

Farmacologische aanpak van pijn: algemene inzichten anno 2018

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Basisprincipes pijnbestrijding

■ By the clock

- Onderhoudsbehandeling volgens vast schema
- 'Noodmedicatie' (doorbraak) beschikbaar en snelwerkend
 - Van allergrootste belang bij wondverzorging!
 - Best pre-emptief (voor verzorging) toe te dienen

■ By the patient

- Rekening houden met individuele kenmerken van elke patiënt en zijn/haar voorgeschiedenis
- Type van pijnklacht in rekening te brengen

■ By the ladder

- Vervangen door lift...bij uitgebreide wonden ...
- Elk analgeticum op correcte wijze doseren!

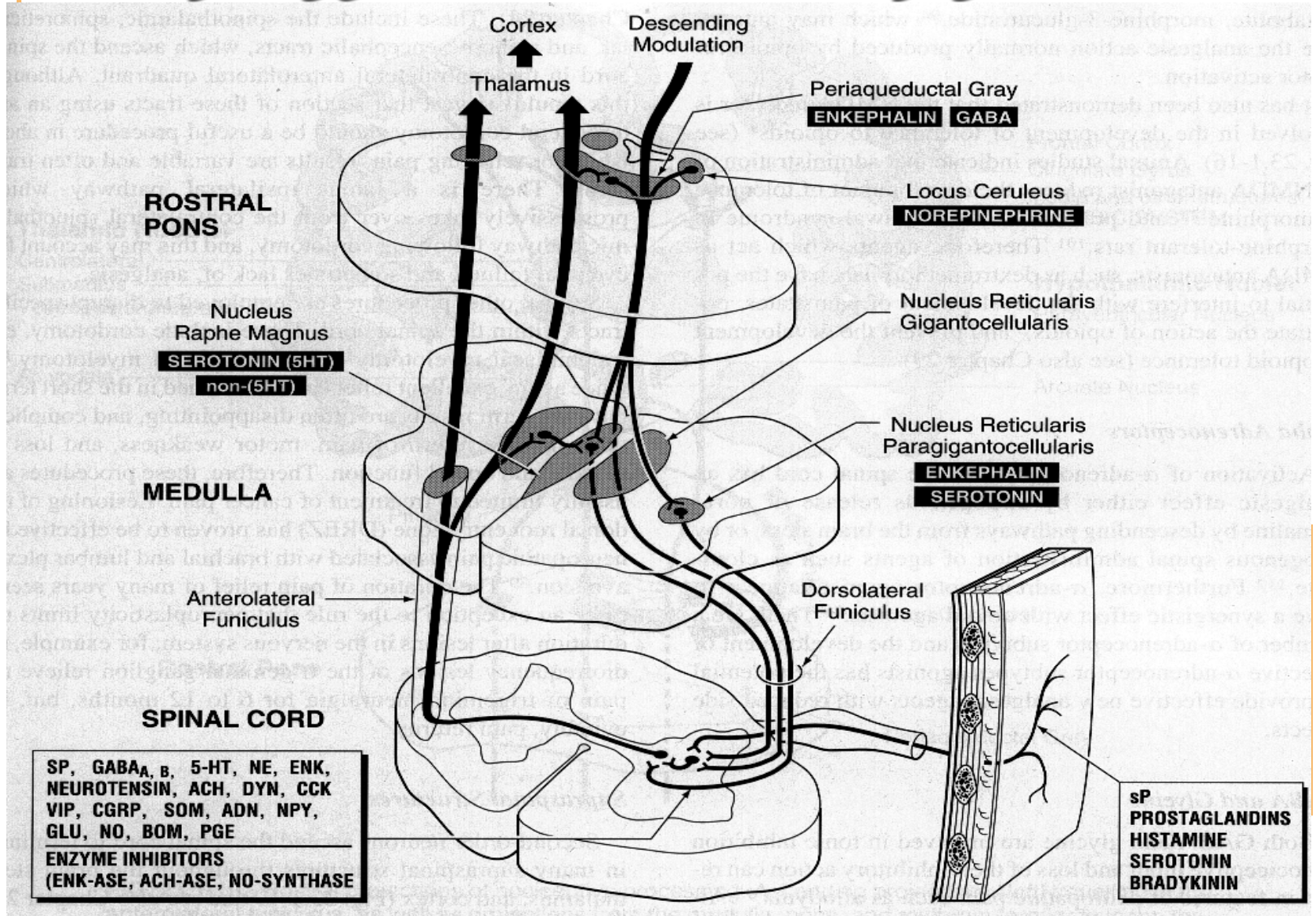
Regelmatige evaluatie

- Analgetisch effect
 - Voldoende tijd in acht nemen ($t_{1/2}$)
 - Cave: NASID's, methadon, ...
 - Verschillende doseringen testen
 - **Multimodale aanpak van pijnklacht**
 - Combinatie van analgetica/behandelmethoden met verschillend werkingsmechanisme
- Neveneffecten
 - Steeds afweging maken van pro's en con's
 - Intensiteit/ernst van neveneffecten !

Adjuvantia !

- Toenemende rol in de pijnbestrijding
 - Opioid sparend
 - Betere werkzaamheid tegen bepaalde pijntypes
 - Oa. neuropathische pijn
- Interactie met specifiek "target"
 - Descenderende inhiberende banen
 - Dorsale hoorn
 - Corticale structuren

Opstijgende en Dalende pijnbanen

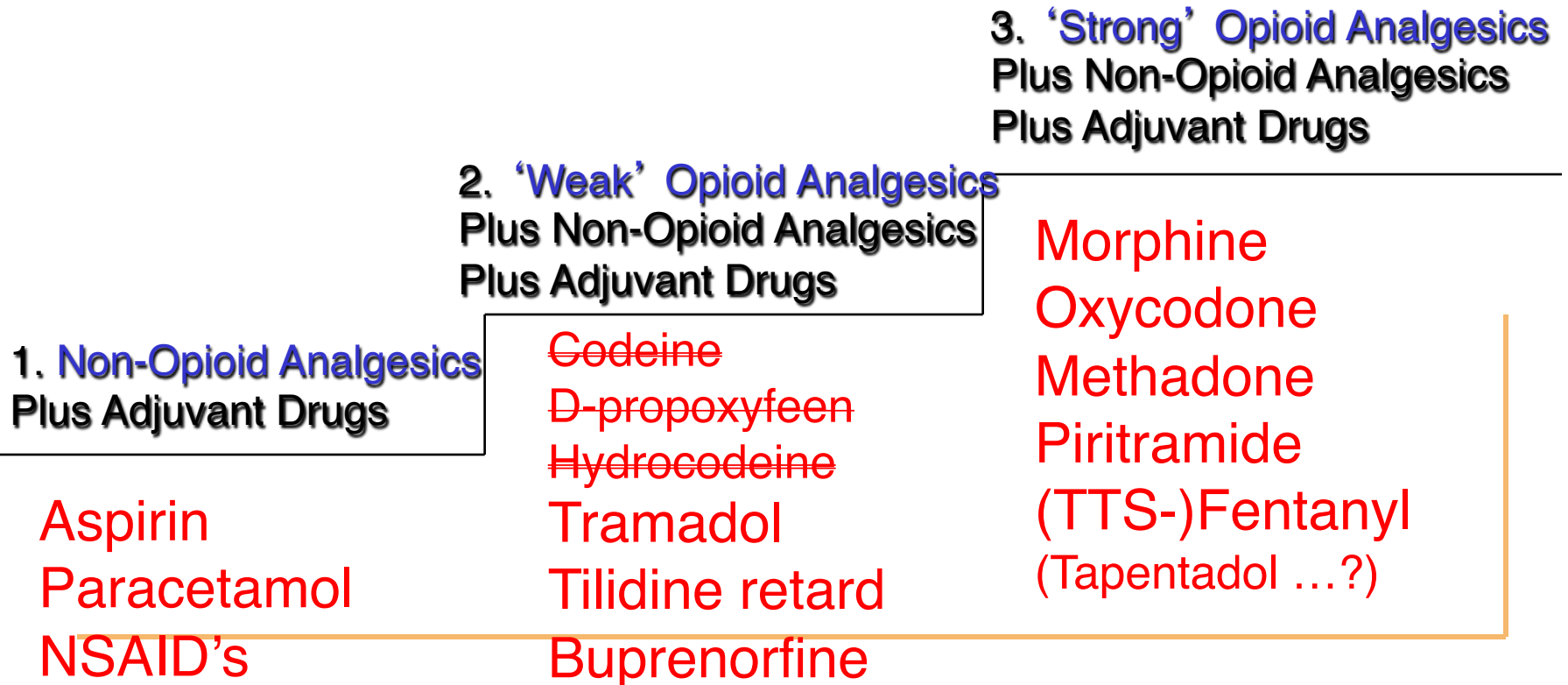


Typering van pijnklacht(en)

- **Somatische pijn**
 - Bot, ligamenten, spieren
- **Viscerale pijn**
 - Holle organen
- **Neuropathische pijn (niet-nociceptieve pijn)**
 - Letsel of beschadiging in het zenuwstelsel

Behandeling 'Step by Step'

ANALGETISCHE LADDER OF LIFT

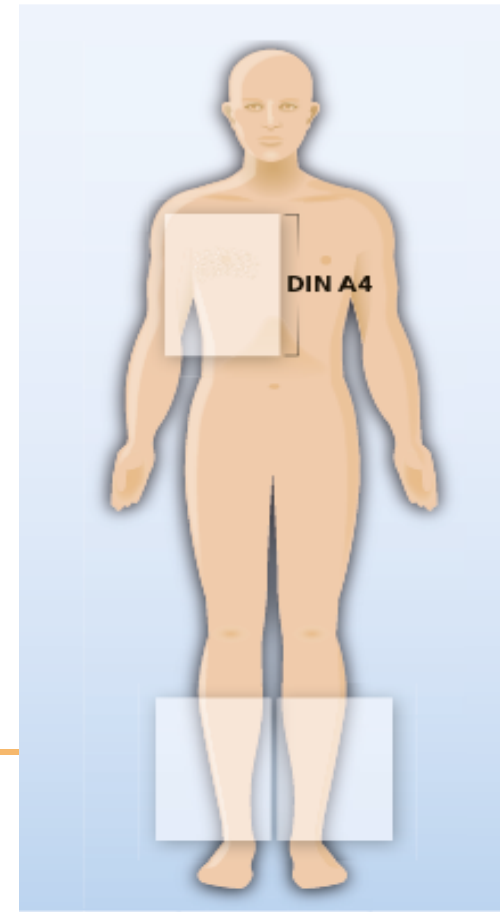


Topical analgesia

- Localized neuropathic pain syndromes (LNP)

- Topical lidocaine

- Topical capsaicin



Peripheral Antinociceptive Modulation by NSAIDs (2)

- Inhibition of *Cyclo-Oxygenase*
 - (at least) 3 distinct categories of inhibitors
 - **Reversible competitive** inhibition
 - Ibuprofen; piroxicam
 - **Reversible non-competitive** inhibition
 - Paracetamol
 - **Irreversible inactivation**
 - Aspirin, indomethacin

High Potency - Fast Elimination

■ Arylpropionic : Ketoprofen

- **Rofenid[®]**; Rofenid Enteric[®]; Rofenid Long Acting[®]; Rofenid Retard[®]
- 0.5-2h T_{max} , 1.1-4h $T_{1/2}$
- 200mg (-300mg) daily dose

■ Arylacetic acids

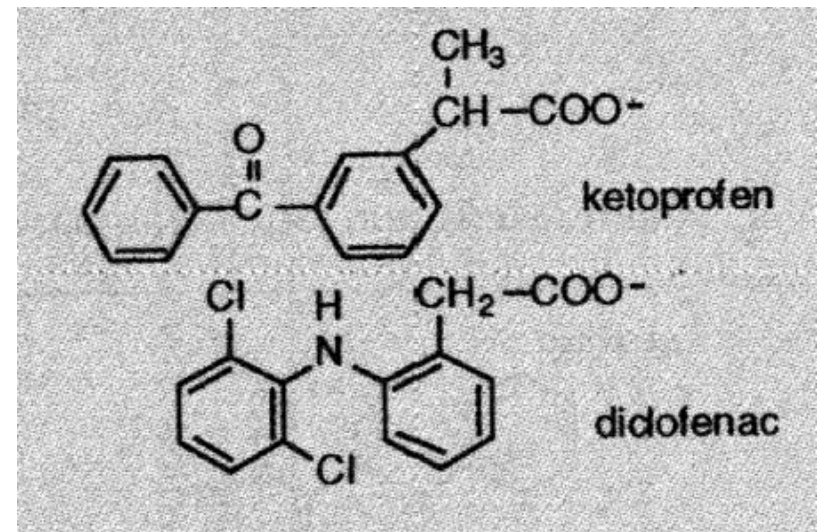
- 0.5-2h T_{max} , 4-10h $T_{1/2}$

● **Diclofenac (Voltaren, Cataflam[®])**

- Dissolve in stomach
- Short half-life of 1 - 2 h
- Daily dose: 100 - 150 mg

● **Ketorolac (Taradayl[®])**

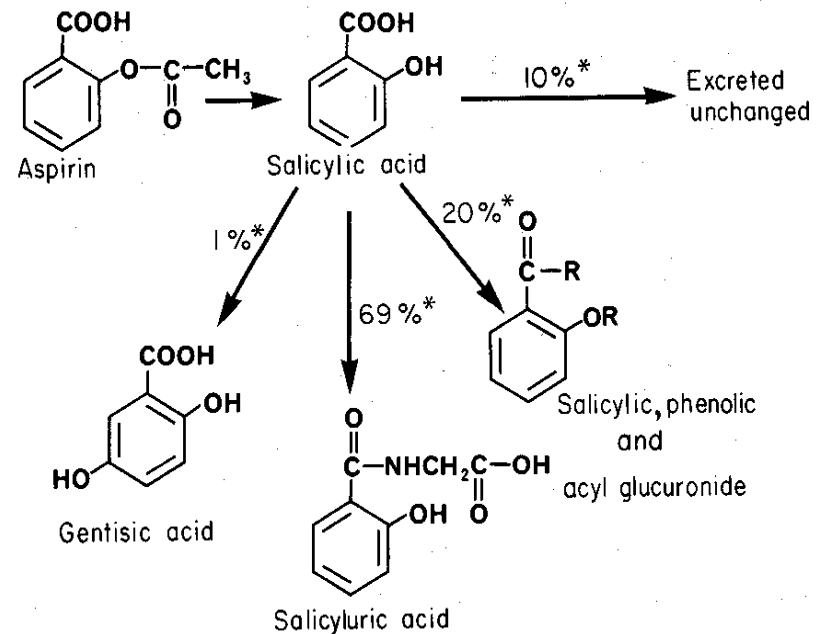
- 100% bio-availability IM/PO
- 10 - 30mg every 6-8 hours
- 60 (elderly) to 90 mg daily dose
- IM/IV max 2 days



Low Potency - Fast Elimination

■ Salicylates

- +/- 0.25h T_{max}
- +/- 20min $T_{1/2}$
- Low dose (500mg, 2x/d)
 - Analgesic & antipyretic effect
- High dose (1000mg, 3x/d)
 - Anti-inflammatory effect
- Individual variation in absorption
 - Dosage not predictable



■ Lysin - acetylsalicylic acid (Aspegic®)

- water soluble salt, sodium free
- 1.8g aspegic = 1.0g aspirin
- fast absorption
- 500 - 1000mg, 2 to 3 x /day

High Potency - Slow Elimination

■ Oxicams

● Piroxicam (Feldene®)

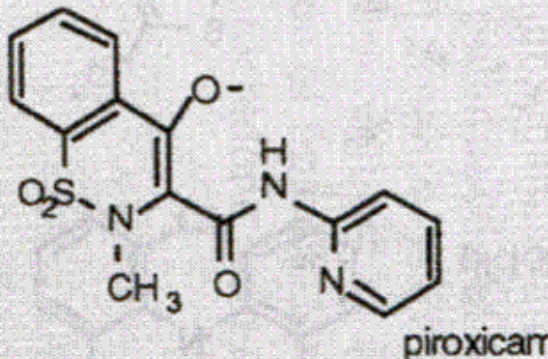
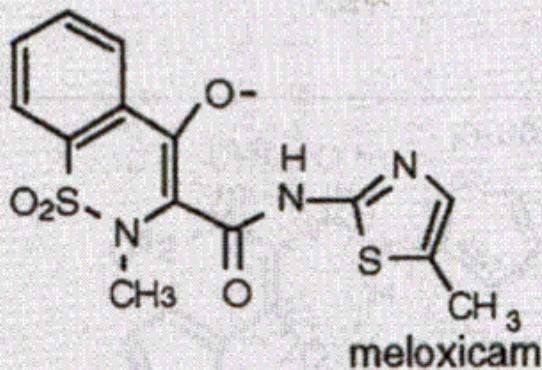
- 3-5h T_{max} , 35-70h $T_{1/2}$
- 20mg-40mg, daily dose
- Lyotabs equal T_{max} , $T_{1/2}$
- Elevated aminotransferase levels in 15%

– Monitor liver enzymes first 8 wk

● Tenoxicam (Tilcotil®)

- 100% bio-availability PO
- 3-5h T_{max} , 42-98h $T_{1/2}$
- 20mg-40mg daily dose
- Inhibitor of metalloproteinase

– Degenerative bone diseases!



Intermediate Potency

Intermediate Elimination

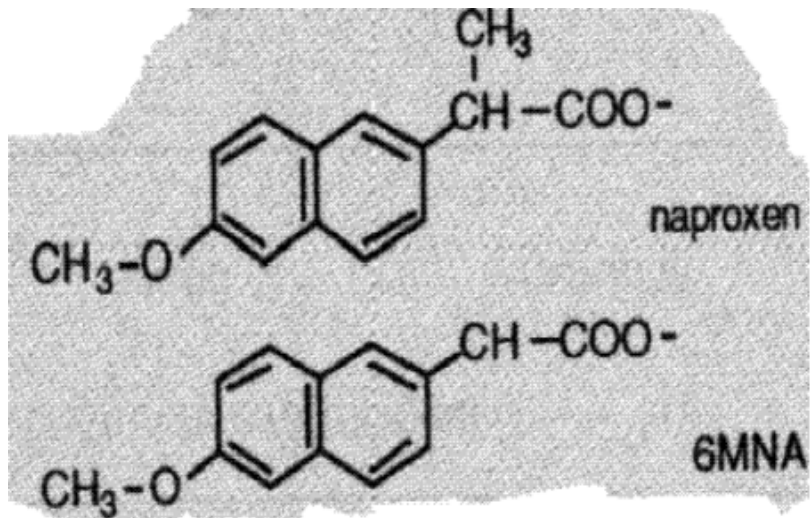
■ Arylpropionic acids

● Naproxen EG[®]; Naprosyne[®]

- 2-4h T_{max}
- 12-15u $T_{1/2}$
- 500 - 1000mg daily dose
- Extremely good penetration
 - Synovia
 - Inflammatory tissues

● Apranax[®] (*sodium naproxen*)

- < 1h T_{max}
- 12 - 15u $T_{1/2}$
- 550 mg, 2 x day



Selective COX-2 Inhibitors

■ Celecoxib (Celebrex[®])

- 2-4 h T_{max} , 9-15 h $T_{1/2}$
- 400mg max daily dose

■ ~~Rofecoxib (Vioxx[®])~~

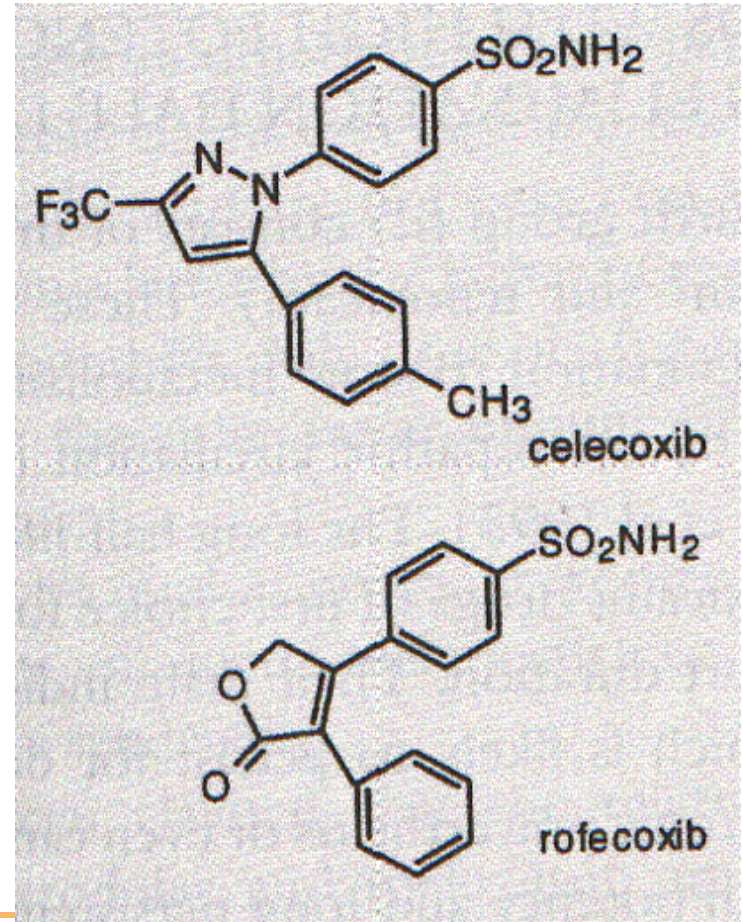
- 2-4 h T_{max} , +/- 12h $T_{1/2}$
- 50mg max daily dose (acute conditions!)

■ ~~Valdecoxib (Bextra[®])~~

- 20mg max daily dose
- no dose adjustments in elderly

■ Etoricoxib (Arcoxia[®])

- faster effect
- long-term effect (once daily)
- no information on side effects yet ...



Paracetamol (1)

■ Non-acidic antipyretic analgesic

(Dafalgan[®], Perdolan Mono[®]; Efferalgan, Dolprone...)

- Very weak inhibitor cyclooxygenase (central, indirect ?)
- Strong *antipyretic* effect
- Lacks significant anti-inflammatory property
- **Maximum analgesic effect at 1000 mg**
 - Central action (synthesis of prostaglandins)
 - Importance of high and quick peak plasma concentration
 - Dose-effect correlation in CNS
 - Ceiling of analgesic effect at 1g PO, and this 3 x day
 - ~~Better than 60 mg Codeine and Tramadol 100 mg~~
 - Combinations remain possible !

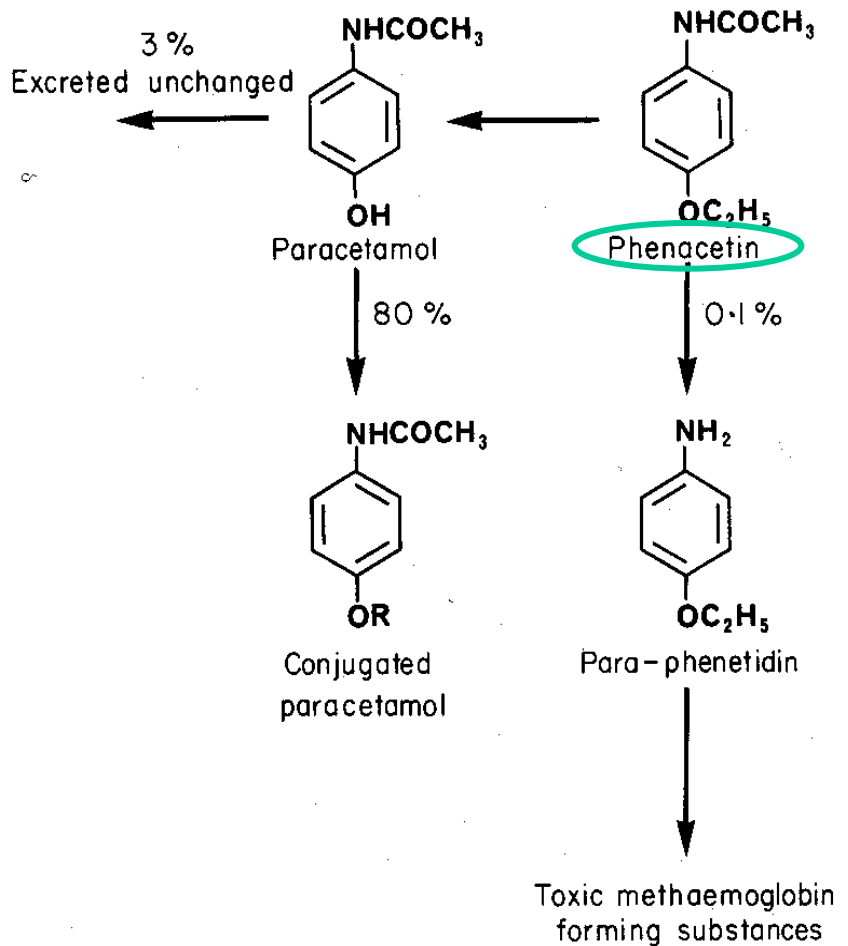
Paracetamol (2)

Short term use

- < 4 gm / day

Long term use

- < 3.2 gm / day
- < 2.4 gm / day
 - Elderly
 - Debilitated persons
 - Alcohol intake
 - Malnutrition



Paracetamol (3)

■ **Perfusalgan (IV)**

- Concentration of 10 mg/ml
- Water soluble form of paracetamol
- 1:1 ratio vs. oral formulation
- **Faster onset of action than orally**
 - More efficacious ?
- First day : 6g ?, 2g better than 1g ?
- **Longer duration of action**
- **Slow administration (!)** otherwise possible hypotension
- Good local tolerance
 - Osmolarity and pH close to human plasma

**opioid-sparing
effect!**

Tramadol Hydrochloride (1)

■ **Synthetic, *centrally* acting analgesic**

(Contramal[®], Dolzam[®], Tradonal[®]; Tramium[®]; ...)

● **Dual mechanism of action:**

- Specific selectivity and low affinity for μ -opioid receptor
 - » 6000 times less than morphine
- Interaction with neurotransmitter transmission
 - » Stimulation neuronal serotonin release
 - » Inhibition pre-synaptic reuptake NA and serotonin

● **Analgesic effect of each component is modest**

- Low incidence of certain opioid-like adverse effects
- Low tolerance and dependence potential

● **RESPONDERS and NON-RESPONDERS ?**

Tramadol Hydrochloride (2)

- **No respiratory depression in therapeutic range**
- **Almost no risk of constipation**
- **Nausea/vomiting; somnolence; transpiration**
- **No euphoria**
- **Low plasma protein binding (20%)**
 - **No interference other drugs (except MAO-I, 5-HT antagonisten)**
 - **Combination with NSAIDs allowed**
- **Not a non-steroidal anti-inflammatory drug**
 - **No anti-inflammatory activity**
 - **No prostaglandines side effects**

Tramadol Hydrochloride (3)

- **Conversion in liver to active M₁ metabolite**
 - Excretion as unaltered drug and metabolites in urine
 - Low-affinity of parent compound + high-affinity binding of M1 metabolite to μ -opioid receptor
- **Risk of seizures ! (2nd most important side effect)**
 - Doses above recommended range
 - Decreasing seizure threshold
 - Tricyclic antidepressants
 - SSRI's
 - MAO-inhibitors

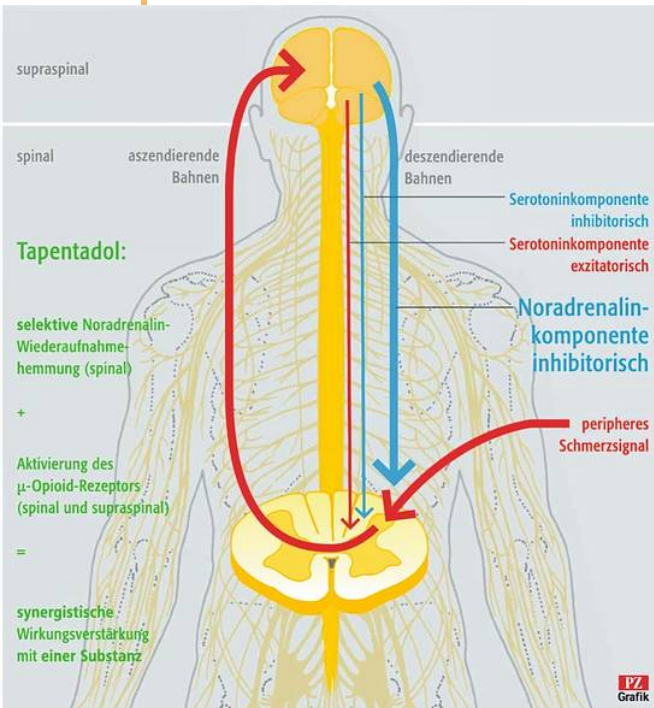
Tramadol Hydrochloride (4)

- Potency:
 - IV: 100mg tramadol = 10mg morphine
 - PO: 50mg tramadol = 10mg morphine
 - Bio-availability: tramadol 70% vs. morphine 20-25%
 - Duration of 3 - 6 h ,*T_{max}* PO 1 - 2 h; Parenteral 45 min
 - Max daily dose 400mg
 - No changes in elderly (<75 years)
 - Increase interval
 - Liver failure
 - Higher levels tramadol
 - Decreased levels of M1
 - Renal failure
 - Creatinine clearance < 30mL/min
- » 50-100mg every 12h

Tramadol + ... (5)

- **Combination analgesic (Zaldiar®, Tramadol/Paracetamol EG)**
 - **Paracetamol (325mg) + Tramadol hydrochl. (37.5mg)**
 - The rationale for combining complementary analgesics acting by different pathways is an improved benefit/risk ratio through enhancement of analgesia (synergism or addition) and/or reduction of side effects
- No undesirable interactions when the two analgesics are given in combination as either single or repeated doses
- Time to achieve maximal plasma concentrations is about 30-60 minutes for paracetamol and 2 hours for tramadol
- Both drugs are metabolised via the liver, but each compound is broken down along separate metabolic pathways
- Cave: long-acting drug forms !???

MOR-NRI (tapentadol)



- Tweevoudig werkingsmechanisme
 - μ -opioid receptor
 - ↓ heropname NA
 - Vgl. Venlafaxine in diermodellen
- Werkzaamheid nociceptieve pijn
 - Vergelijking met oxycodone
 - Studies in viscerale pijn !
- ↓ GI neveneffecten
 - Nausea, obstipatie en braken
- ↓ tolerantie

Opioids

- Full agonists do not antagonise/reverse effects of other agonists given simultaneously
- No “analgesic ceiling” ??????
 - Dosing limited only by side effects

Partial agonists have dose-related ceiling effect

-Less potent analgesics

Mixed agonists/antagonists also ceiling effect

-Possibility of withdrawal syndrome

~~Full agonist : Codeine~~

■ Alkaloid of opium

- Analgesic effect 5-10x <M+
- Duration of action: 5 hrs
- Also anti-tussivum, -diaretic
- Weak resp. depression

■ Associations !

● With paracetamol

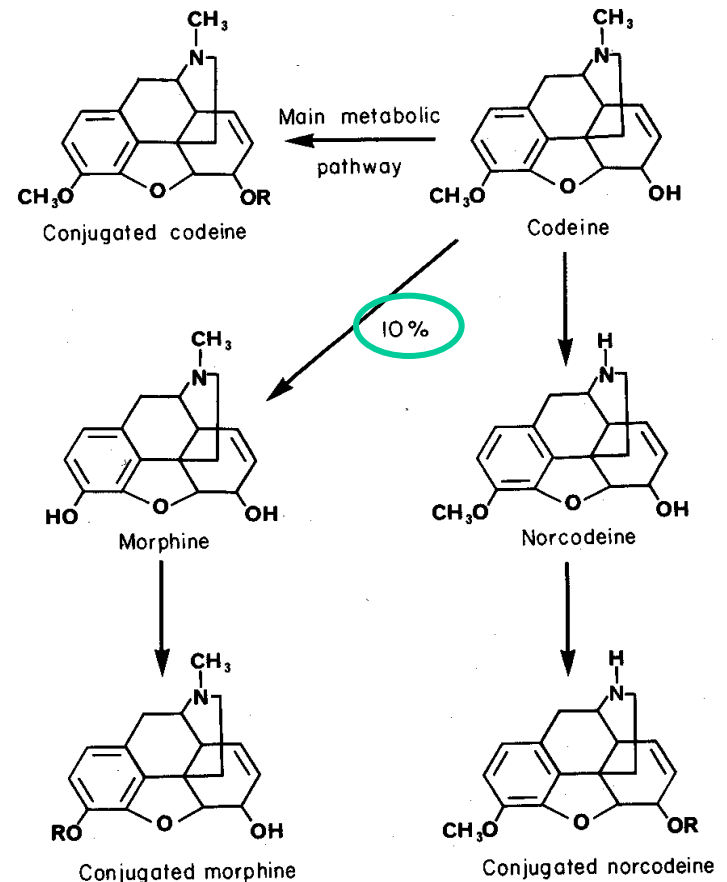
- Dafalgan codeine, Perdolan
- Panadol codeine, Lonarid N

● With aspirin

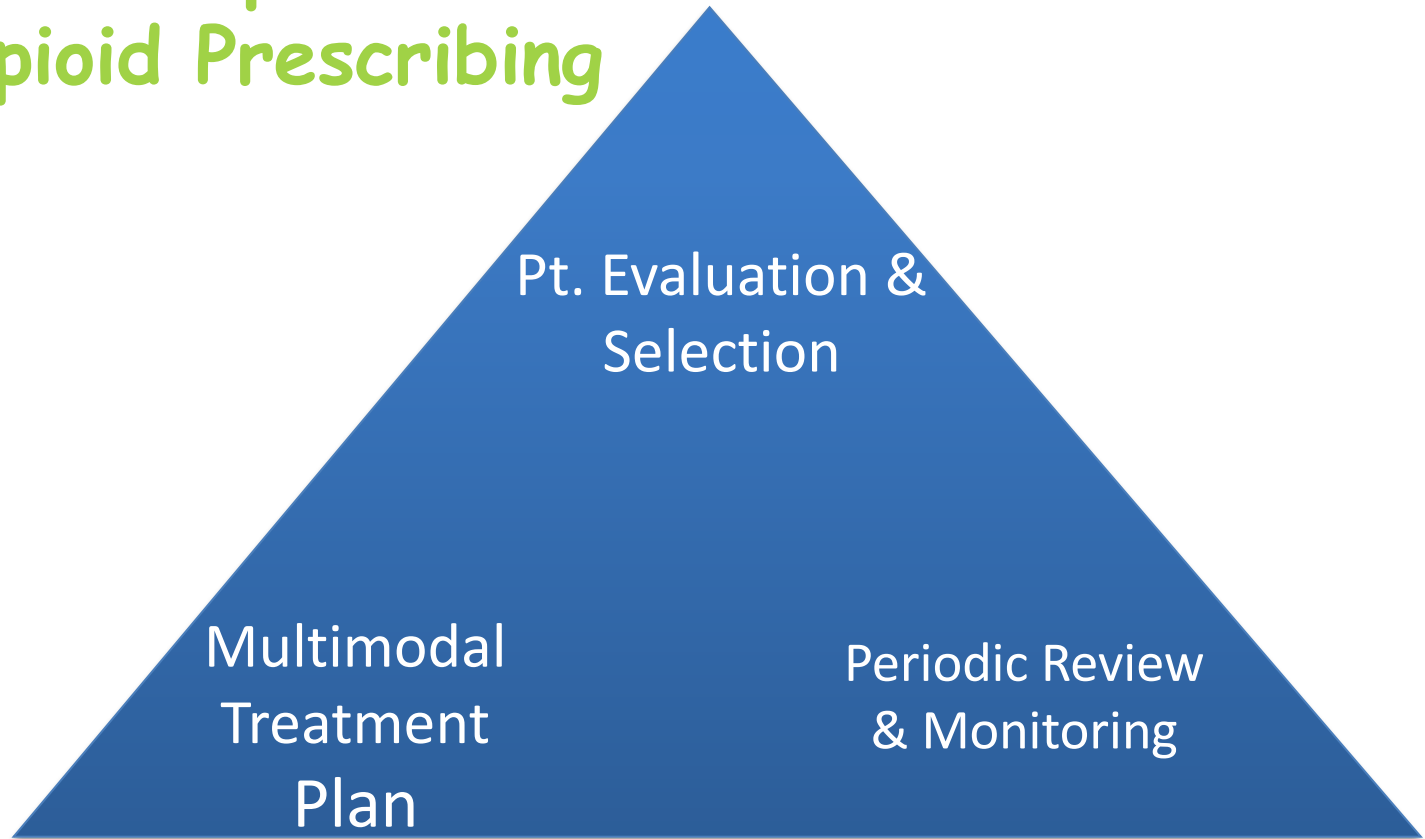
- Dolviran

● Codeine derivatives

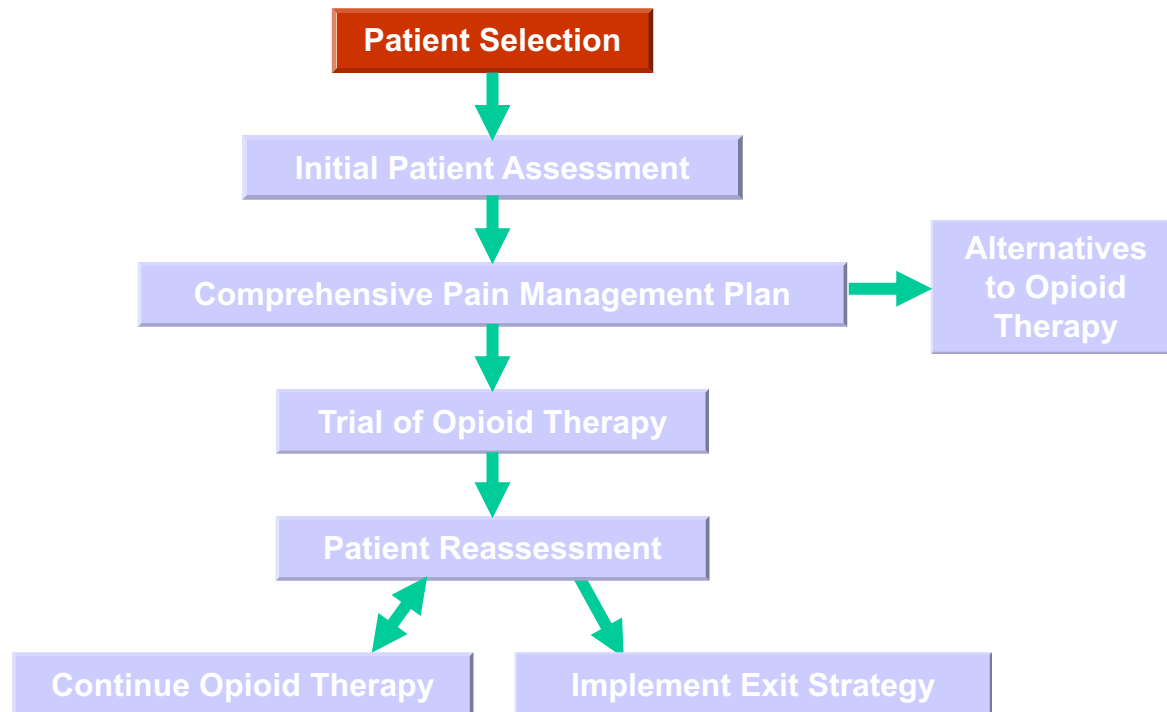
- Dihydrocodeine (Codicontin), with longer duration (up to 12 h)



Fundamental Tenets of Responsible Opioid Prescribing



Algorithm for Opioid Treatment of Chronic Pain



Meaningful Pain Reduction: How Much?

- Using a VAS or Numeric scale of 0-10
 - (4-6= moderate pain; 7-10= severe pain)
- For Moderate pain (mean=6)
 - Meaningful reduction=2.4 (40%)
 - Very much better=3.5 (45%)
- For Severe pain (mean=8)
 - Meaningful reduction=4.0 (50%)
 - Very much better=5.2 (56%)

M. Soledad Cepeda et al.
Proc 10th world Cong on Pain vol
24; pp 601-609

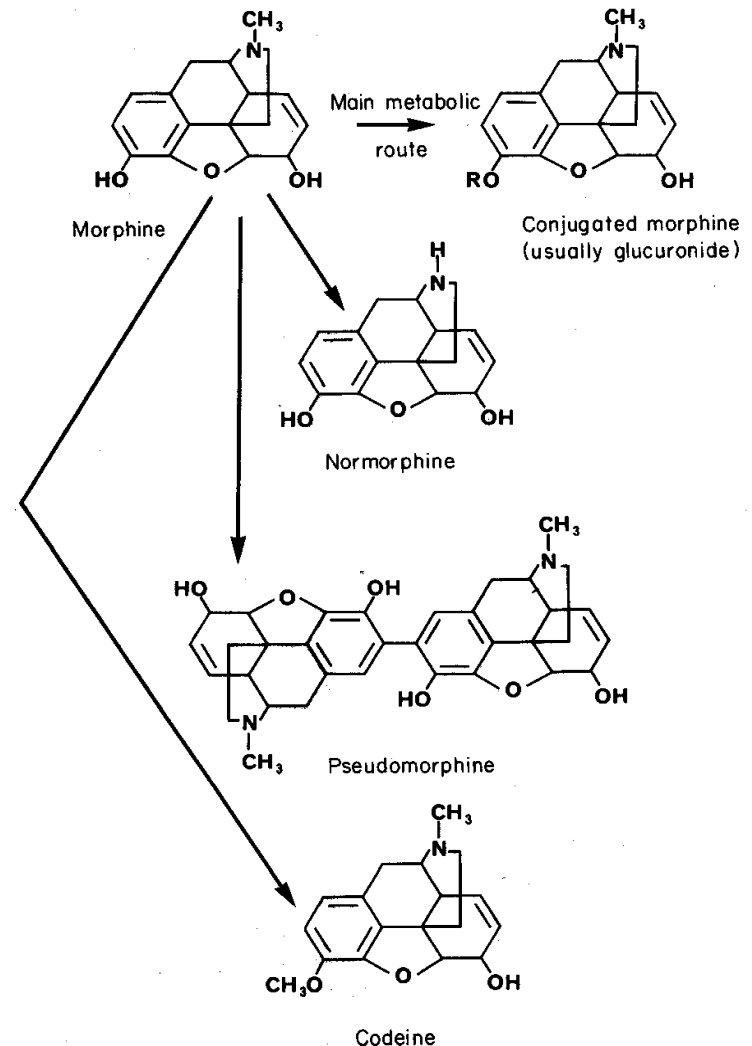
Conversion table opioids

Morfine oraal (mg/24 uur)	Morfine s.c./i.v. (mg/24 uur)	Oxycodon oraal (mg/24 uur)	Oxycodon s.c./i.v. (mg/24 uur)	Fentanyl transderm. (mcg/uur)	Hydro- morfon oraal (mg/24 uur)
30	10	15	7,5	12	4
60	20	30	15	25	8
120	40	60	30	50	16
180	60	90	45	75	24
240	80	120	60	100	32
360	120	180	90	150	48
480	160	240	120	200	64

Full Agonist : Morphine

- Principal and....most
- *active* alkaloid of opium
- Many routes (versatile)
- Immediate-release
- Sustained-release
- 25-35% first-pass
- SC / IM: 10 mg / 70 kg
- IV: 2 - 10 mg / 70 kg
- Oral : bioavailability 20%

Parenteral dose: 5 - 10 mg every 3-6 h
Local application in cream ... ?



Full Agonists : Piritramide

IM: 0.2 - 0.3 mg/kg (20mg) every 6 h
(max daily of 80 mg)

■ Piritramide (Dipidolor®)

- Derived from 3,3-difenylpropylamine
- Less potent than morphine (15-20mg=10mg M+)
- Special clinical profile
 - Less nausea; constipation; resp. depression
 - More sedation
 - Few cardiovascular effects
- Onset after **IM injection**: 15 to 20 min
- Duration: 4 to 6 hours
- IV ? : 2-4mg/bolus

Full Agonists : Methadone !

- 100% synthetic substance (L-isomer)
- High protein binding in tissue
- Low plasma concentration
 - Low tolerance
 - Longlasting suppression of heroine withdrawal
 - N-demethylation
 - Anti-tussive but
 - actually better substances with
 - Less dependency

Full (synthetic) Agonists

■ Fentanyl and Sufentanil

- More potent than morphine (F50 μ g = 10mg M+)
- Sufentanil = Fentanyl $\times$ 4-6
- Special clinical profile
 - More sedation
 - Few cardiovascular effects
- Onset after IV injection: <5min.
- Duration: 2 to 6 hours
- Transdermal (Durogesic) as main chronic therapy
- Effective as breakthrough pain
 - Transmucosal, intranasal, transbucal,

Oxycodone

- Traag-werkende vorm (Oxycontin)
 - Onderhoudsbehandeling
 - 12 uur durende werking
- Snelwerkende vorm (**Oxynorm Instant**)
 - Toediening zonder water mogelijk
 - Aanvang van analgesie na 30 minuten
- 3,5:1 verhouding tov. Morfine
 - Idem neveneffectenprofiel (meer agitatie!)
 - Géén voordeel tov. andere opioïden
- Géén voorafgaande goedkeuring door mutualiteit meer nodig (vanaf 01/10/2012)

“Partial” Agonist Opioid

- **Buprenorphine (Temgesic[®]; Transtec[®])**
 - Semisynthetic derivative of morphine alkaloid thebaine
 - Partial agonist effect at μ -opioid receptor in CNS
 - High affinity at μ -opioid receptors
 - Low intrinsic activity at μ -opioid receptors
 - Relaxation of Oddi Sphincter
 - Sublingual administration:
 - 50% biological availability
 - Peak clinical effect within 1 to 4 hours
 - Elimination half-life between 24 to 37 hours
 - Metabolism in liver (glucuronide conjugation + N-dealkylation)
 - Principally excreted in faeces and urine
 - High lipid solubility, very high protein binding
 - Remaining in tissues for several days

- *Transdermal*

- 3 different doses

- 35 µg/h (total dose of 20 mg buprenorphine)
- 52.5 µg/h (total dose of 30 mg)
- 70 µg/h (total dose of 40 mg)

- Active during 72 hours

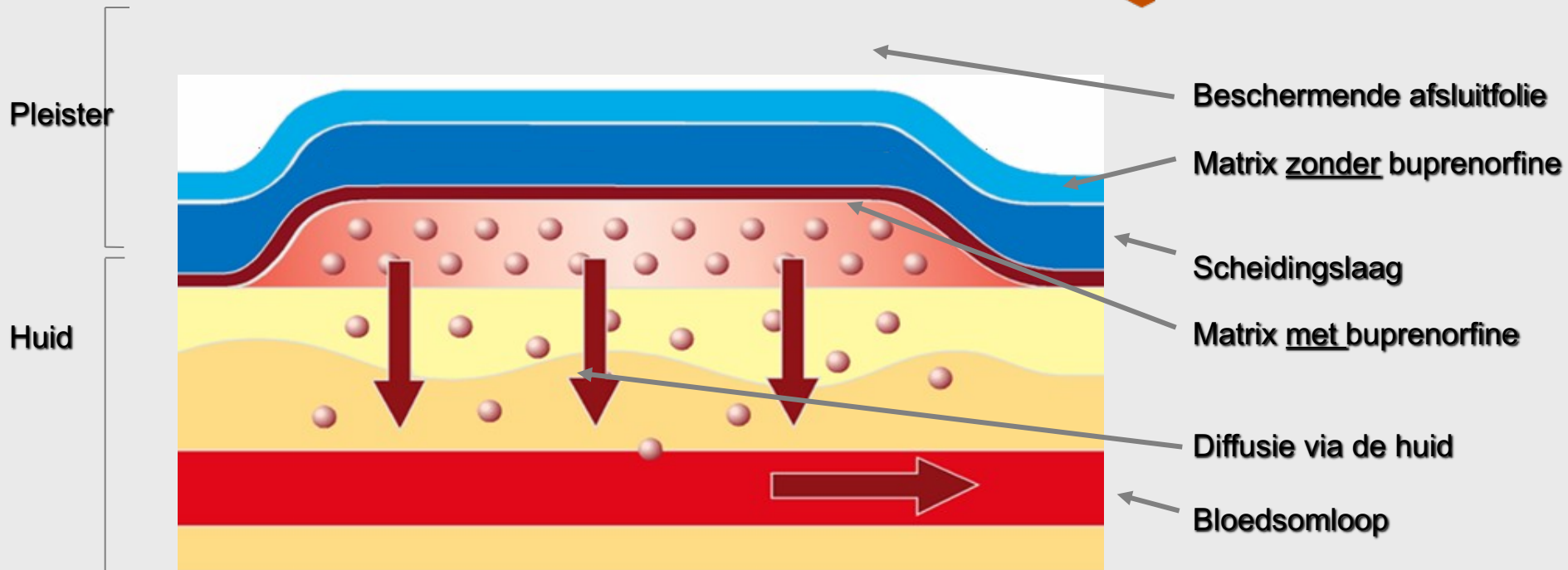
- **Matrix** technology

- No leakage ! (1/2 patch possible)
- Less substance abuse possible !

Brand Name		Daily Dose of Buprenorphine	Duration of Use per Patch
TRANSTEC 35 µg/h		0.8 mg	3 days
TRANSTEC 52,5 µg/h		1.2 mg	3 days
TRANSTEC 70 µg/h		1.6 mg	3 days

Matrixsysteem

**Grote reserve
72u werking!**



Partial Agonist or Ag-Antag ?

- **Pentazocine** (Fortal[®]), derivate from Phenazocine
 - Synthetic opioid, too weak antagonistic effect
 - Related to kappa-opioid receptor stimulation
 - Weak antagonist μ -opioid activity
 - Deliberately produced to decrease drug abuse
 - 30 mg (60mg better ?) pentazocine = 10 mg M+
 - Duration of action : 3-6h
 - Metabolised in liver, excreted by the kidneys
 - IV administration increases systemic vascular resistance, and systemic, pulmonary arterial pressure
 - No repeated injections into the skin (fibrosis!)
 - Psychotomimetic reactions
 - Antagonised by naloxone only.

Agonist + Antagonist (2)

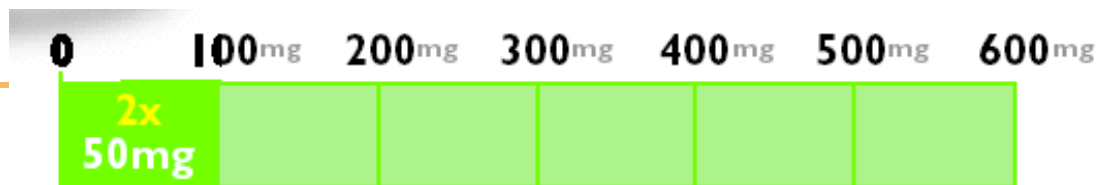
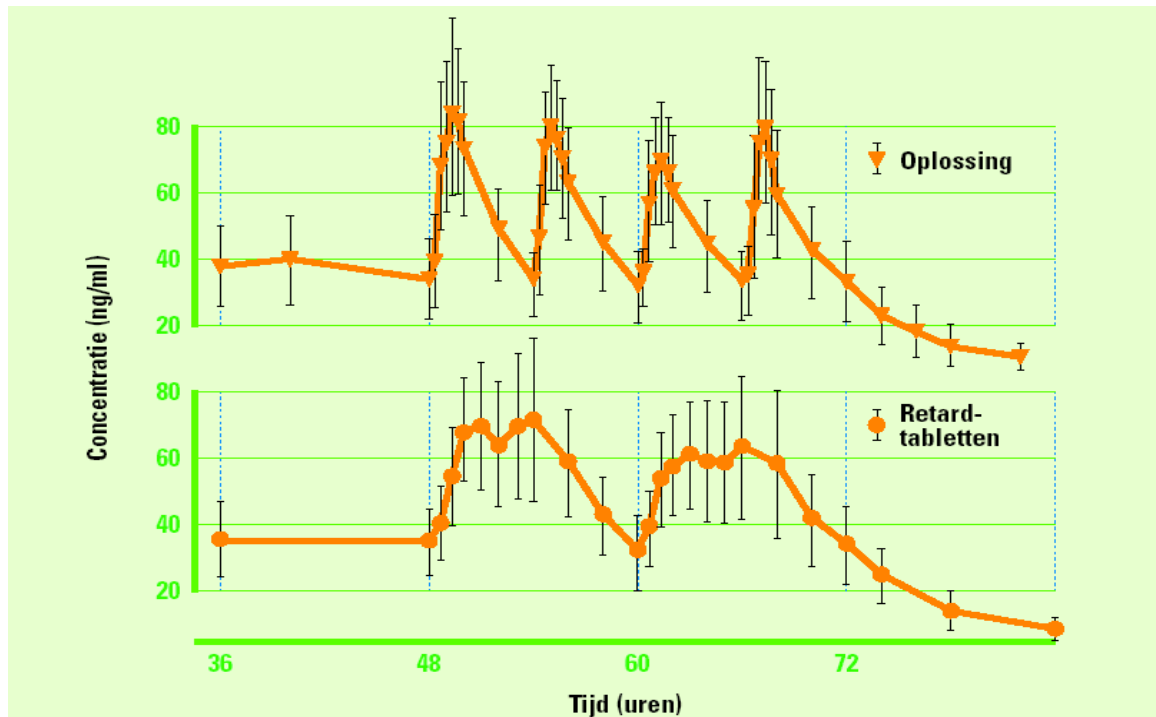
- **Tilidine (Valoron) + Naloxone (Valtran®)**
 - 100mg = 10mg morphine
 - Analgesic effect 10 - 20 minutes after PO
 - Duration: 4 to 6 hours
 - No cough depression, no cardiovasc. Effects
 - Naloxone < 8mg no clinical effect (analgesia!)
 - First-pass effect of naloxone
 - Overdosage : fear for resp. depression
 - Antagonistic effect proportional to dose

PO Dose: 10 - 20 drops every 6-8 h
Max dose of 4 x 40 drops

Agonist + Antagonist

- Long-acting form (Valtran Retard[®])

Verlengde werking : 12 uren $\Rightarrow$ 2 x per dag



Agonist + Antagonist (3)

- ~~■ Oxycodone + Naloxone (Targinact)~~
 - ~~● Identical analgesic effect compared to oxycodone~~
 - ~~● Less gastro-intestinal side effects (obstipation)~~
 - ~~• Scientific evidence very weak~~
- ~~■ Many more such combinations to expect in the (near) future, focusing on the obstipation induced by opioids...~~

Adjuvantia

- **Locale anestetica**
- **Adrenaline**
- **Clonidine** (*postop, labor, chron pijn*)
- **Ketamine** (*postop, postzona*)
- **Neostigmine** (*labor*)
- **Corticoiden** (*chronische pijn, postop*)
- **Midazolam** (*labor*)
- **Magnesium**
- **Adenosine**
- *Baclofen*