlossningsepidural.*
  - *Alla fick 8 ml i bolusdos följt av en kontinuerlig infusion med 6 ml/tim.*

Bieffekter

- Blodtrycksfall
- Illamående
- Klåda
- Temperaturstegring
- Shivering
- Motorisk påverkan
  - Påverkan på blåsfunktion

Spinal Anatomin





Läkemdel

- Marcain tung (5 mg/ml) 2-3 ml
  + Sufenta 2,5 – 5 µg

  Vätska
  Vänster sidoläge

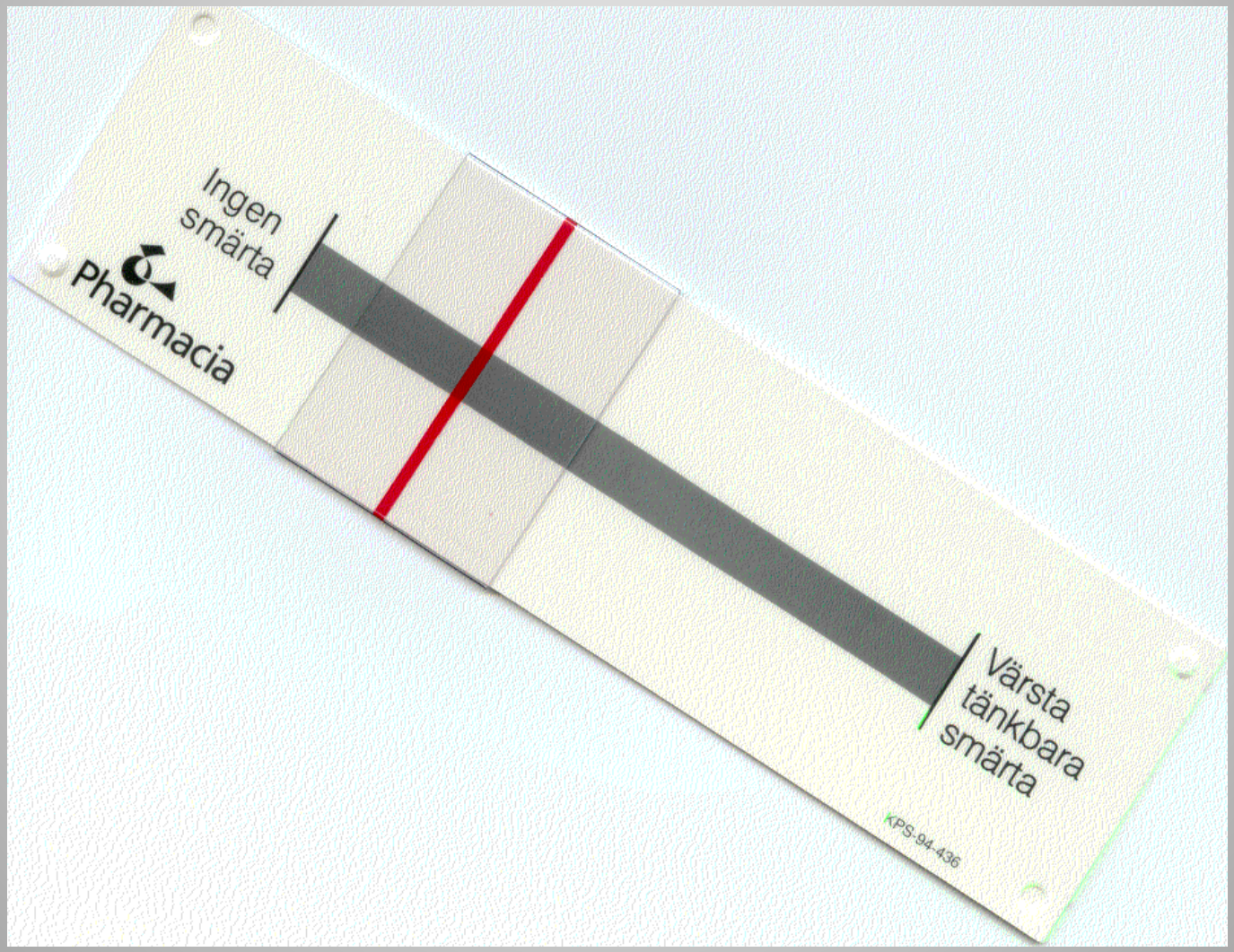
Bieffekter

- Blodtrycksfall
- Illamående
- Klåda
- Temperaturstegring
- Shivering

Bieffekter

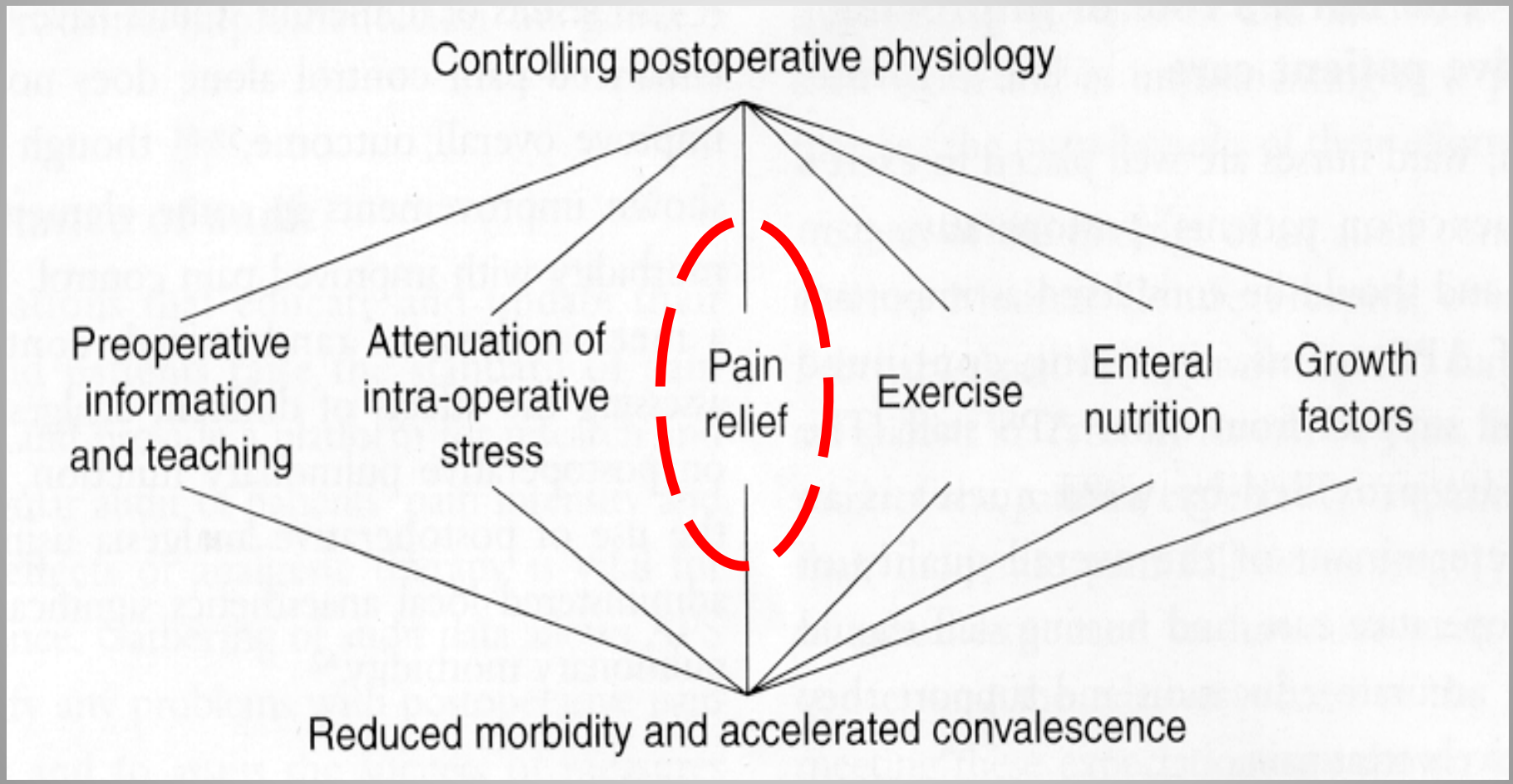
	Placebo	Fentanyl	Sufentanil 2.5 μg	Sufentanil 5 μg
Analgesics intraoperatively	0	0	0	1
Antipruritic agents intraoperatively	0	0	1	1
Antipruritic agents postoperatively	1	0	1	9*
Antiemetics intraoperatively	5*	0	0	1
Sedatives intraoperatively	1	0	0	0

Att “mäta” smärta



Anaesthetic service for the new millennium

*The perioperative **multi-modal approach***



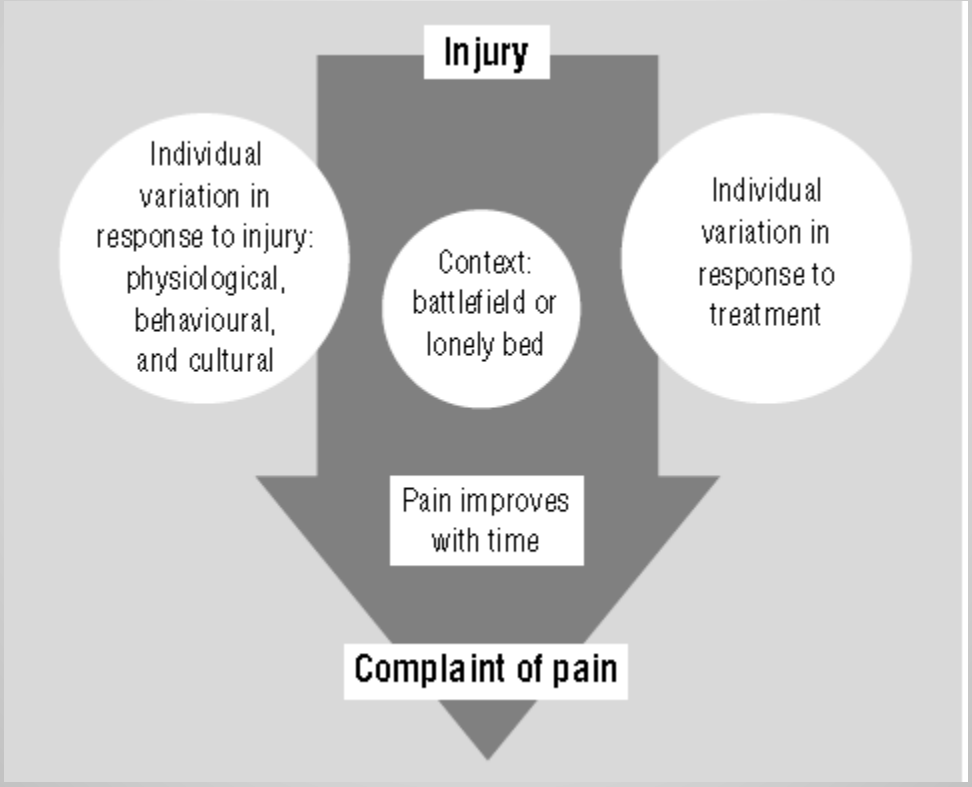
Vad är viktigt för patienterna?

Post-operative recovery: day surgery patients' preferences.

Jenkins K, Grady D, Wong J, Correa R, Armanious S, Chung F.
Br J Anaesth. 2001 Feb;86(2):272-4.

- Avoiding **post-operative pain**, gagging on the tracheal tube and nausea and vomiting are major priorities for day-case patients.

Smärta - *lidande*



- http://www.läkemedelsboken.se/#q1_sma_smartbehandl_2013fm10.html?search=&iso=false&imo=false&nplId=null&id=q1_57&_suid=1412400504953043881618905873 87

Akut smärta

- Terapirekommendationer – Behandling av kortvarig nociceptiv smärta
- **Lindrig eller måttligt svår smärta**
- **Paracetamol**, maximal dos 1 g x 4
- Vid misstanke om inflammatoriskt inslag: COX-hämmare,
  - t ex **ibuprofen** 200–400 mg x 3 eller **naproxen** 250–500 mg x 2
- **Kraftigare smärta**
- **Tramadol** 50–100 mg x 4
- **Kodein + paracetamol** (t ex Citodon 1–2 x 4)

Opioidanalgetika

- Opioidanalgetika verkar genom att binda till opioidreceptorer som vid aktivering ger en central smärthämmande effekt.
- **Alla opioider har ungefär samma biverkningar som är dosberoende.**
  - Dessa är sedation, muntorrhet, illamående, förstoppning, klåda och vid högre doser andningsdepression (hämning av andningscentrum då både andningsfrekvens och storleken på andetagen minskar).
    - » Barn < 3 månader är särskilt känsliga för andningspåverkan. Alla opioidreceptorrelaterade effekter kan reverseras med naloxon, och naloxon bör alltid finnas till hands när man använder opioider vid akuta tillstånd. Vissa opioider har dock ytterligare effekter som medieras via andra mekanismer, t ex aminåterupptagshämning av tramadol. Alla opioider medför också tolerans vilket gör att man för morfin måste öka dosen efter ca 2 veckor för att bibehålla effekten. Detta medför också att abstinenssymtom utvecklas om utsättning efter denna tid går för fort.
- *Det finns individuella variationer för hur olika opioidanalgetika verkar både vad gäller effekt och biverkningar. Detta gör att det kan löna sig att vid behov byta från en opioid till en annan.*

Morfin

- **Morfin** är standard för all akut behandling av svår smärta.
  - Morfin binder till μ-receptorn i centrala nervsystemet och verkar där genom att hämma vidare fortledning av smärtsignalen.
- Effekten av morfin är mycket individuell och man måste titrera ut dosen.
  - **Oralt givet morfin tas upp till ca 30% (variation 10-60%) av** motsvarande parenterala dos vilket främst har betydelse när man ska hitta rätt dos vid inledning av en behandling.
  - Morfin har flera metaboliter med både analgetisk och anti-analgetisk effekt. Vid hög dosering eller njursvikt kan dessa aktiva metaboliter bidra med farmakologisk effekt.
    - För användning till barn se avsnittet Läkemedel och barn . För användning i palliativ vård se kapitlet Palliativ vård, avsnittet Opioider .

Alternativ

- **Ketobemidon** har ungefär samma potens som morfin och samma orala biotillgänglighet, dvs ca 35%.
- **Oxikodon** har samma farmakologiska potens som morfin, **men oral biotillgänglighet är 60–70%.**
- Vid enstaka doser är 5 mg oxikodon ekvieffektivt med 10 mg morfin.
- Vid upprepad dosering med individuell titrering blir förhållandet för ekvieffektiva doser snarare 7,5/10 mg.
  - DDD för oxikodon anges till 75 mg, och för morfin 100 mg.

Mer specialpreparat

- **Buprenorfin** är en stark opioid som i höga doser fungerar som antagonist på opioidreceptorerna. I smärtbehandling används buprenorfin nästan uteslutande som plåster, i låg dos, och är då ett *kliniskt alternativ till svaga opioider* vid behandling av långvarig smärta. Även denna behandlingsform kan dock ge biverkningar som illamående och yrsel. Det är oklart om risken för sådana biverkningar är markant lägre med buprenorfinplåster än vid behandling med tramadol.
- **Tapentadol** är en ny opioid som även hämmar återupptaget av noradrenalin, vilket kan påverka biverkningsprofilen.
  - Det är dock ännu för tidigt att avgöra om tapentadol har några avgörande kliniska fördelar framför morfin och oxikodon På grund av brist på data bör tapentadol inte ges alls vid *kraftigt* nedsatt njurfunktion.
- **Fentanyl** är en mycket potent opioid, vilket bör beaktas även när den ges i plåsterform. Fentanyls metabolism sker till stor del via enzymet CYP3A4, som är känsligt för hämning av t ex erytromycin, klaritromycin och systemiska medel mot svampinfektioner, t ex flukonazol, itrakonazol och ketokonazol. Användning av sådana medel kan leda till ackumulation av fentanyl och därmed överdosering med risk för andningsdepression.

Oxykodon - Oxynorm

- Graviditet
- **Kategori C.**
- **Erfarenhet av behandling under graviditet saknas.**
  - **Under graviditet bör oxikodon endast ges på strikt indikation och sedan moderns behov vägts mot riskerna för barnet.**
    - **Vid långvarig behandling under graviditet bör risk för neonatal abstinens beaktas.**
- **Analgetika av morfintyp kan förorsaka neonatal andningsdepression.**
  - **Under 2-3 timmar före väntad förlossning bör dessa preparat endast ges på strikt indikation och sedan moderns behov vägts mot riskerna för barnet.**
- Amning
- **Grupp III.**
- **Oxikodon passerar över i bröstmjölk och kan orsaka hos den nyfödda. Koncentrationsförhållandet mellan mjölk och plasma var 3,4:1.**
  - ***OxyNorm är kontraindicerat under amning.***

Oxikodon - Oxicontin

- Graviditet (Läs mer om graviditet)
- **Kategori C.**
- **Användning av denna produkt skall i möjligaste mån undvikas till gravida eller ammande kvinnor.**
  - **Erfarenhet av behandling under graviditet är begränsad. Under graviditet bör oxikodon endast ges på strikt indikation och sedan moderns behov vägts mot riskerna för barnet.**
- **Nyfödda barn till mödrar som har fått er under de senaste 3 till 4 veckorna före förlossning bör kontrolleras med avseende på andningsdepression.**
  - **Administrering av oxikodon under graviditet kan leda till abstinenssymptom hos det nyfödda barnet.**
  - **Oxikodon passerar placenta. Djurstudier med oxikodon har inte visat några eller embryotoxiska effekter.**
    - ***OxyContin ska endast användas under graviditet om nyttan uppväger de möjliga riskerna för fostret/det nyfödda barnet.***
-

- Amning (Läs mer om amning)
- **Grupp III.**
- **Oxikodon passerar över i bröstmjölk och kan framkalla andningdepression hos det nyfödda barnet.**
- **Koncentrationsförhållandet mellan mjölk och var 3,4:1.**
    - ***OxyContin bör därför inte användas under amning.***

Opioid antagonists for prevention and treatment of opioid-induced gastrointestinal effects.

- ***Targin*® - oral oxycodone/naloxone prolonged-release tablet now launching across Europe to control severe chronic pain <u>with significantly reduced risk of opioid-induced constipation</u>**
  - *SUMMARY: The availability of opioid receptor antagonists with restricted access to the central nervous system provides a novel opportunity to specifically control opioid-induced constipation and other peripheral adverse effects of opioid analgesics. Further studies are needed to evaluate the long-term efficacy, safety and cost-effectiveness of this approach.*

Holtzer P Curr Opin Anaesthesiol. 2010 Oct;23(5):616-22.

- Indikationer
- **Svår smärta där endast er erbjuder tillräcklig effekt.**
    - **Andra linjens behandling av svårt till mycket svårt idiopatiskt restless legs syndrom (RLS) när inte haft effekt.**
  - **Med opioidantagonisten naloxon motverkas opioidinducerad förstoppning genom att oxikodons lokala effekt i tarmen blockeras.**
- ***Dosering; Vuxna***
- **Den vanliga startdosen för en patient som inte tidigare har behandlats med er är 10 mg/5 mg oxikodonhydroklorid/naloxonhydroklorid var 12:e timme.**
- ***Verkningsmekanism***
- **Oxikodon och naloxon har en för kappa-, my- och delta-opioidreceptorer i hjärnan, ryggmärgen och perifera organ (t.ex. tarmarna). Oxikodon agerar som en opioidreceptoragonist vid dessa receptorer och binder till de endogena opioidreceptorerna i det . Naloxon är å andra sidan en ren som verkar på alla typer av opioidreceptorer.**
- ***Farmakodynamiska effekter***
- **Till följd av den uttalade första-passage-en, är naloxons vid < 3 %. Av detta skäl är en kliniskt relevant systemisk effekt osannolik.**

Oxycontin

- Indikationer
  - **Långvarig svår opioidkänslig smärta såsom smärta vid cancer.**
  - **Startdos för patienter som icke tidigare fått er är 10-20 mg var 12:e timme, men högre startdos kan krävas beroende på patientens behov av smärtkontroll.**
  - **Oxikodon är ett opioidanalgetikum med kraftig effekt. Oxikodon är en ren utan någon antagonistverkan.**
    - **Dess viktigaste verkan förefaller försiggå genom myopioidreceptorerna men för delta- eller kappaopiodreceptorer har också påvisats. Dess verkan påminner om morfin. Oralt oxikodon är ekvipotent med oralt morfin i förhållandet 1:2. Den analgetiska effekten beror dels på en förändrad smärtupplevelse och dels på en höjning av smärttröskeln. Verkningsmekanismen innefattar -opioidreceptorer för kroppsegna föreningar med opioidliknande aktivitet. Oxikodon utövar sin analgetiska effekt på olika nivåer inom .**

Palexia

- Indikationer
- **Palexia är indicerat för lindring av måttlig till svår smärta hos vuxna där endast opioidanalgetika ger tillräcklig effekt.**
- Dosering
- **Doseringsregimen skall anpassas individuellt med hänsyn till smärtintensiteten, tidigare behandling och möjligheten att övervaka patienten.**
- **Patienten bör starta behandlingen med en enkel av 50 mg tapentadol som filmdragerad tablett var 4:e till 6:e timme.**
  - **Högre startdoser kan vara nödvändiga beroende på smärtintensitet och patientens tidigare smärtlindringsbehov.**
- Farmakodynamik
  - **Tapentadol är ett starkt med μ-agonistopioida och därtill noradrenalinåterupptagshämmande egenskaper. Tapentadol utövar direkt sin analgetiska effekt direkt utan någon farmakologiskt aktiv .**

Pharmacotherapy for the prevention of chronic pain after surgery in adults.

- Cochrane Database Syst Rev. 2013 Jul 24;7:CD008307. Chaparro LE1, Smith SA, Moore RA, Wiffen PJ, Gilron I.
- **BACKGROUND:** Chronic pain can often occur after surgery, substantially impairing patients' health and quality of life. It is caused by complex mechanisms that are not yet well understood. The predictable nature of most surgical procedures has allowed for the conduct of randomized controlled trials of pharmacological interventions aimed at preventing chronic postsurgical pain.
- **OBJECTIVES:** The primary objective was to evaluate the efficacy of systemic drugs for the prevention of chronic pain after surgery by examining the proportion of patients reporting pain three months or more after surgery. The secondary objective was to evaluate the safety of drugs administered for the prevention of chronic pain after surgery.
- **SEARCH METHODS:** We identified randomized controlled trials (RCTs) of various systemically administered drugs for the prevention of chronic pain after surgery from CENTRAL, MEDLINE, EMBASE and handsearches of other reviews and trial registries. The most recent search was performed on 17 July 2013.
- **SELECTION CRITERIA:** Included studies were double-blind, placebo-controlled, randomized trials involving adults and evaluating one or more drugs administered systemically before, during or after surgery, or both, which measured pain three months or more after surgery.
- **DATA COLLECTION AND ANALYSIS:** Data collected from each study included the study drug name, dose, route, timing and duration of dosing; surgical procedure; proportion of patients reporting any pain three months or more after surgery, reporting at least 4/10 or moderate to severe pain three months or more after surgery; and proportion of participants dropping out of the study due to treatment-emergent adverse effects.
- **MAIN RESULTS:** We identified 40 RCTs of various pharmacological interventions including intravenous ketamine (14 RCTs), oral gabapentin (10 RCTs), oral pregabalin (5 RCTs), non-steroidal anti-inflammatories (3 RCTs), intravenous steroids (3 RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3 RCTs), oral mexiletine (2 RCTs), intravenous fentanyl (1 RCT), intravenous lidocaine (1 RCT), oral venlafaxine (1 RCT) and inhaled nitrous oxide (1 RCT). Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is < 100 participants per treatment arm), which could lead to the overestimation of treatment effect.
- **AUTHORS' CONCLUSIONS: Additional evidence from better, well designed, large-scale trials is needed in order to more rigorously evaluate pharmacological interventions for the prevention of chronic pain after surgery. Furthermore, available evidence does not support the efficacy of gabapentin, pregabalin, non-steroidal anti-inflammatories, intravenous steroids, oral NMDA blockers, oral mexiletine, intravenous fentanyl, intravenous lidocaine, oral venlafaxine or inhaled nitrous oxide for the prevention of chronic postoperative pain.**

Reanalysis of morphine consumption from two randomized controlled trials of gabapentin using longitudinal statistical methods.

- J Pain Res. 2015 Feb 9;8:79-85.
- Zhang S1, et al.
- **BACKGROUND:** Postoperative pain management in total joint replacement surgery remains ineffective in up to 50% of patients and has an overwhelming impact in terms of patient well-being and health care burden. We present here an empirical analysis of two randomized controlled trials assessing whether addition of gabapentin to a multimodal perioperative analgesia regimen can reduce morphine consumption or improve analgesia for patients following total joint arthroplasty (the MOBILE trials).
- **METHODS:** Morphine consumption, measured for four time periods in patients undergoing total hip or total knee arthroplasty, was analyzed using a linear mixed-effects model to provide a longitudinal estimate of the treatment effect. Repeated-measures analysis of variance and generalized estimating equations were used in a sensitivity analysis to compare the robustness of the methods.
- **RESULTS:** There was no statistically significant difference in morphine consumption between the treatment group and a control group (mean effect size estimate 1.0, 95% confidence interval -4.7, 6.7, P=0.73). The results remained robust across different longitudinal methods.
- **CONCLUSION: The results of the current reanalysis of morphine consumption align with those of the MOBILE trials. Gabapentin did not significantly reduce morphine consumption in patients undergoing major replacement surgeries. The results remain consistent across longitudinal methods. More work in the area of postoperative pain is required to provide adequate management for this patient population.**

Randomized controlled trial of gabapentin as an adjunct to perioperative analgesia in total hip arthroplasty patients.

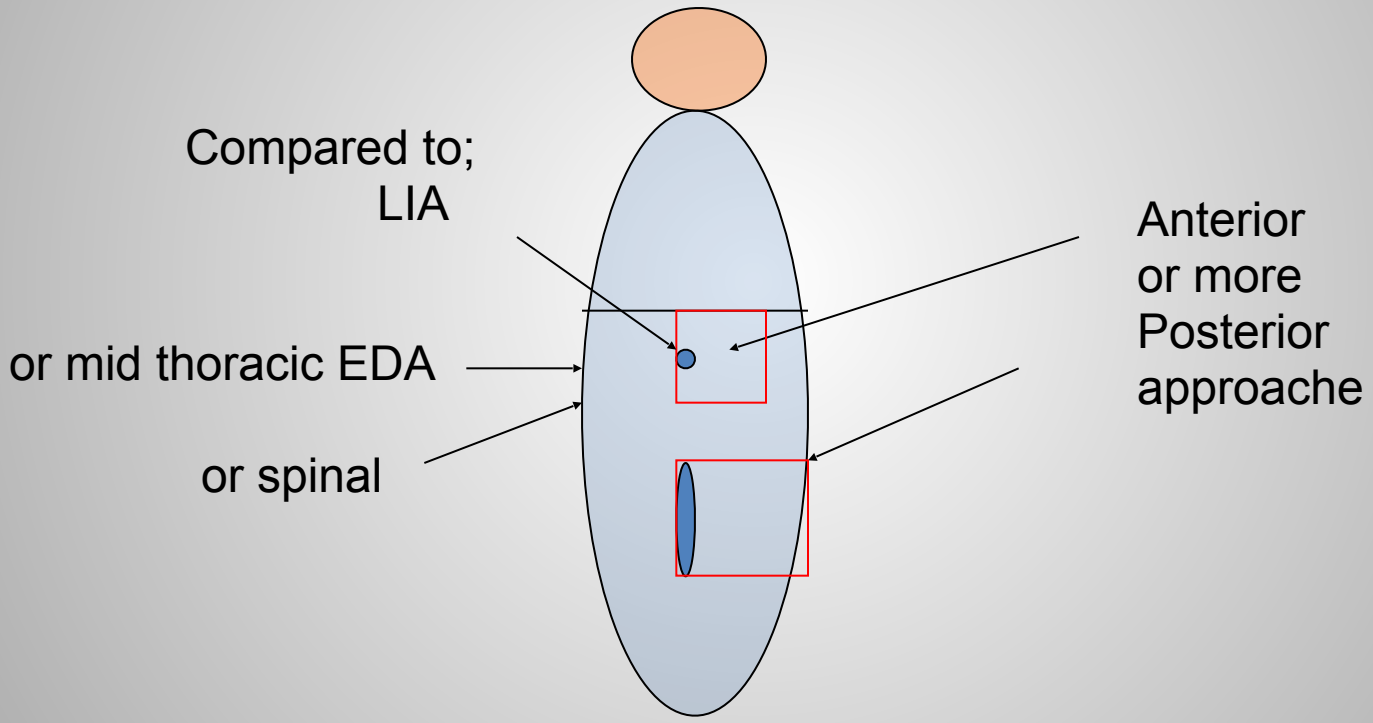
- Paul JE1, et al Can J Anaesth. 2015 May;62(5):476-484.
- **PURPOSE:** Gabapentin was investigated as a single-dose adjunct to morphine for postoperative pain management. The primary objective was to determine if gabapentin given preoperatively and for two days postoperatively as part of multimodal analgesia would decrease postoperative morphine consumption in patients undergoing primary total hip arthroplasty (THA).
- **METHODS:** The study group included 102 patients aged 19-90 years who were undergoing primary THA in a single joint with no contraindications to the study medications, no chronic pain syndrome, and no chronic opioid use. **Intervention group patients (n = 48) received gabapentin 600 mg po preoperatively and 200 mg postoperatively on the day of surgery. They were continued on gabapentin at 200 mg three times daily for two days. Control group patients (n = 54) received placebo** in a similar fashion. Preoperatively, all patients were given 30 mg of ketorolac intravenously and acetaminophen 1000 mg po. Postoperatively, they received intravenous patient-controlled analgesia with morphine, along with ketorolac 15 mg iv and acetaminophen 1000 mg po every six hours.
- **RESULTS:** The primary outcome was mean (SD) postoperative morphine consumption at 72 hr which was 55.8 (39.2) mg in the gabapentin groups vs 60.7 (37.2) mg for the control group (mean difference, -4.91 mg, 95% confidence intervals [CI]: -21.2 to 11.35; P = 0.550). There were no significant differences between the groups regarding secondary outcomes: pain scores, side effects, range of motion. Patient satisfaction on day 3 was more favourable in the placebo group. Length of hospitalization was marginally shorter in the placebo group.
- **CONCLUSIONS: This trial indicated that gabapentin treatment had no clinically important reduction in postoperative morphine consumption at 72 hr in patients undergoing THA. Multimodal analgesia may account for the similar primary and secondary outcomes found in the groups.**

Perifera blockader

Ultraljudsledda blockader

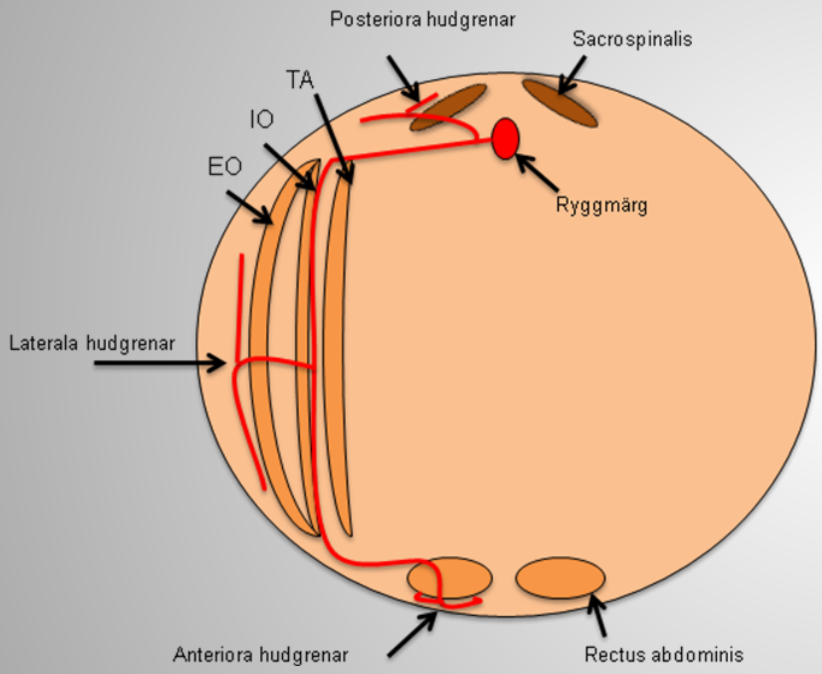
- Upper extremity
  - Plexus blocks
- Abdominal surgery
  - TAP blocks
- Lower extremity
  - Peripheral blocks

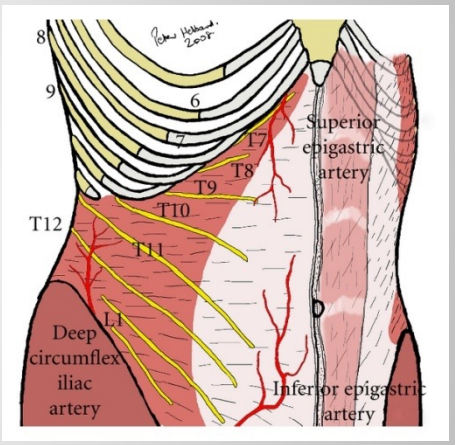
Tap technique and surgical stress



Surgical trauma minimal invasive or open surgery

TAP

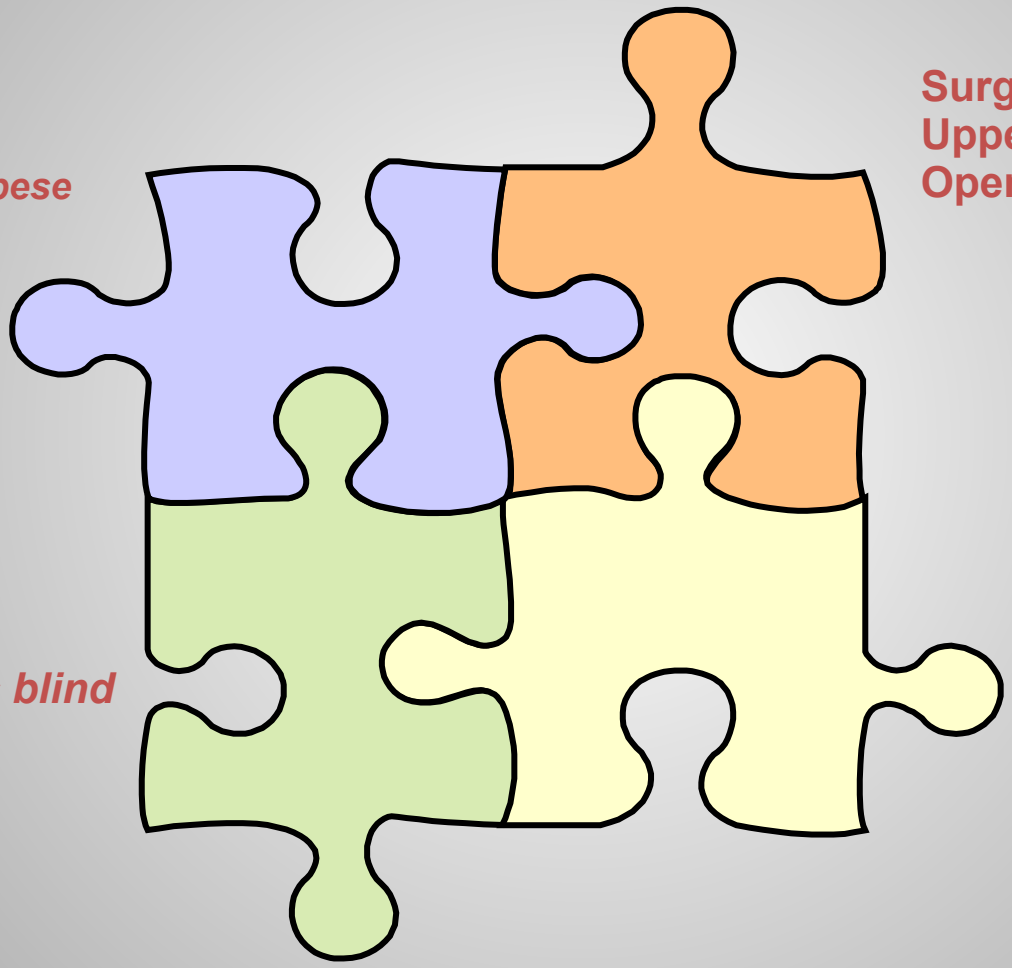

Posteriora hudgrenar
Sacrospinalis
TA
IO
EO
Ryggmärg
Laterala hudgrenar
Anteriora hudgrenar
Rectus abdominis


8
9
6
7
T7
T8
T9
T10
T11
T12
L1
Superior epigastric artery
Deep circumflex iliac artery
Inferior epigastric artery

The TAP efficacy puzzle

Patient
Lean vs obese

Surgery
Upper vs. lower
Open vs. minamal invasive.



Technique
Ultra Sound vs blind
Ant vs post

Pain management
Comparator;
LIA
Spinal
Epidural
…

Transversus abdominis-plane block versus local anesthetic wound infiltration in lower abdominal surgery: a systematic review and meta-analysis of randomized controlled trials.

- BMC Anesthesiol. 2014 Dec 15;14:121. doi: 10.1186/1471-2253-14-121. eCollection 2014.

- Yu N1, Long X1, Lujan-Hernandez JR2, Succar J3, Xin X4, Wang X1.

- **BACKGROUND:** Postoperative pain management is of great importance in perioperative anesthetic care. Transversus abdominis plane (TAP) block has been described as an effective technique to reduce postoperative pain and morphine consumption after open lower abdominal operations. Meanwhile, local anesthetic infiltration (LAI) is also commonly used as a traditional method. However, the effectiveness of these two methods has not been compared before.
- **METHODS:** A meta-analysis of all relevant randomized controlled trials (RCTs) was conducted to compare the efficacy of single shot TAP block with that of single shot LAI for postoperative analgesia in adults. Major medical databases and trial registries were searched for published and unpublished RCTs. The endpoints include postoperative visual analog scale (VAS) pain score, morphine requirement, and rate of postoperative nausea and vomiting (PONV). For continuous data, weighted mean differences (WMDs) were formulated; for dichotomous data, risk ratios (RR) were calculated. Results were derived using a random-/fixed-effects model with 95% confidence interval (CI).
- **RESULTS:** Four RCTs, encompassing 96 TAP-block and 100 LAI patients, were included in the final analysis. Patients in the TAP-block group had lower VAS pain scores 24 hours postoperatively compared with the LAI group, both at rest (WMD [95% CI] = -0.67 [$p < 0.01$] and with movement (WMD = -0.89, $p < 0.01$). There were no significant between-group differences in 24-hour postoperative morphine requirements, the rates if PONV or VAS pain scores at 2 and 4 h postoperatively.
- **CONCLUSION: TAP block and LAI provide comparable short-term postoperative analgesia, but TAP block has better long-lasting effect.**

Peripheral nerve blocks for postoperative pain after major knee surgery.

Cochrane Database Syst Rev. 2014;12:CD010937.

- Xu J1, Chen XM, Ma CK, Wang XR.
- **BACKGROUND:**

Major knee surgery is a common operative procedure to help people with end-stage knee disease or trauma to regain mobility and have improved quality of life. Poorly controlled pain immediately after surgery is still a key issue for this procedure. Peripheral nerve blocks are localized and site-specific analgesic options for major knee surgery. The increasing use of peripheral nerve blocks following major knee surgery requires the synthesis of evidence to evaluate its effectiveness and safety, when compared with systemic, local infiltration, epidural and spinal analgesia.

OBJECTIVES:

To examine the efficacy and safety of peripheral nerve blocks for postoperative pain control following major knee surgery using methods that permit comparison with systemic, local infiltration, epidural and spinal analgesia.

SEARCH METHODS:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2014), MEDLINE and EMBASE, from their inception to February 2014. We identified ongoing studies by searching trial registries, including the metaRegister of controlled trials (mRCT), clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

SELECTION CRITERIA:

We included participant-blind, randomized controlled trials of adult participants (15 years or older) undergoing major knee surgery, in which peripheral nerve blocks were compared to systemic, local infiltration, epidural and spinal analgesia for postoperative pain relief.

DATA COLLECTION AND ANALYSIS:

Two review authors independently assessed study eligibility and extracted data. We recorded information on participants, methods, interventions, outcomes (pain intensity, additional analgesic consumption, adverse events, knee range of motion, length of hospital stay, hospital costs, and participant satisfaction). We used the 5-point Oxford quality and validity scale to assess methodological quality, as well as criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We conducted meta-analysis of two or more studies with sufficient data to investigate the same outcome. We used the I^2 statistic to explore the heterogeneity. If there was no significant heterogeneity (I^2 value 0% to 40%), we used a fixed-effect model for meta-analysis, but otherwise we used a random-effects model. For dichotomous data, we present results as a summary risk ratio (RR) and a 95% confidence interval (95% CI). Where possible, we calculated the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH), together with 95% CIs. For continuous data, we used the mean difference (MD) and 95% CI for similar outcome measures. We describe the findings of individual studies where pooling of data was not possible.

MAIN RESULTS:

According to the eligibility criteria, we include 23 studies with 1571 participants, with high methodological quality overall. The studies compared peripheral nerve blocks adjunctive to systemic analgesia with systemic analgesia alone (19 studies), peripheral nerve blocks with local infiltration (three studies), and peripheral nerve blocks with epidural analgesia (one study). No study compared peripheral nerve blocks with spinal analgesia.Compared with systemic analgesia alone, peripheral nerve blocks adjunctive to systemic analgesia resulted in a significantly lower pain intensity score at rest, using a 100 mm visual analogue scale, at all time periods within 72 hours postoperatively, including the zero to 23 hours interval (MD -11.85, 95% CI -20.45 to -3.25, seven studies, 390 participants), the 24 to 47 hours interval (MD -12.92, 95% CI -19.82 to -6.02, six studies, 320 participants) and the 48 to 72 hours interval (MD -9.72, 95% CI -16.75 to -2.70, four studies, 210 participants). Subgroup analyses suggested that the high levels of statistical variation in our analyses could be explained by larger effects in people undergoing total knee arthroplasty compared with other types of surgery. Pain intensity was also significantly reduced on movement in the 48 to 72 hours interval postoperatively (MD -6.19, 95% CI -11.76 to -0.62, two studies, 112 participants). There was no significant difference on movement between these two groups in the time period of zero to 23 hours (MD -6.95, 95% CI -15.92 to 2.01, five studies, 304 participants) and 24 to 47 hours (MD -8.87, 95% CI -27.77 to 10.03, three studies, 182 participants). The included studies reported diverse types of adverse events, and we did not conduct a meta-analysis on specific types of adverse event. The numbers of studies and participants were also too few to draw conclusions on the other prespecified outcomes of: additional analgesic consumption; median time to remedication; knee range of motion; median time to ambulation; length of hospital stay; hospital costs; and participant satisfaction. There were insufficient data to compare peripheral nerve blocks and local infiltration or between peripheral nerve blocks and epidural analgesia.

- **AUTHORS' CONCLUSIONS:**
  - All of the included studies reported the main outcome of pain intensity but did not cover all the secondary outcomes of interest.
- **The current review provides evidence that the use of peripheral nerve blocks as adjunctive techniques to systemic analgesia reduced pain intensity when compared with systemic analgesia alone after major knee surgery.**
- **There were too few data to draw conclusions on other outcomes of interest. More trials are needed to demonstrate a significant difference when compared with local infiltration, epidural analgesia and spinal analgesia.**

Pharmacotherapy for the prevention of chronic pain after surgery in adults.

- Cochrane Database Syst Rev. 2013 Jul 24;7:CD008307. Chaparro LE1, Smith SA, Moore RA, Wiffen PJ, Gilron I.
- **BACKGROUND:** Chronic pain can often occur after surgery, substantially impairing patients' health and quality of life. It is caused by complex mechanisms that are not yet well understood. The predictable nature of most surgical procedures has allowed for the conduct of randomized controlled trials of pharmacological interventions aimed at preventing chronic postsurgical pain.
- **OBJECTIVES:** The primary objective was to evaluate the efficacy of systemic drugs for the prevention of chronic pain after surgery by examining the proportion of patients reporting pain three months or more after surgery. The secondary objective was to evaluate the safety of drugs administered for the prevention of chronic pain after surgery.
- **SEARCH METHODS:** We identified randomized controlled trials (RCTs) of various systemically administered drugs for the prevention of chronic pain after surgery from CENTRAL, MEDLINE, EMBASE and handsearches of other reviews and trial registries. The most recent search was performed on 17 July 2013.
- **SELECTION CRITERIA:** Included studies were double-blind, placebo-controlled, randomized trials involving adults and evaluating one or more drugs administered systemically before, during or after surgery, or both, which measured pain three months or more after surgery.
- **DATA COLLECTION AND ANALYSIS:** Data collected from each study included the study drug name, dose, route, timing and duration of dosing; surgical procedure; proportion of patients reporting any pain three months or more after surgery, reporting at least 4/10 or moderate to severe pain three months or more after surgery; and proportion of participants dropping out of the study due to treatment-emergent adverse effects.
- **MAIN RESULTS:** We identified 40 RCTs of various pharmacological interventions including intravenous ketamine (14 RCTs), oral gabapentin (10 RCTs), oral pregabalin (5 RCTs), non-steroidal anti-inflammatories (3 RCTs), intravenous steroids (3 RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3 RCTs), oral mexiletine (2 RCTs), intravenous fentanyl (1 RCT), intravenous lidocaine (1 RCT), oral venlafaxine (1 RCT) and inhaled nitrous oxide (1 RCT). Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is < 100 participants per treatment arm), which could lead to the overestimation of treatment effect.
- **AUTHORS' CONCLUSIONS: Additional evidence from better, well designed, large-scale trials is needed in order to more rigorously evaluate pharmacological interventions for the prevention of chronic pain after surgery. Furthermore, available evidence does not support the efficacy of gabapentin, pregabalin, non-steroidal anti-inflammatories, intravenous steroids, oral NMDA blockers, oral mexiletine, intravenous fentanyl, intravenous lidocaine, oral venlafaxine or inhaled nitrous oxide for the prevention of chronic postoperative pain.**

Reanalysis of morphine consumption from two randomized controlled trials of gabapentin using longitudinal statistical methods.

- J Pain Res. 2015 Feb 9;8:79-85.
- Zhang S1, et al.
- **BACKGROUND:** Postoperative pain management in total joint replacement surgery remains ineffective in up to 50% of patients and has an overwhelming impact in terms of patient well-being and health care burden. We present here an empirical analysis of two randomized controlled trials assessing whether addition of gabapentin to a multimodal perioperative analgesia regimen can reduce morphine consumption or improve analgesia for patients following total joint arthroplasty (the MOBILE trials).
- **METHODS:** Morphine consumption, measured for four time periods in patients undergoing total hip or total knee arthroplasty, was analyzed using a linear mixed-effects model to provide a longitudinal estimate of the treatment effect. Repeated-measures analysis of variance and generalized estimating equations were used in a sensitivity analysis to compare the robustness of the methods.
- **RESULTS:** There was no statistically significant difference in morphine consumption between the treatment group and a control group (mean effect size estimate 1.0, 95% confidence interval -4.7, 6.7, P=0.73). The results remained robust across different longitudinal methods.
- **CONCLUSION: The results of the current reanalysis of morphine consumption align with those of the MOBILE trials. Gabapentin did not significantly reduce morphine consumption in patients undergoing major replacement surgeries. The results remain consistent across longitudinal methods. More work in the area of postoperative pain is required to provide adequate management for this patient population.**

Randomized controlled trial of gabapentin as an adjunct to perioperative analgesia in total hip arthroplasty patients.

- Paul JE1, et al Can J Anaesth. 2015 May;62(5):476-484.
- **PURPOSE:** Gabapentin was investigated as a single-dose adjunct to morphine for postoperative pain management. The primary objective was to determine if gabapentin given preoperatively and for two days postoperatively as part of multimodal analgesia would decrease postoperative morphine consumption in patients undergoing primary total hip arthroplasty (THA).
- **METHODS:** The study group included 102 patients aged 19-90 years who were undergoing primary THA in a single joint with no contraindications to the study medications, no chronic pain syndrome, and no chronic opioid use. **Intervention group patients (n = 48) received gabapentin 600 mg po preoperatively and 200 mg postoperatively on the day of surgery. They were continued on gabapentin at 200 mg three times daily for two days. Control group patients (n = 54) received placebo** in a similar fashion. Preoperatively, all patients were given 30 mg of ketorolac intravenously and acetaminophen 1000 mg po. Postoperatively, they received intravenous patient-controlled analgesia with morphine, along with ketorolac 15 mg iv and acetaminophen 1000 mg po every six hours.
- **RESULTS:** The primary outcome was mean (SD) postoperative morphine consumption at 72 hr which was 55.8 (39.2) mg in the gabapentin groups vs 60.7 (37.2) mg for the control group (mean difference, -4.91 mg, 95% confidence intervals [CI]: -21.2 to 11.35; P = 0.550). There were no significant differences between the groups regarding secondary outcomes: pain scores, side effects, range of motion. Patient satisfaction on day 3 was more favourable in the placebo group. Length of hospitalization was marginally shorter in the placebo group.
- **CONCLUSIONS: This trial indicated that gabapentin treatment had no clinically important reduction in postoperative morphine consumption at 72 hr in patients undergoing THA. Multimodal analgesia may account for the similar primary and secondary outcomes found in the groups.**

Peripheral nerve blocks for postoperative pain after major knee surgery.

Cochrane Database Syst Rev. 2014;12:CD010937.

Xu J1, Chen XM, Ma CK, Wang XR.

BACKGROUND:

Major knee surgery is a common operative procedure to help people with end-stage knee disease or trauma to regain mobility and have improved quality of life. Poorly controlled pain immediately after surgery is still a key issue for this procedure. Peripheral nerve blocks are localized and site-specific analgesic options for major knee surgery. The increasing use of peripheral nerve blocks following major knee surgery requires the synthesis of evidence to evaluate its effectiveness and safety, when compared with systemic, local infiltration, epidural and spinal analgesia.

OBJECTIVES:

To examine the efficacy and safety of peripheral nerve blocks for postoperative pain control following major knee surgery using methods that permit comparison with systemic, local infiltration, epidural and spinal analgesia.

SEARCH METHODS:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2014), MEDLINE and EMBASE, from their inception to February 2014. We identified ongoing studies by searching trial registries, including the metaRegister of controlled trials (mRCT), clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

SELECTION CRITERIA:

We included participant-blind, randomized controlled trials of adult participants (15 years or older) undergoing major knee surgery, in which peripheral nerve blocks were compared to systemic, local infiltration, epidural and spinal analgesia for postoperative pain relief.

DATA COLLECTION AND ANALYSIS:

Two review authors independently assessed study eligibility and extracted data. We recorded information on participants, methods, interventions, outcomes (pain intensity, additional analgesic consumption, adverse events, knee range of motion, length of hospital stay, hospital costs, and participant satisfaction). We used the 5-point Oxford quality and validity scale to assess methodological quality, as well as criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We conducted meta-analysis of two or more studies with sufficient data to investigate the same outcome. We used the I^2 statistic to explore the heterogeneity. If there was no significant heterogeneity (I^2 value 0% to 40%), we used a fixed-effect model for meta-analysis, but otherwise we used a random-effects model. For dichotomous data, we present results as a summary risk ratio (RR) and a 95% confidence interval (95% CI). Where possible, we calculated the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH), together with 95% CIs. For continuous data, we used the mean difference (MD) and 95% CI for similar outcome measures. We describe the findings of individual studies where pooling of data was not possible.

MAIN RESULTS:

According to the eligibility criteria, we include 23 studies with 1571 participants, with high methodological quality overall. The studies compared peripheral nerve blocks adjunctive to systemic analgesia with systemic analgesia alone (19 studies), peripheral nerve blocks with local infiltration (three studies), and peripheral nerve blocks with epidural analgesia (one study). No study compared peripheral nerve blocks with spinal analgesia.Compared with systemic analgesia alone, peripheral nerve blocks adjunctive to systemic analgesia resulted in a significantly lower pain intensity score at rest, using a 100 mm visual analogue scale, at all time periods within 72 hours postoperatively, including the zero to 23 hours interval (MD -11.85, 95% CI -20.45 to -3.25, seven studies, 390 participants), the 24 to 47 hours interval (MD -12.92, 95% CI -19.82 to -6.02, six studies, 320 participants) and the 48 to 72 hours interval (MD -9.72, 95% CI -16.75 to -2.70, four studies, 210 participants). Subgroup analyses suggested that the high levels of statistical variation in our analyses could be explained by larger effects in people undergoing total knee arthroplasty compared with other types of surgery. Pain intensity was also significantly reduced on movement in the 48 to 72 hours interval postoperatively (MD -6.19, 95% CI -11.76 to -0.62, two studies, 112 participants). There was no significant difference on movement between these two groups in the time period of zero to 23 hours (MD -6.95, 95% CI -15.92 to 2.01, five studies, 304 participants) and 24 to 47 hours (MD -8.87, 95% CI -27.77 to 10.03, three studies, 182 participants). The included studies reported diverse types of adverse events, and we did not conduct a meta-analysis on specific types of adverse event. The numbers of studies and participants were also too few to draw conclusions on the other prespecified outcomes of: additional analgesic consumption; median time to remedication; knee range of motion; median time to ambulation; length of hospital stay; hospital costs; and participant satisfaction. There were insufficient data to compare peripheral nerve blocks and local infiltration or between peripheral nerve blocks and epidural analgesia.

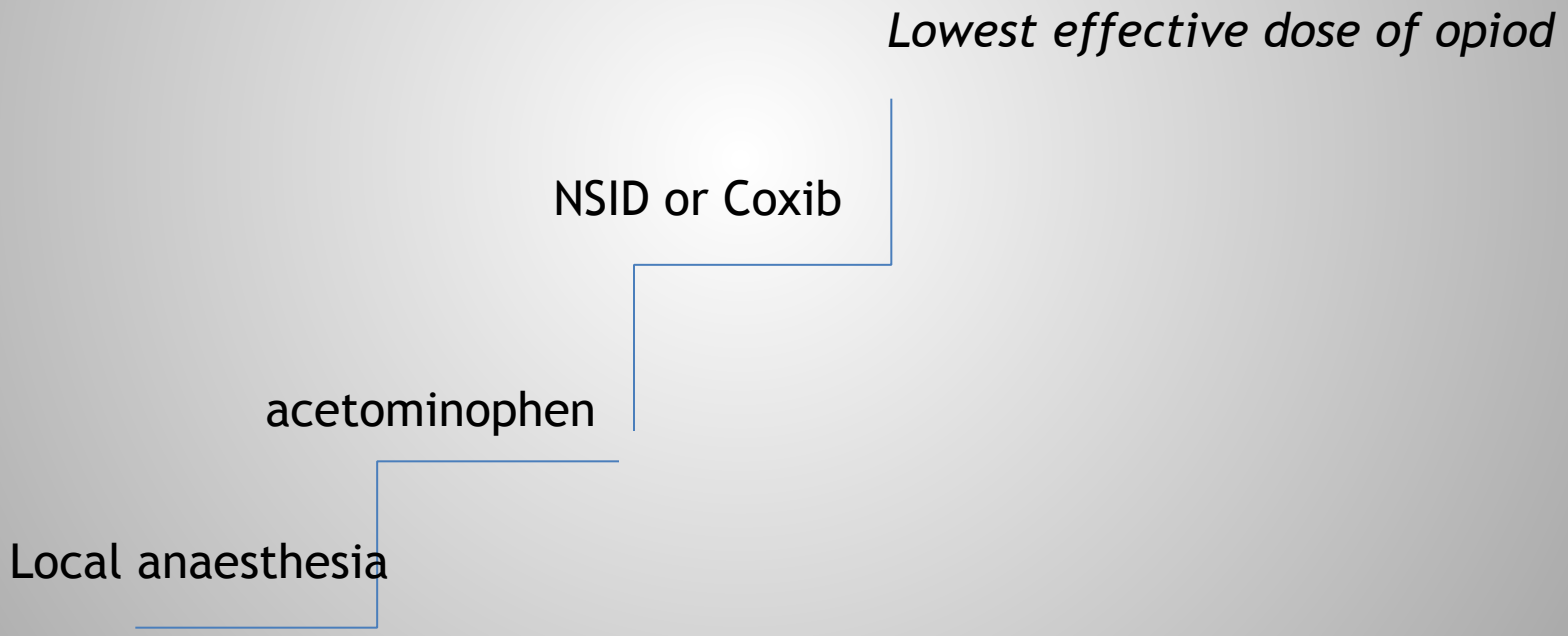
AUTHORS' CONCLUSIONS:

- All of the included studies reported the main outcome of pain intensity but did not cover all the secondary outcomes of interest.

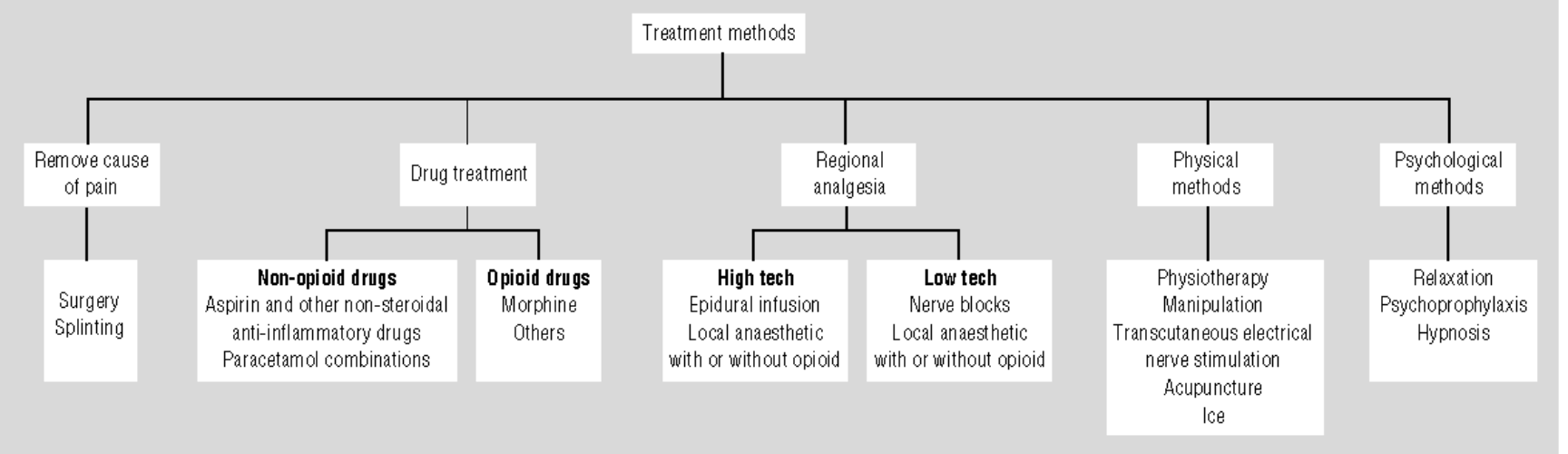
The current review provides evidence that the use of peripheral nerve blocks as adjunctive techniques to systemic analgesia reduced pain intensity when compared with systemic analgesia alone after major knee surgery.

There were too few data to draw conclusions on other outcomes of interest. More trials are needed to demonstrate a significant difference when compared with local infiltration, epidural analgesia and spinal analgesia.

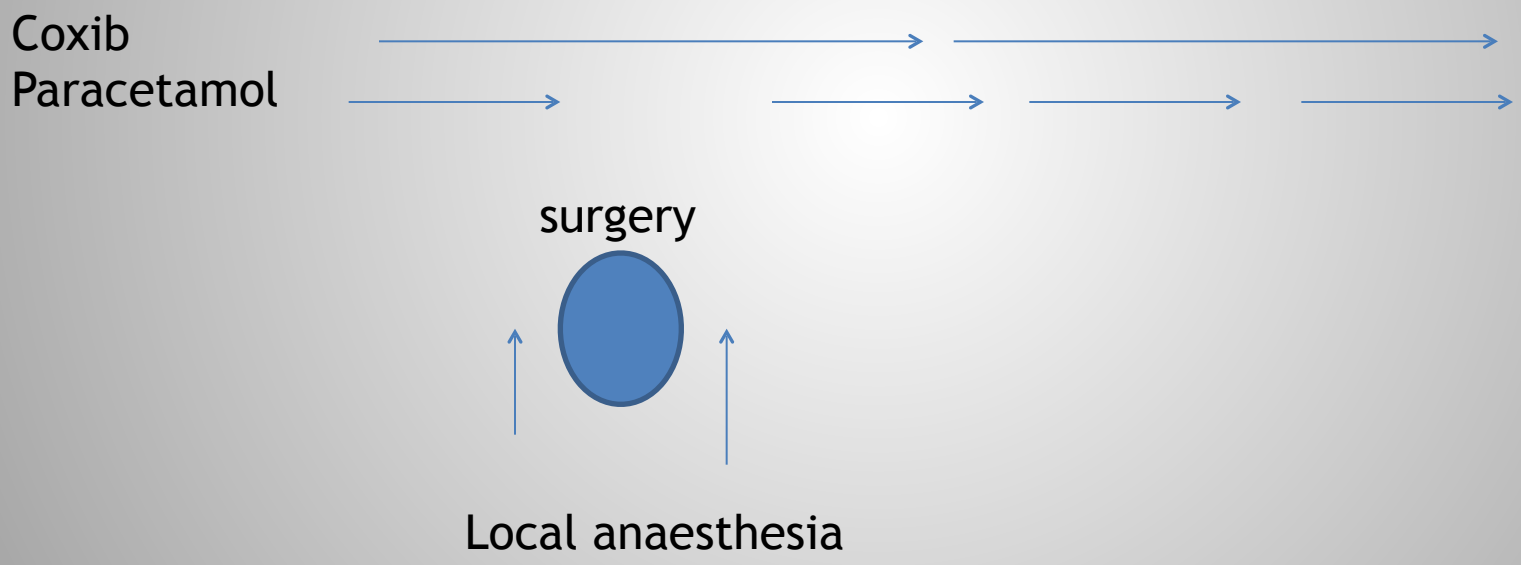
The basic analgesic ladder



Kombination för att ge en bra behandling



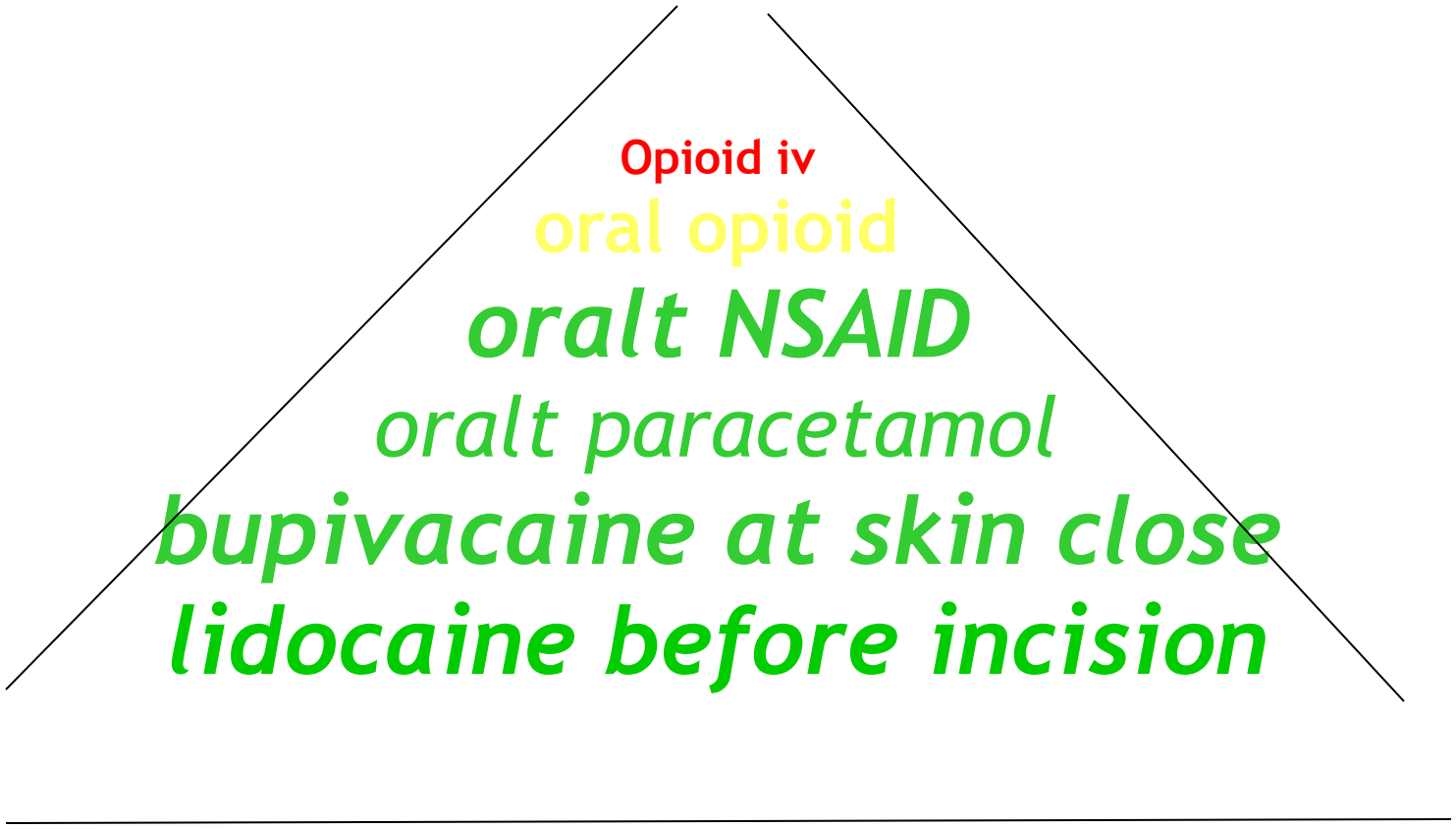
Cover the surgical trauma



VAS < 4 med så lite opiat som möjligt,

En opiatsparande multimodal smärtbehandling

Att hantera smärta vid op

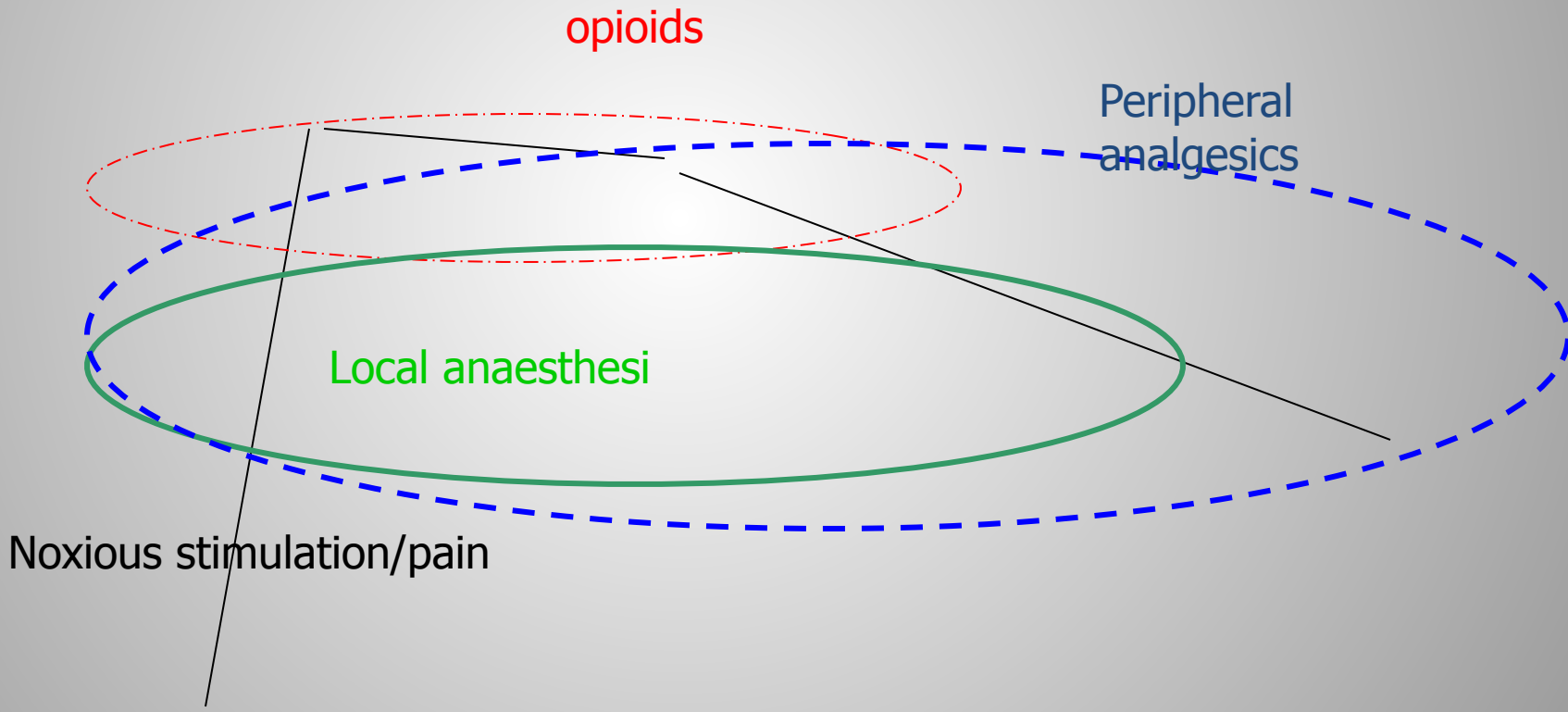


…alltid lokalbedövning

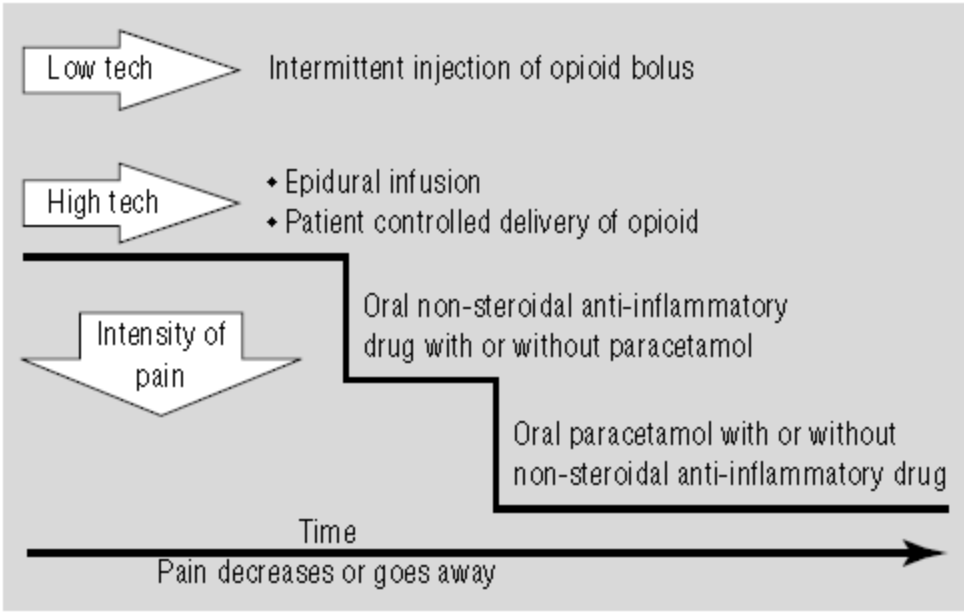
Table 2 Indications for, advantages of, and problems with different types of regional analgesia

	Indications	Advantages	Problems
Low tech			
Topical agents	Surface surgery	Simple	Short duration
Wound infiltration	Most wounds	Simple	Short duration
Peripheral nerve blocks	Surgery to arms and legs; trauma	Catheter may be used	
Plexus blocks	Surgery to arms and legs	Catheter may be used	Nerve damage and motor block
High tech			
Epidural (including caudal)	Major surgery (thoracoabdominal, legs)	Catheter may be used; risk of thromboembolism is reduced	Surveillance of adverse effects
Intrathecal infusion	Major surgery (thoracoabdominal, legs)	Long duration relief is possible from single injection of low dose opioid	Surveillance of adverse effects

Multimodal smärthantering



..behandla efter behov



Balanced analgesia improves recovery and outcome after outpatient tubal ligation

H. Eriksson, A. Tenhunen and K. Korttila
Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland

Outpatient surgery benefits patients only if postoperative sequelae are effectively treated. After laparoscopic tubal ligation (TL) intense pain and consequent postoperative nausea and vomiting (PONV) has been a problem delaying recovery and resulting in hospital admission.

Ninety patients were randomised to this double-blind study, the aim being to evaluate the effect of balanced analgesia on postoperative pain and recovery after sterilization. The balanced analgesia group received 5 ml of 2% lidocaine gel on the sterilization clips and perioperatively 200 mg of ketoprofen i.v. The lidocaine group received 5 ml of 2% lidocaine gel on the clips and placebo i.v. perioperatively. The placebo group received 5 ml of placebo gel on the clips and placebo i.v. perioperatively. Infusion of propofol and 67% nitrous oxide in oxygen were used for maintenance of anesthesia. Succinylcholine and vecuronium were used for muscle relaxation and 0.1 mg of fentanyl i.v. was given to all patients at induction of anesthesia.

Postoperative pain and analgesic requirements, incidence of PONV and need for antiemetic medication were all significantly lower in the balanced analgesia group. Home readiness was consistently achieved 70–90 min sooner in the balanced analgesia group compared to the other groups ($P<0.01$ between the balanced analgesia and the placebo group), and the patients were able to return to normal activity sooner (cumulatively 93% of the patients in the balanced analgesia group vs. 60% in the other two groups ($P<0.01$ between the balanced analgesia and the other groups) had returned to normal activity on the 2nd postoperative day).

It is concluded that in patients undergoing laparoscopic TL the combination of analgesic regimens with different mechanisms of action offer a simple and efficient way of postoperative pain relief, as well as an improvement of quality (i.e. less PONV) and speed of recovery.

Received 5 June, accepted for publication 23 June 1995

Key words: Balanced analgesia; day surgery; ketoprofen; lidocaine gel; outpatient; recovery; sterilization; tubal ligation.

Preoperative Multimodal Analgesia Facilitates Recovery After Ambulatory Laparoscopic Cholecystectomy

Christina Michaloliakou, MD, MSc, Frances Chung, FRCPC, and Sharad Sharma, FFARSI

Department of Anaesthesia, Toronto Hospital, University of Toronto, Toronto, Ontario, Canada

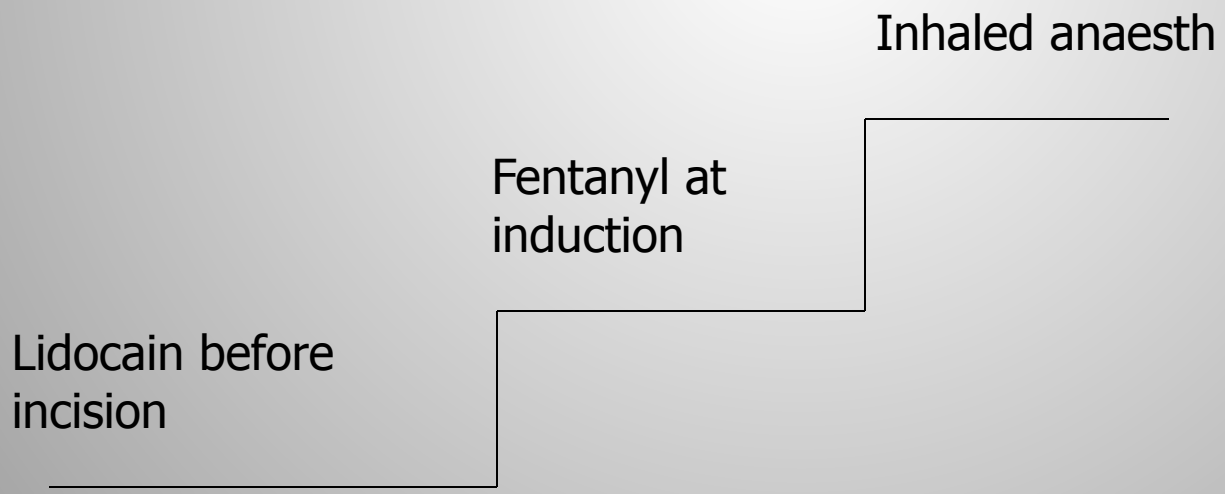
Laparoscopy approach to cholecystectomy has shortened the recovery period, reducing discharge times from 1 to 3 days to same-day discharge. We hypothesize that the use of more than one modality to prevent postoperative pain may be more efficacious than single modality. Patients were randomized to a treatment (n = 24) or control (n = 25) group and studied using a prospective, double-blind design. Preoperatively, at 45 min before induction of anesthesia, the treatment group received an intramuscular (IM) bolus injection of meperidine 0.6 mg/kg and ketorolac 0.5 mg/kg. The control group received two bolus IM injections of placebo (normal saline). Ten minutes before incision, local anesthesia (treatment group) or saline (control group) was infiltrated into the skin of each patient. Anesthetic management, postoperative pain, and nausea treatment were standardized. Pain and nausea assessment were done 1 h preoperatively, 0, 0.5, 1, 2, 3, and 4 h postoperatively, at discharge, and 10, 24, and 48 h postoperatively. Patients were discharged by scoring criteria. Postoperatively, significantly more patients in the treatment group were without pain on arrival in the postanesthesia care unit (PACU), 12/21 (57.1%) vs 1/24 (4.2%) in the control group ($P < 0.001$). Similarly, the severity of pain was sixfold less in the treatment group than in the control group. The incidence of nausea in the PACU was significantly less in the treatment group; 4.7% vs 29.5% in the control group ($P < 0.05$). Patients from the treatment group satisfied Postanesthesia Discharge Score significantly earlier than those in the control group (281 ± 12 min vs 375 ± 19 min; $P < 005$). The concomitant use of local anesthetic and nonsteroidal antiinflammatory and opioid drugs proved to be highly effective in our patients, resulting in faster recovery and discharge.

(Anesth Analg 1996;82:44–51)

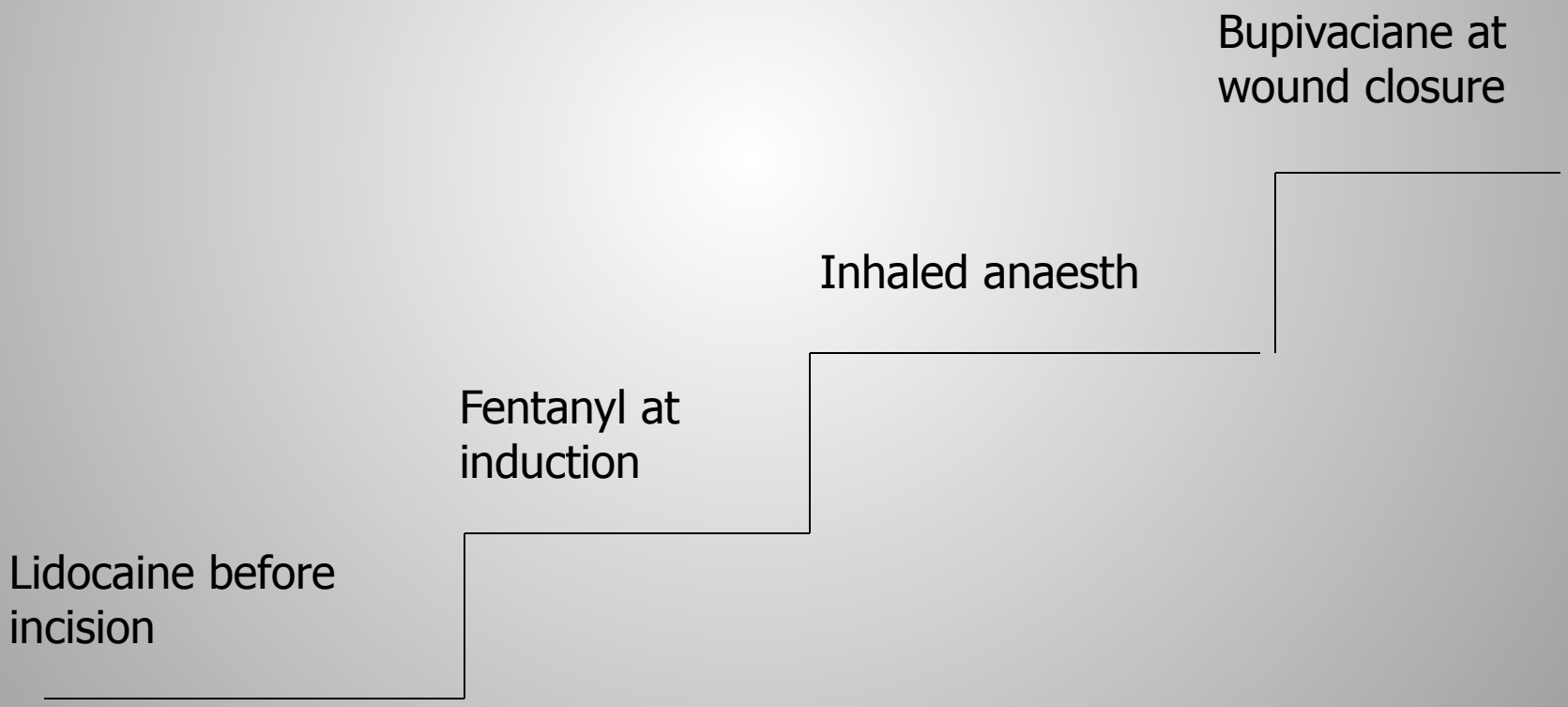
Lidocain before incision

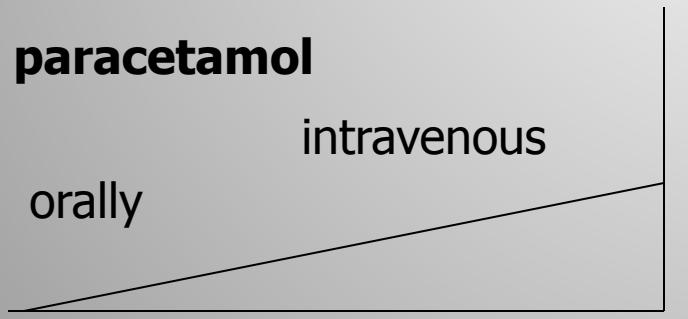
Fentanyl at induction

Lidocain before incision

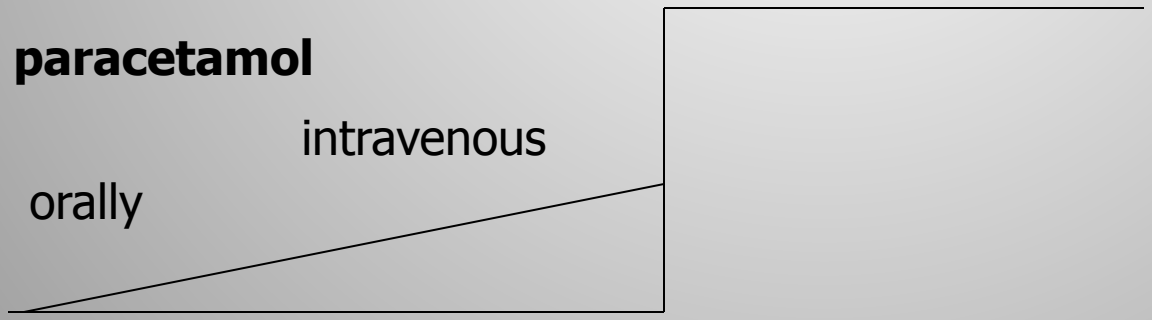

Inhaled anaesth
Fentanyl at induction
Lidocain before incision

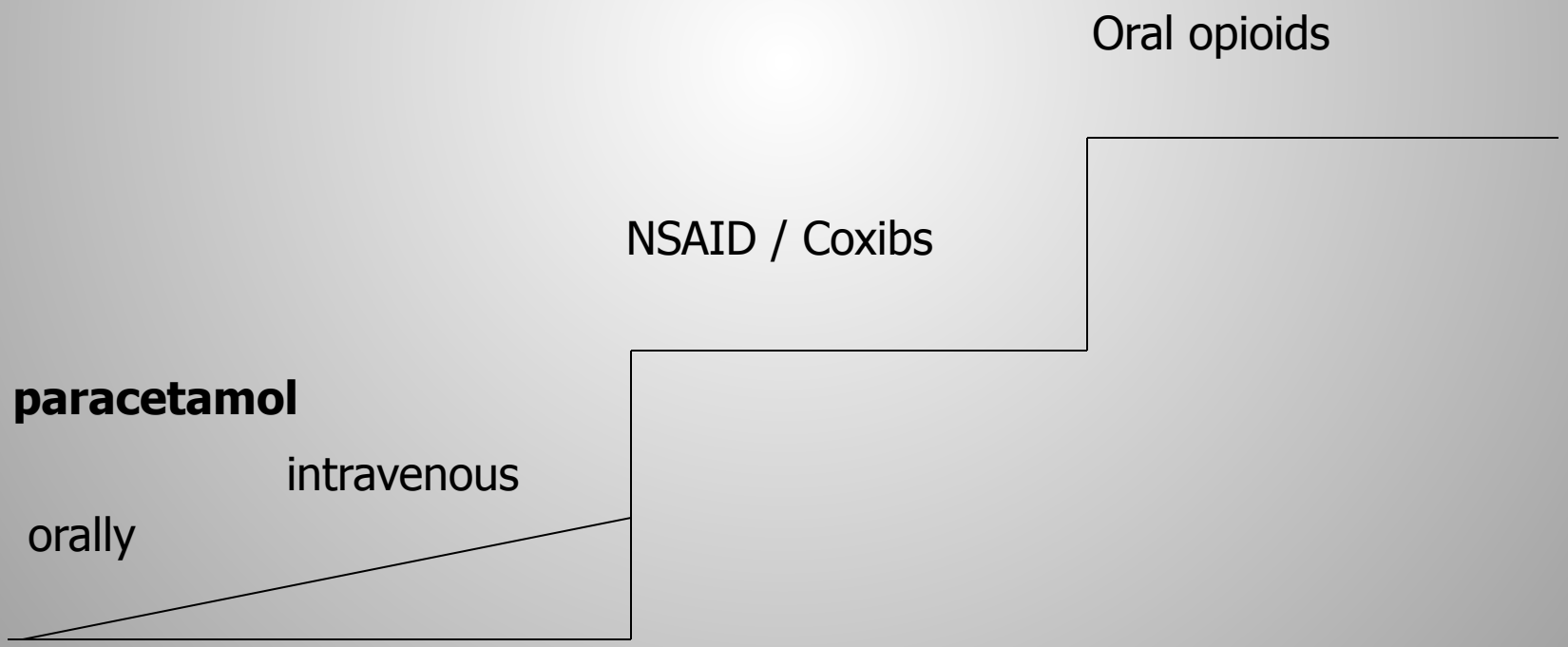
Smärtlindring vid op



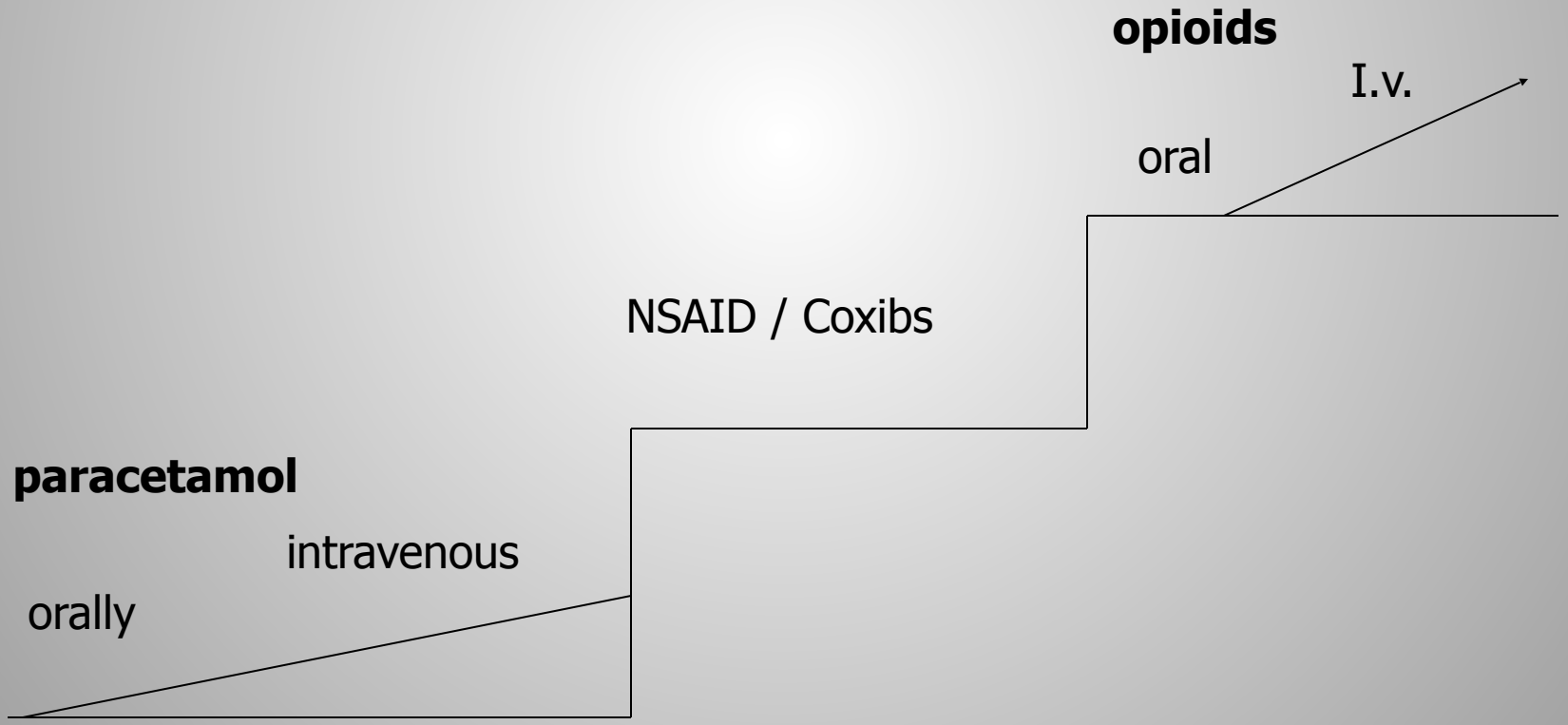

paracetamol
intravenous
orally

NSAID / Coxibs

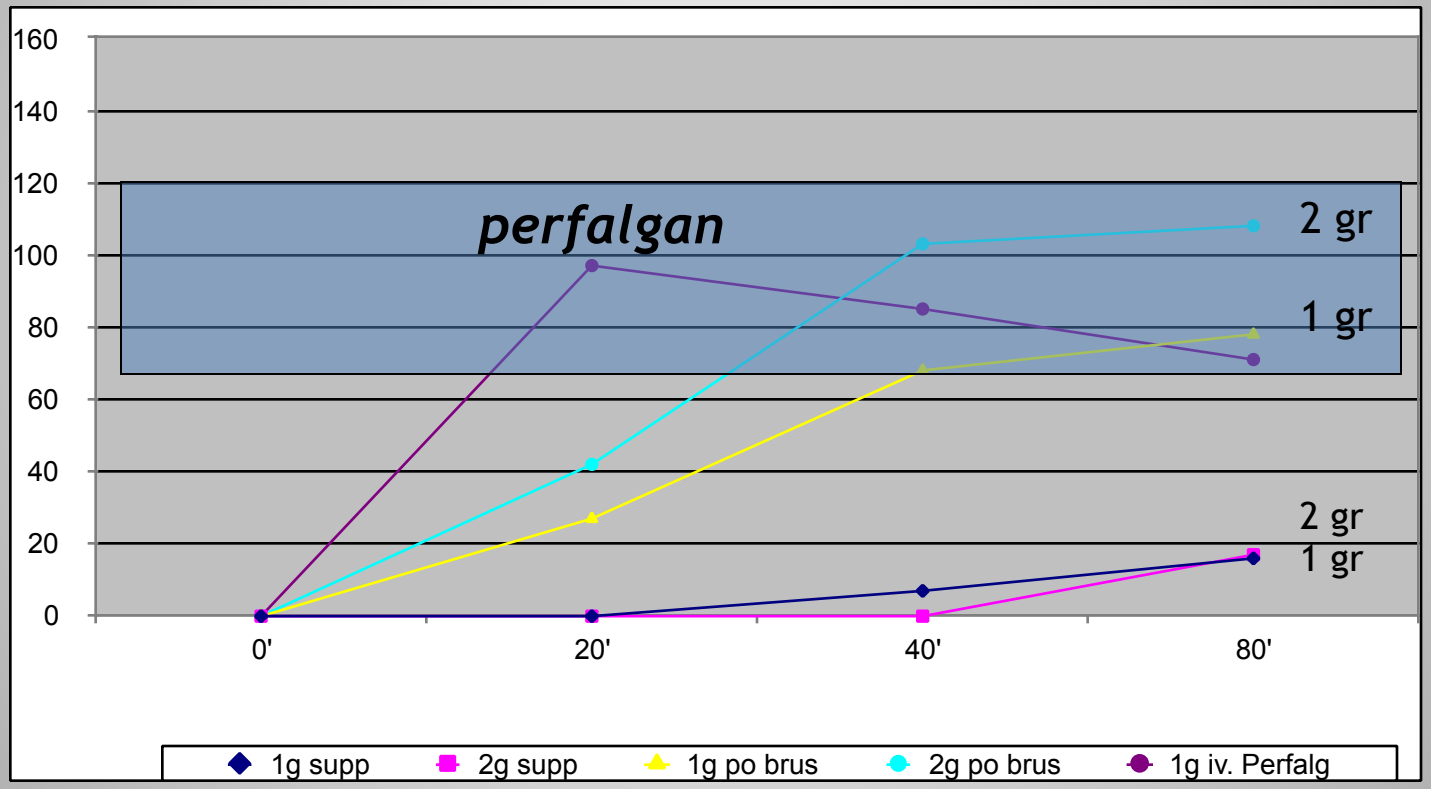



Oral opioids
NSAID / Coxibs
paracetamol
intravenous
orally

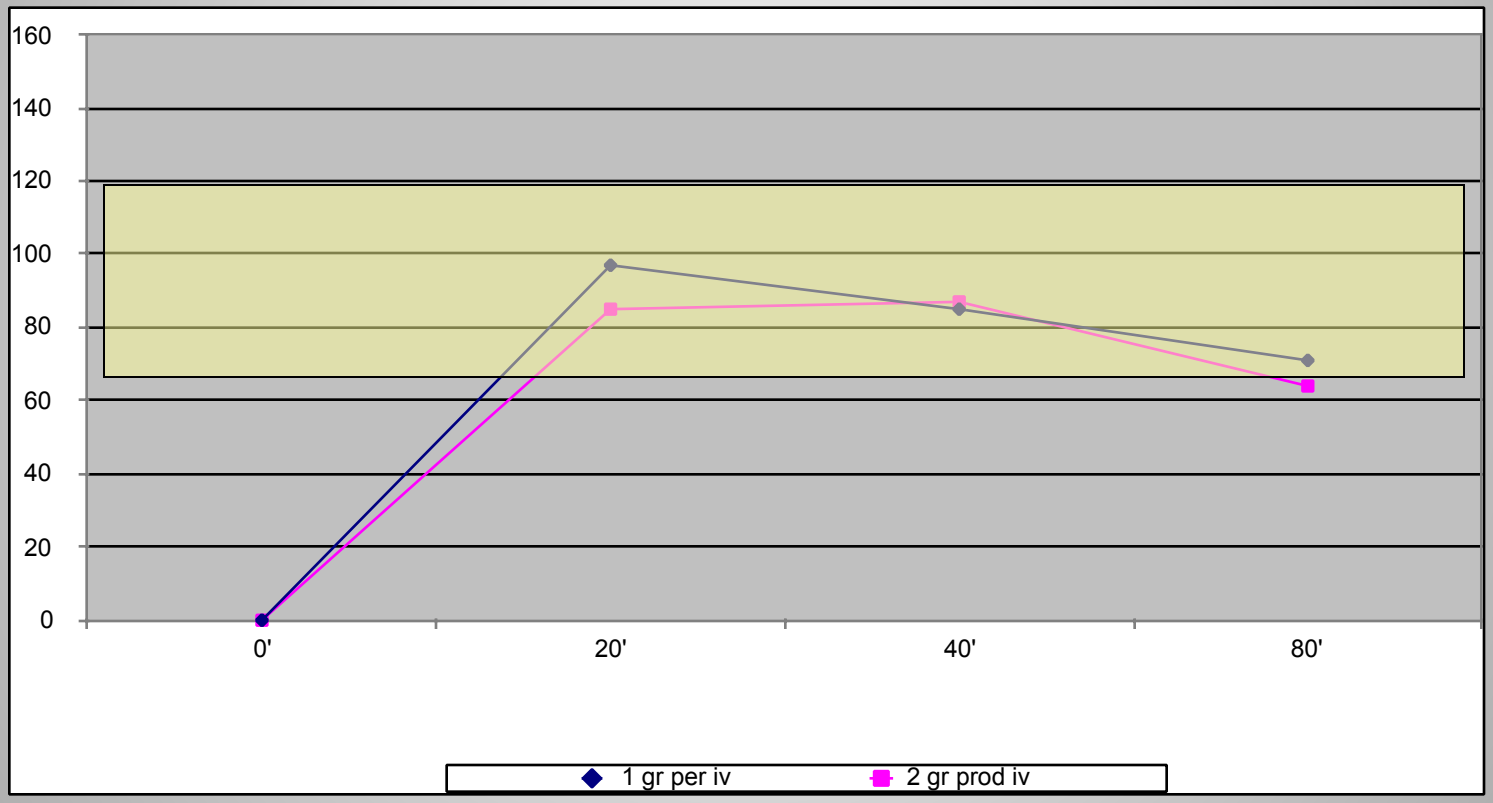
Smärtlindring vid op



Paracetamol, vikten av rätt administationsväg



Prodafalgan vs perfalgan



Therapeutic serum levels,

within 20 minutes

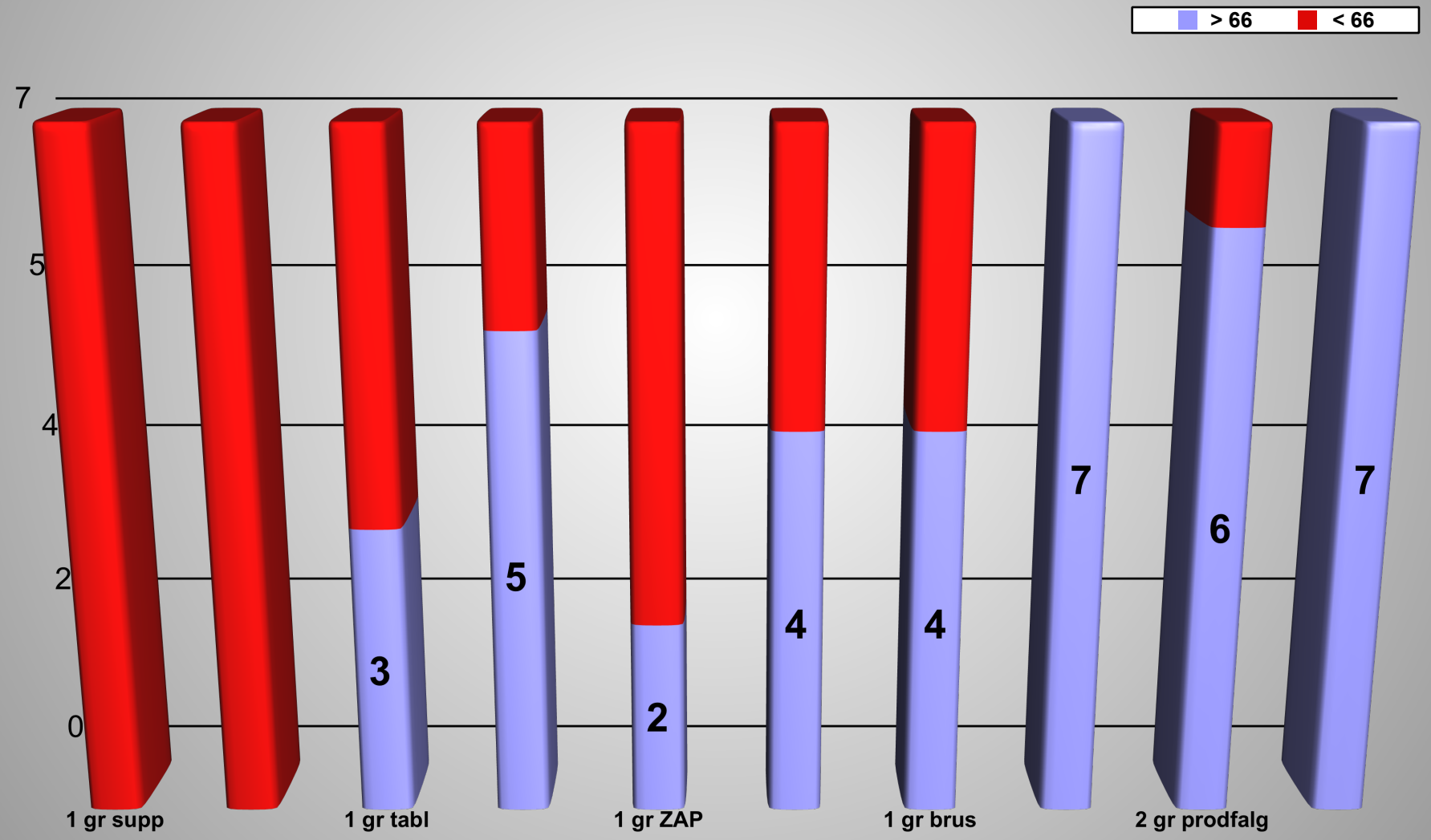
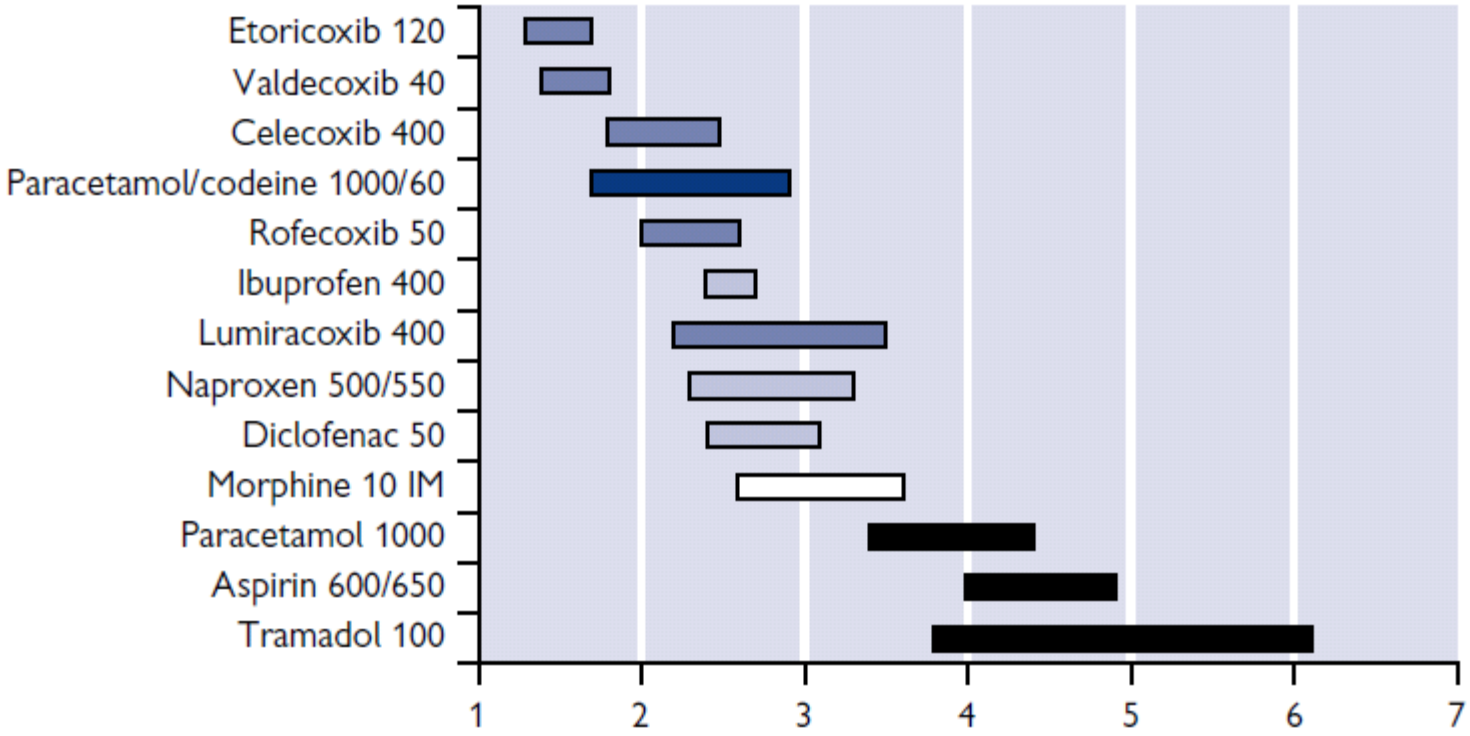


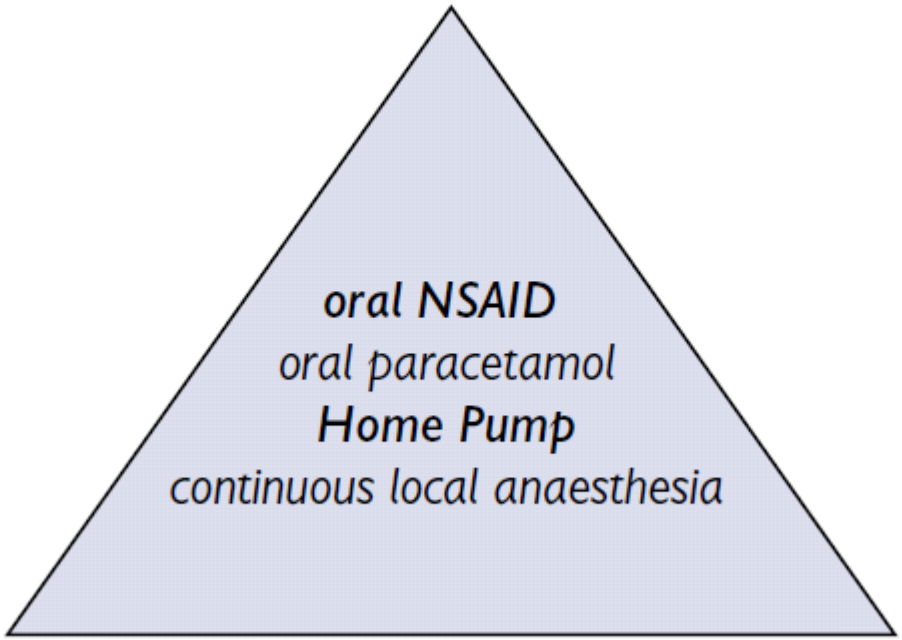
Figure 4.5 2007 league table of number needed to treat (NNT) for at least 50% pain relief over 4–6 hours in patients with moderate to severe pain, all oral analgesics except IM morphine



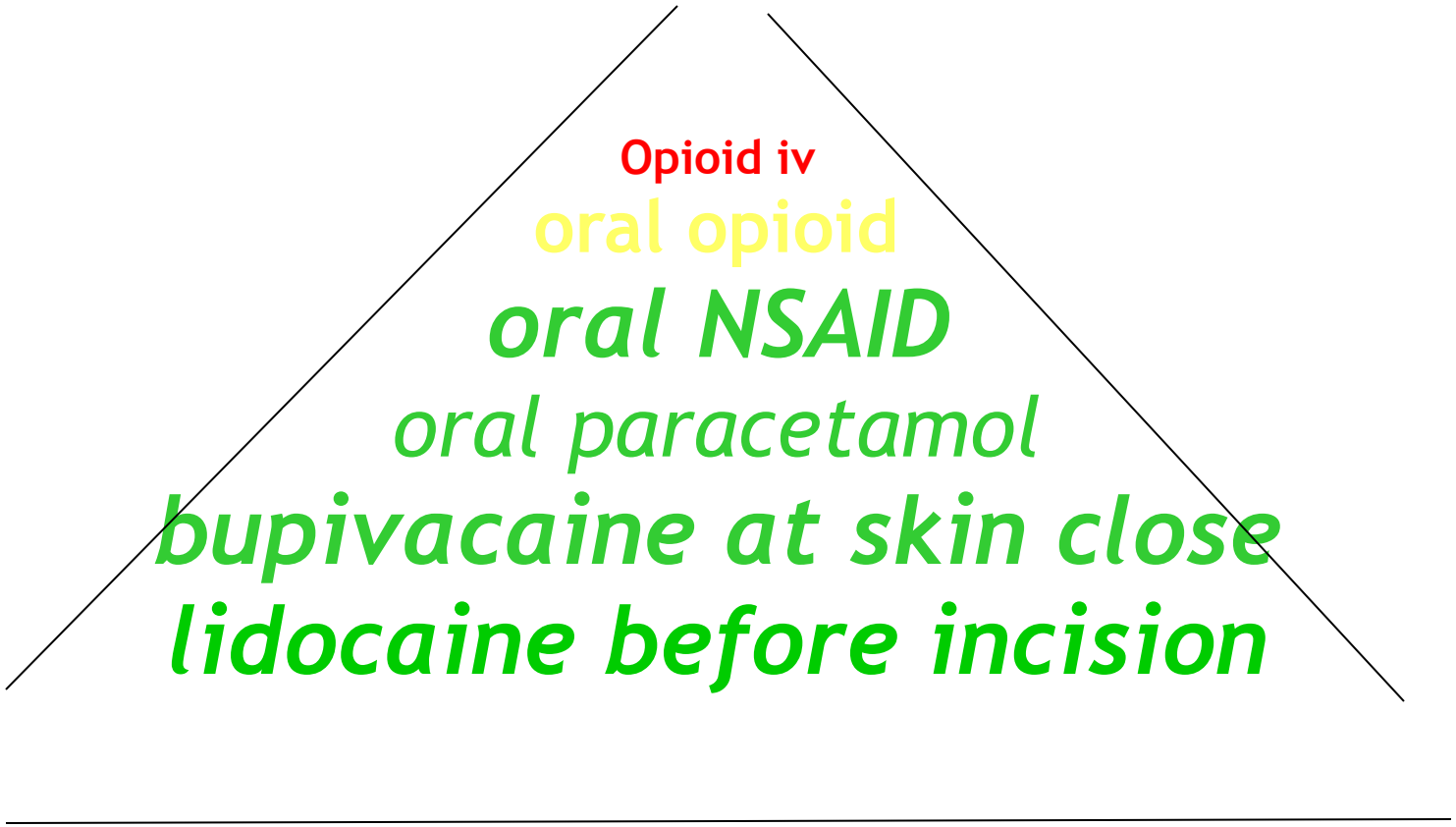
Source:http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html

Hantera smärta

Figure 4.6 Pain management "pyramid": from the basics up to rescue medication when needed



Hantera smärta



Premedicinering att förbättra före, under och EFTER operationen

Standard

- T. Alvedon 30 mg/kg
- T Celebra 400 mg/ Naproxen 500 mg
- T Postafen mot illamående
- Betapred 8mg preop mot illamående
  - *Catapresan 75 microgram*
  - *Lyrica*
  - *Gabapetin*
  - *Ja det finns mycket att testa*

När vi startar

- Ligga bekvämt & varmt, gärna toppluva
  - Kolla streck
  - Nål
  - Ringeracetat
    - » (1000 ml *vi får scanna blåsan*)
    - Propofol 20 – 30 mg
      - Fentanyl ca 10 µg
    - **Betapred 8 mg**
  - Tvätta klä
    - **Kirurg på sal**
  - **Söv**
    - 0.625 Dridol iv.

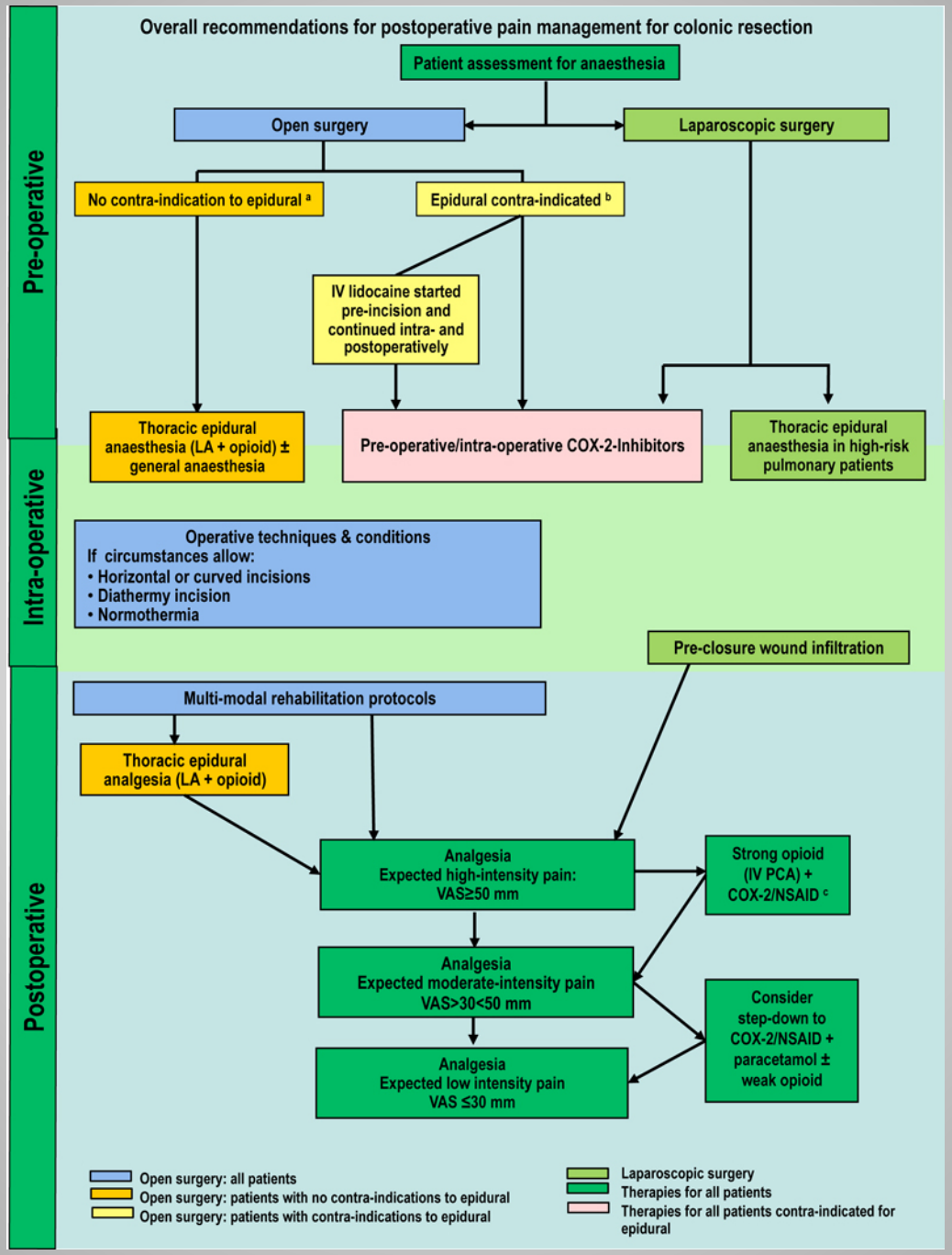
Tillägg vid alla operationer

- **Alltid lokalbedövning innan kirurgen får kniven!!;**
  - Blockad
  - Infiltrera sårområdet Marcain 5 mg/ml innan incision
  - Infiltrerar såret Marcain 5 mg/ml innan ni börjar sy ihop

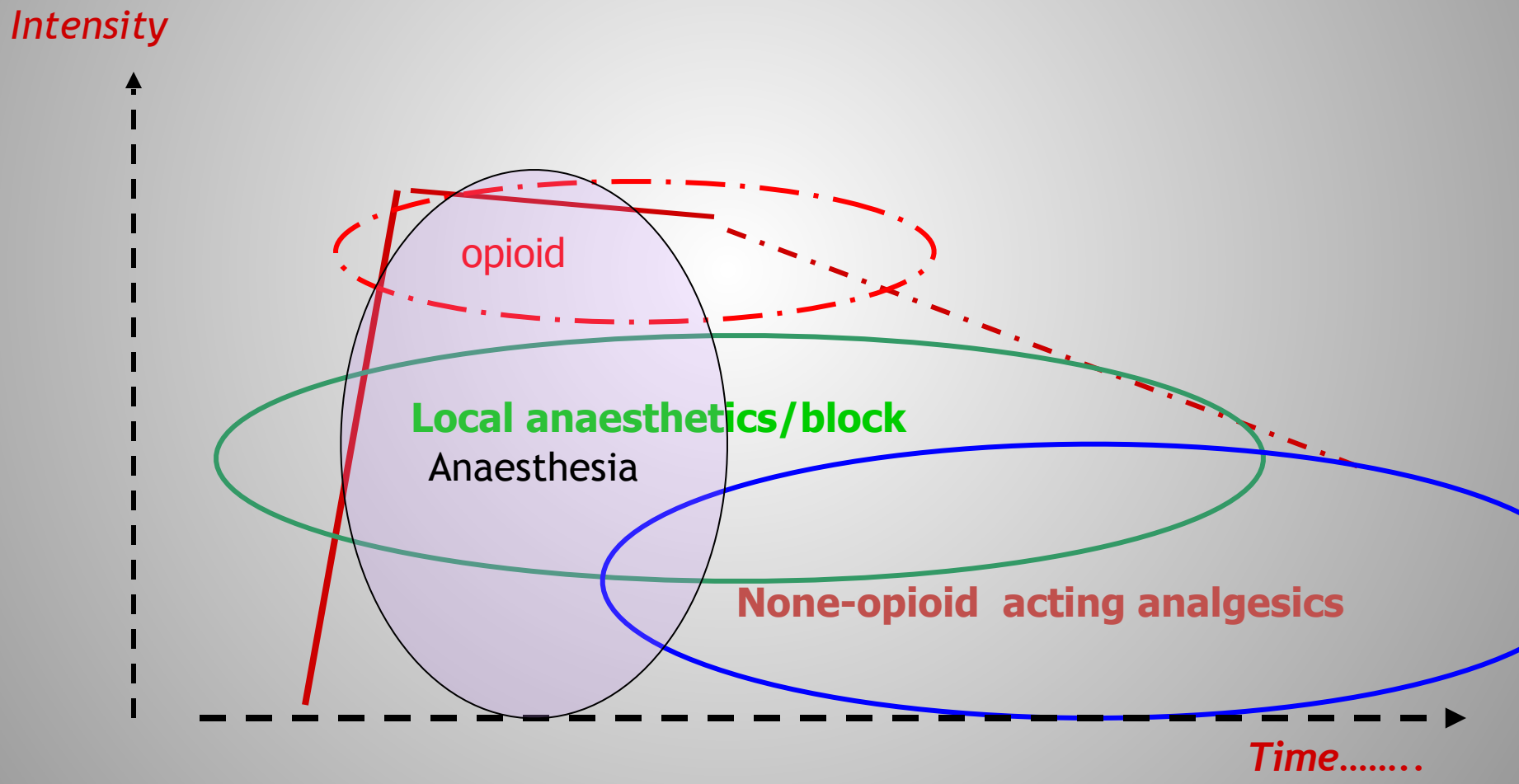
http://www.postoppain.org/frameset.htm

PROCEDURE-SPECIFIC RECOMMENDATIONS:

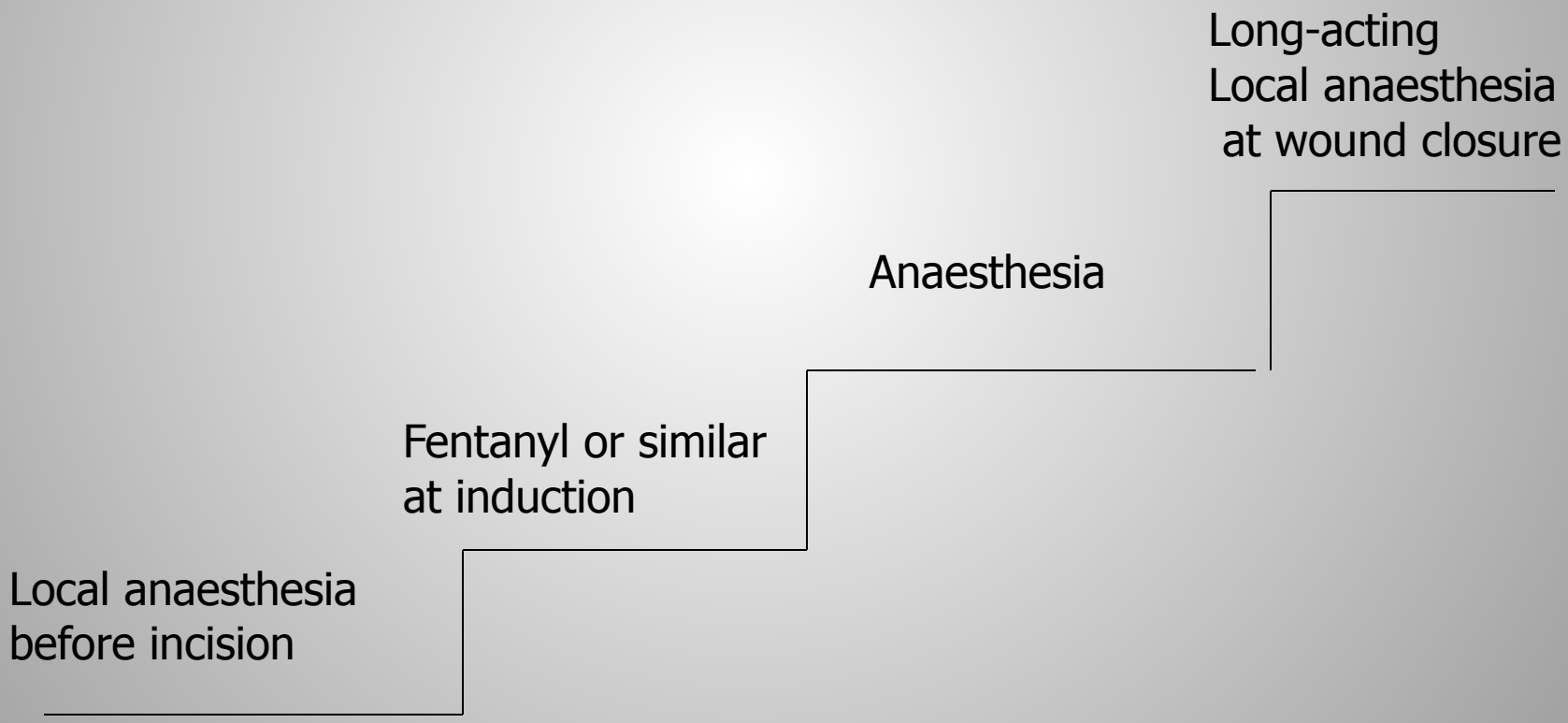
- Abdominal Hysterectomy
- Colonic Resection
- Haemorrhoid Surgery Herniorraphy Laparoscopic Cholecystectomy
- Non-cosmetic Breast Surgery
- Thoracotomy
- Total Hip Arthroplasty
- Total Knee Arthroplasty


Overall recommendations for postoperative pain management for colonic resection
Pre-operative
Intra-operative
Postoperative
Patient assessment for anaesthesia
Open surgery
Laparoscopic surgery
No contra-indication to epidural a
Epidural contra-indicated b
IV lidocaine started pre-incision and continued intra- and postoperatively
Thoracic epidural anaesthesia (LA + opioid) ± general anaesthesia
Pre-operative/intra-operative COX-2-Inhibitors
Thoracic epidural anaesthesia in high-risk pulmonary patients
Operative techniques & conditions
If circumstances allow:
• Horizontal or curved incisions
• Diathermy incision
• Normothermia
Pre-closure wound infiltration
Multi-modal rehabilitation protocols
Thoracic epidural analgesia (LA + opioid)
Analgesia
Expected high-intensity pain:
VAS≥50 mm
Strong opioid (IV PCA) + COX-2/NSAID c
Analgesia
Expected moderate-intensity pain
VAS>30<50 mm
Consider step-down to COX-2/NSAID + paracetamol ± weak opioid
Analgesia
Expected low intensity pain
VAS ≤30 mm
Open surgery: all patients
Open surgery: patients with no contra-indications to epidural
Open surgery: patients with contra-indications to epidural
Laparoscopic surgery
Therapies for all patients
Therapies for all patients contra-indicated for epidural

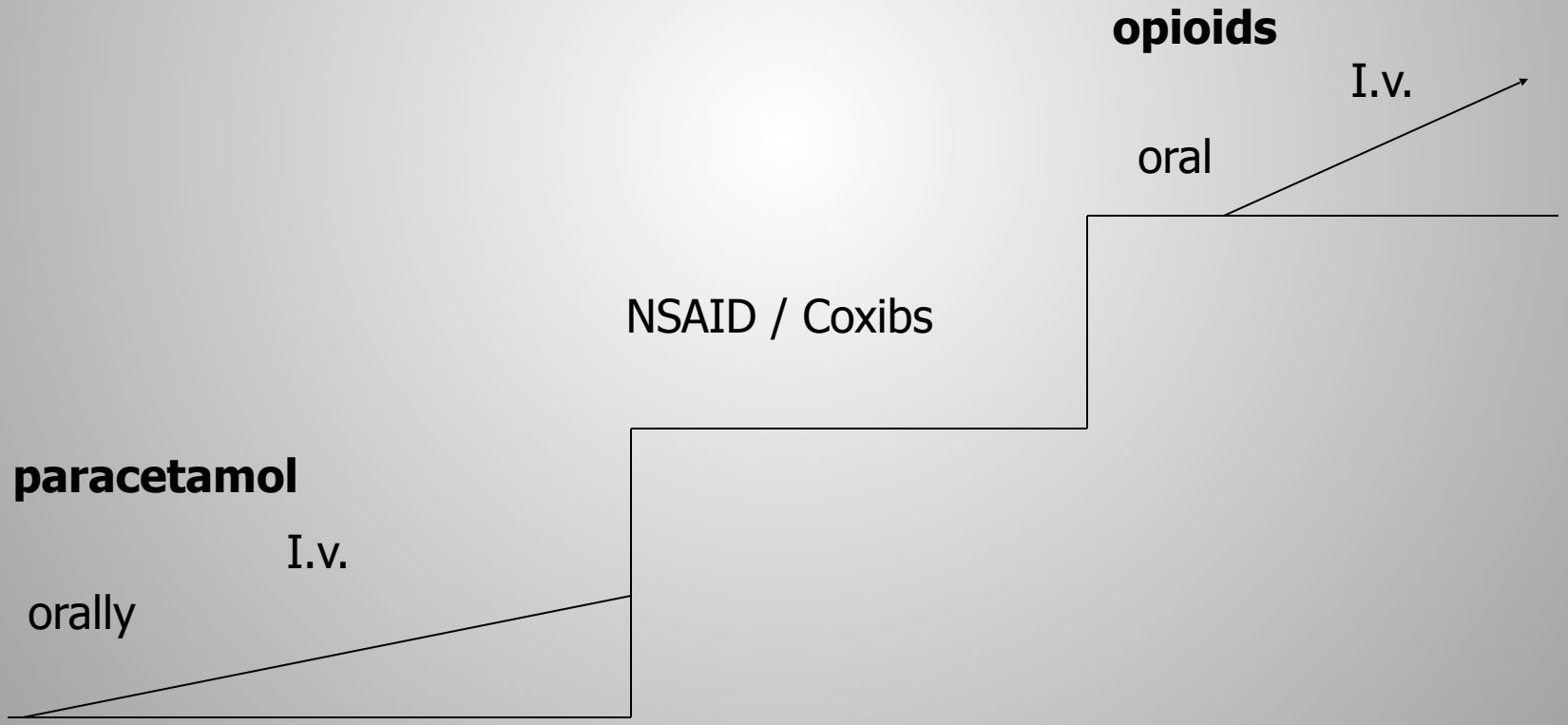
Multi-modal approach



Intraoperatively



Postoperative pain management in days surgery



Handling of pain after discharge

- Level I
  - Paracetamol 1 Gr. 4 times daily
  - NSAID/Coxib
    - Naproxen 500 mg 2 times daily
      - Etoricoxib 120 mg once daily
- Level II
  - Codeine or tramadol
- Level III
  - Classic opioid
    - Oxycodone slow-release (Oxycontin 10 mg)
- Rescue analgesic
  - Oxycodone (Oxynorm 5 – 10 mg)

Premedicinering att förbättra före, under och EFTER operationen

Standard

- T. Alvedon 30 mg/kg
- T Celebra 400 mg/ **Naproxen 500 mg**
- T Postafen
  - *Catapresan 75 microgram*
  - *Lyrica (doser 300 mg)*
  - *Gabapetin (slutenvård)*
    - » *Ja det finns mycket att testa*