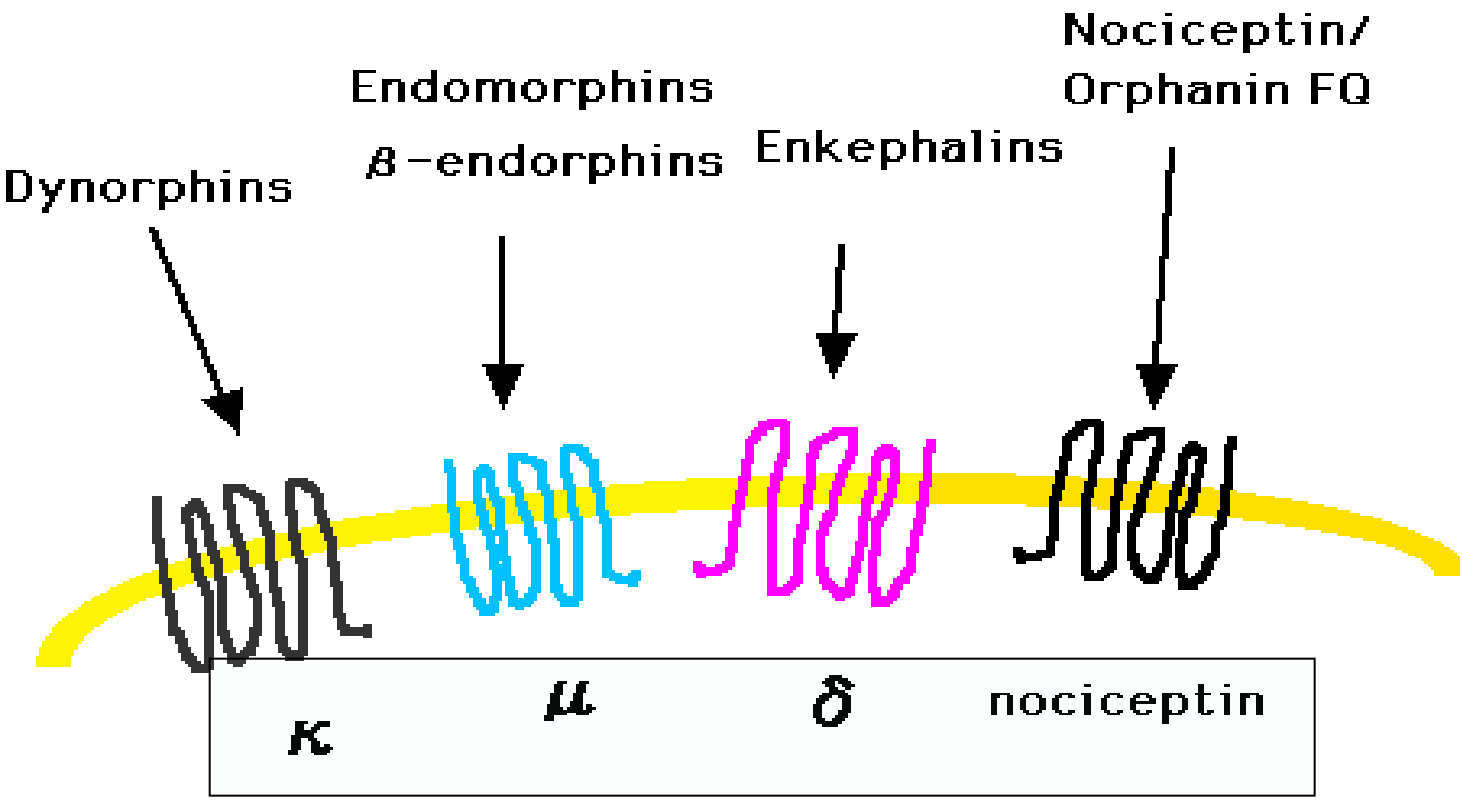
Opioid analgesics (narcotic analgesics) and antagonists

1. Classification of opiates

- Natural opiates: morphine, codeine, papaverine and thebaine;
- Semi-synthetic opiates: hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, diacetylmorphine (Heroin), nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine;
- Fully synthetic opioids: fentanyl, pethidine, methadone, tramadol and propoxyphene;
- Endogenous opioid peptides: endorphins, enkephalins, dynorphins, and endomorphins.

2. Opioid receptors



3. Opioids

Summary of opioid analgesics and antagonists:

Strong agonists: **fentanyl, heroin, pethidine, methadone, morphine**

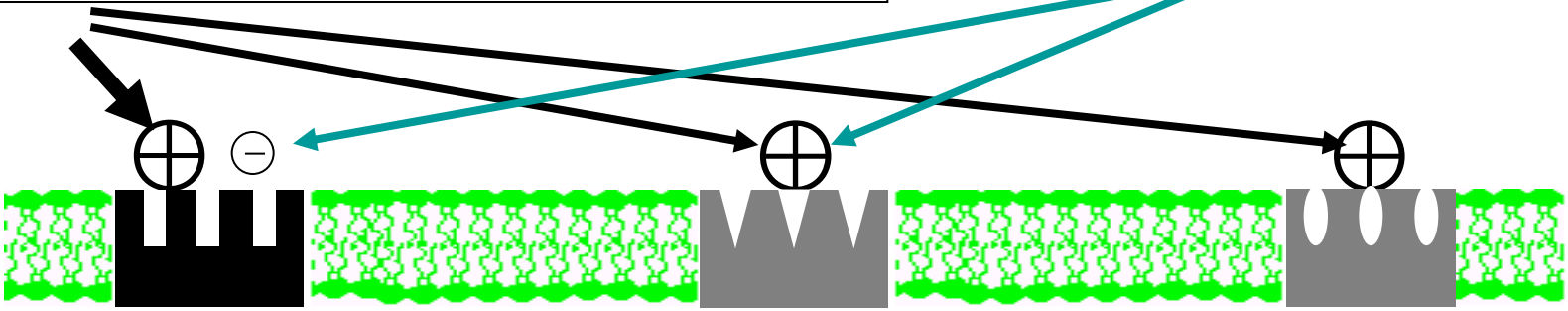
Moderate agonists: **codeine**

Mixed agonist-antagonists: **pentazocine**

Antagonists: **naloxone, naltrexone**

Mainly agonist action atμreceptors, but some actions on other receptors
- **Morphine**
- **Heroin**
- **Codeine**
- **Fentanyl**

Agonist action at κreceptors, with partial antagonist action at μ receptors
- **Pentazocine**



μ opioid receptor

Analgesia
Respiratory depression
Euphoria/sedation
Physical dependence
Decreased GI motility
Pupil constriction

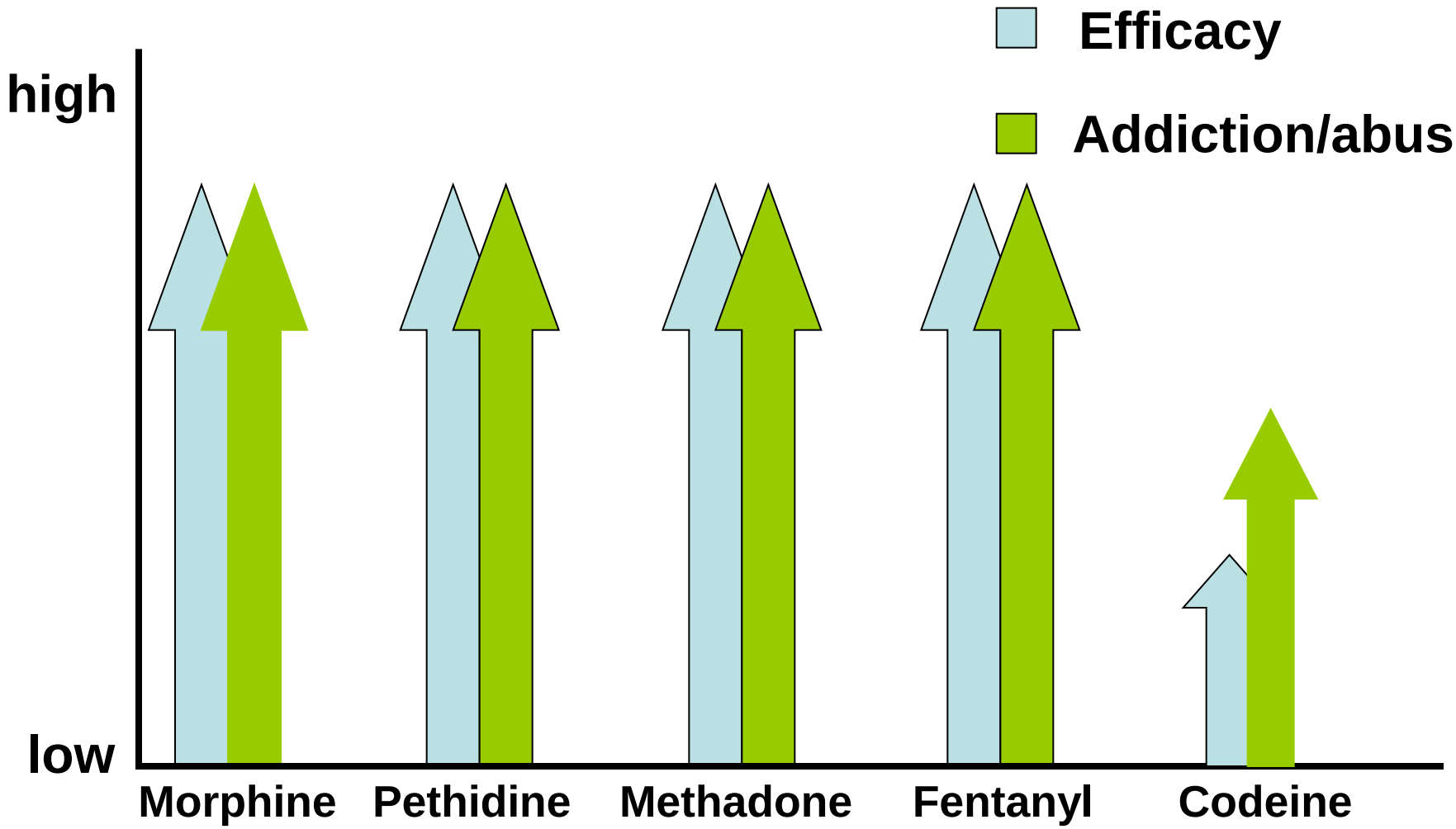
κ opioid receptor

Analgesia
Sedation/dysphoria
Pupil constriction

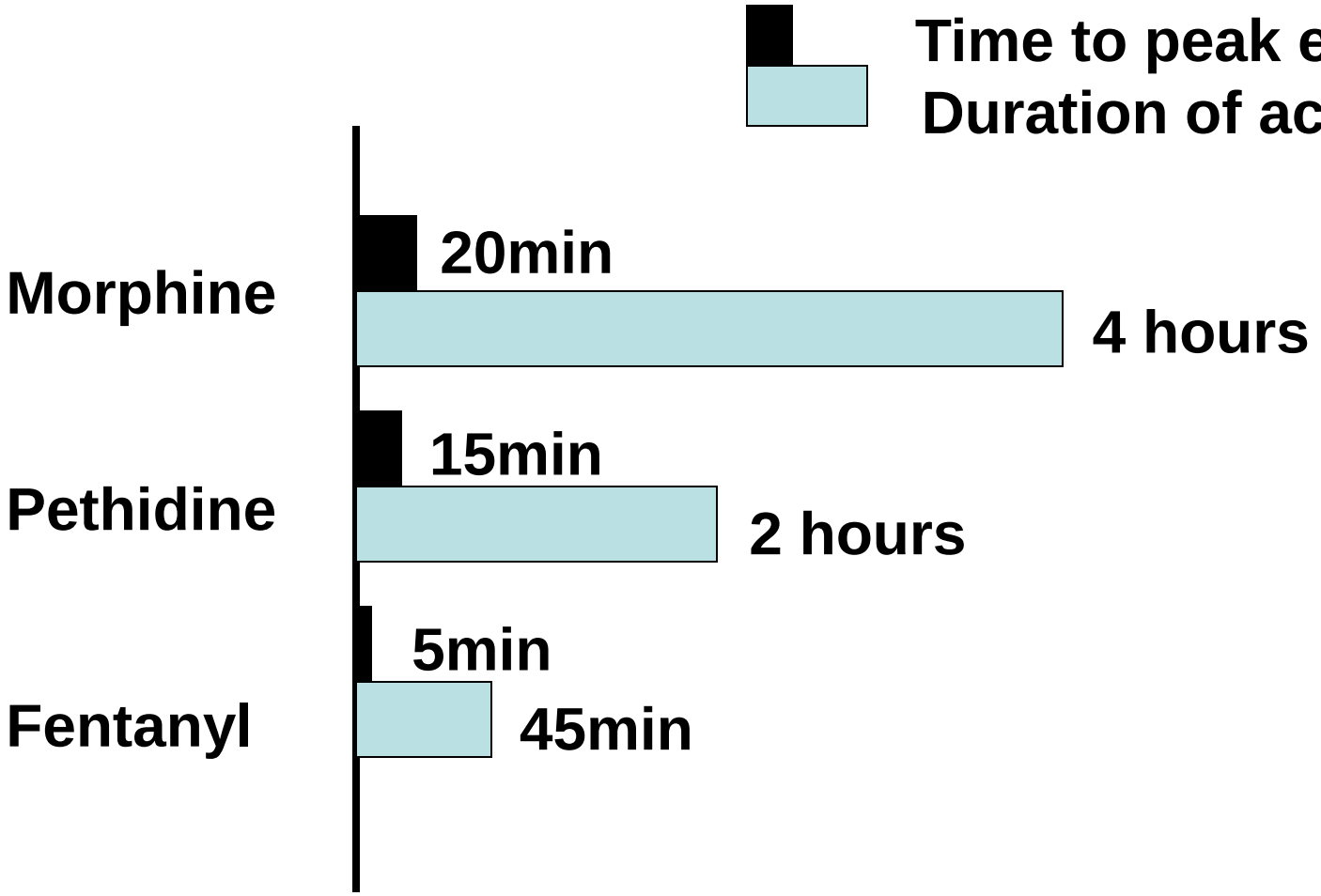
δ opioid receptor

Analgesia

Antagonist act at μ, κ, δ receptors
- **Naloxone**
- **Naltrexone**



A comparison of the maximum <u>efficacy and addiction/abuse liability</u> of commonly used narcotic analgesics



Time to peak effect and duration of action of several opioids administered intravenously

4. Morphine

4.1 Pharmacological effects:

A Analgesia:

- Raises the pain threshold at the spinal cord level, alters nociception in the brain.
- Relieves anxiety and fear

B Euphoria:

- Produces a powerful sense of contentment and well-being by stimulation of the ventral tegmentum.

4. Morphine

C Respiration:

- Causes respiration depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide.

D Depression of cough reflex:

- May allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

-Replaced by other safer antitussives .

4. Morphine

E Miosis:

- The pinpoint pupil is the characteristic of morphine use, little tolerance.

F Emesis:

- Causes vomiting by stimulating the CTZ in the medulla but with no unpleasant sensations.

4. Morphine

G Sedation:

- Causes drowsiness and clouding of mentation, even disrupting sleep

H Gastrointestinal effect:

- Decreases motility of smooth muscle and increases tone, which causes constipation and increases pressure in the biliary tract (worsens abdominal colic, eg. Sphincter oddi contraction).

4. Morphine

I Cardiovascular :

- **Has no major effects on the cardiovascular system.**
- **Is usually <u>contraindicated in</u> individuals with severe <u>brain injury</u> (because that increased PCO_2 induced by respiration depression leads to cerebral vasodilation and consequential increase in cerebral blood flow and intracranial pressure).**
- **Causes postural hypotension sometimes.**

4. Pharmacodynamics- morphine

J Histamine release:

- Causes pruritus, urticaria, sweating, vasodilation and bronchoconstriction.

K Hormonal actions:

- Inhibits release of LH.
- Increases GRH, ADH , PRL

M Immune depression

4. Morphine

4.2 Therapeutic uses:

A Analgesia:

- **Used for various pain, especially acute, obstinate constant pain (e.g. burn, cancer pain);**
- **Fixed interval of administration reduces tolerance and dependence;**
- **Severe pain of renal and biliary colic + MR blockers.**

4. Morphine

B Cardiac asthma:

- **Acute left ventricular heart failure induces pulmonary edema**
- **Reduces anxiety, cardiac preload and afterload.**
- **Particularly useful for painful myocardial ischemia with pulmonary edema.**

C Treatment of diarrhea: synthetic surrogates

4. Morphine

D Relief of cough: synthetic antitussives

E Premeditate drugs before anesthesia :

sedative, anxiolytic, and analgesic properties. For high-risk surgery administered systemically; for local (epidural) anesthesia.

Caution: respiratory suppression

4. Morphine

4.3 Adverse effects:

- **Respiratory depression**
- **Vomiting, constipation, biliary colic**
- **Dysphoria**
- **Allergy-enhanced or postural hypotensive effects**
- **Urinary retention (prostatic hypertrophy)**
- **Elevation of intracranial pressure (head injury)**
- **Immune depression**

4. Morphine

Tolerance and Physical Dependence

- Repeated use produces tolerance to the respiratory depression, analgesic, euphoric and sedative effects, but not to pupil-constricting and constipating effects.
- Physical and psychologic dependence readily occur for strong μagonists, especially used on necessities.

4. Morphine

Tolerance and Physical Dependence

- Withdrawal symptoms: a series of autonomic, motor and psychological response that incapacitate the individual (rhinorrhea, lacrimation, yawning, chills, gooseflesh, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, and hostility).

4. Morphine

4.4 Contraindications:

- **Women during labor or lactation**
- **New-born infants**
- **Chronic obstructive pulmonary disease (COPD)**
- **Asthma**

5. Pethidine (meperidine)

5.1 Actions and mechanisms:

- **Binds to opioid receptors, particularly μ receptor.**
- **Actions similar to but less potent than morphine.**

----Transient decrease of gastro-intestinal motility and increase of the tone

---- Indistinctly central depression of cough reflex.

5. Pethidine (meperidine)

5.2 Therapeutic uses:

- **Analgesia: various severe pain, including during obstetric labor (less depression of respiration in newborn infants)**
- **Cardiac asthma**
- **Administration before anesthesia and artificial hibernation, combined with chlorpromazine and promethazine**

6. Pentazocine

- **An agonist on κ receptor, but a weak antagonist at μ and δ receptors (partial agonist).**
- **Actions (less potent compared with morphine): analgesia and respiratory depression, indistinct euphoria and dependence. Dysphoria, hallucinations and hypertension in high dose**
- **Used for moderate or chronic pain.**

7. Naloxone

- **Competitive blocker of opioid receptor, with ten-fold higher affinity for μ receptor than for κ.**
- **Actions:**

  --- precipitates withdrawal symptoms;

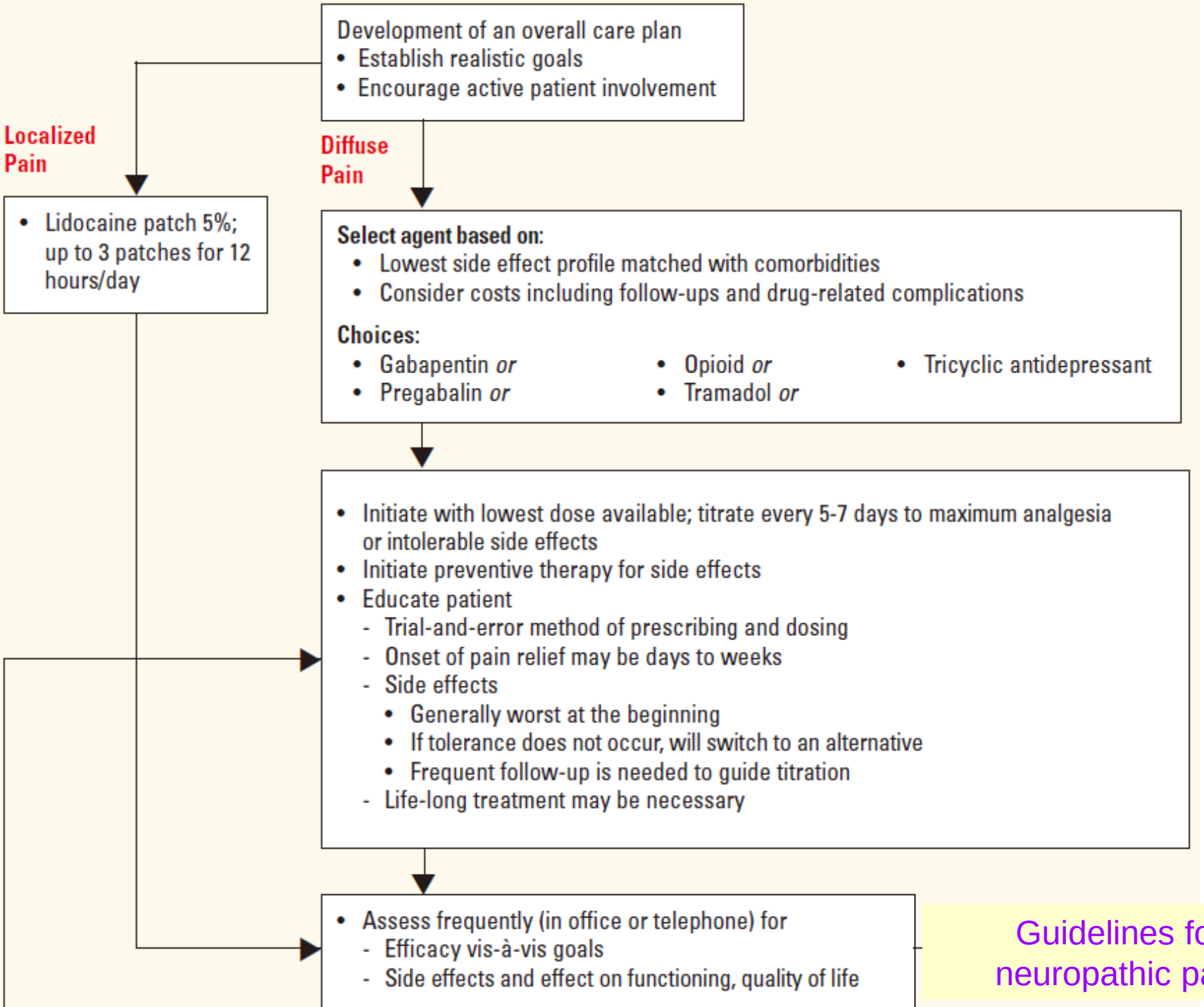
  ---reverses the coma and respiratory depression of opioid overdose (short action duration! Naltrexone with much longer action duration);

  --- eliminates some adverse effects with opioids

8. Other analgesics

- **Tramadol: weak μ receptor agonist, inhibits uptake of NA and 5-HT, effective on moderate to severe acute and chronic pain.**
- **Tetrahydropalmatine: effective on persistent blunt pain**


CHRONIC PAIN TREATMENT CONTINUUM
DIAGNOSIS
LEVEL 1
PAIN THERAPIES
Cognitive & Behavioral Modification
TENS
Rehabilitation Therapy
NSAIDS
Over-the-Counter Pain Medications
Exercise Programs
LEVEL 2
PAIN THERAPIES
Thermal Procedures
Neurolysis
Systemic Opioids
Nerve Blocks
LEVEL 3
PAIN THERAPIES
Spinal Cord Stimulation
Neuroablation
Surgery
Implantable Drug Pumps



Guidelines for neuropathic pain

WHO Step III

C – Opioid for moderate to severe pain
Morphine
Methadone
Oxycodone
Hydromorphone
Buprenorphine
Dextromoramide
± nonopioid
± adjuvants

WHO Step II *If pain persists or increases*

B – Opioid for mild to moderate pain
Tramadol
Codeine
Dihydrocodeine
Dextropropoxyphene
± nonopioid
± adjuvants

WHO Step I *If pain persists or increases*

A – Nonopioid
Acetaminophen
Dipyrone
NSAIDs
± adjuvants

Chemotherapy/Radiotherapy ----------
Physical/Psychological/Behavioral Therapy ----------
Empathy/Care ----------

WHO guidelines for cancer pain