Opioid analgesics

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Pain

PAIN is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

- “We must all die. But that I can save a person from days of torture, that is what I feel is my great and ever-new privilege. Pain is a more terrible lord of mankind than even death itself.”

Albert Schweitzer

Acute pain

- acute pain is short-term pain (day or weeks) or pain with an easily identifiable cause
- acute pain “is the body's warning of present damage to tissue or disease
- acute pain is centralized in one area before becoming somewhat spread out
- this type of pain responds well to medications – usually monotherapy

Chronic pain

- chronic pain is pain that last much longer than pain normally would (more than 3-6 months) with a particular injury.

- chronic pain can be constant or intermittent and is generally harder to treat than acute pain – usually drug combination + nonpharmacology treatment

- pain can also be grouped by its source and related pain detecting neurons such as cutaneous pain, somatic pain, visceral pain, and neuropathic pain

Antinociceptive effect of drugs according site of action

1) Decrease of nociceptor sensitivity a/ local anesthetics – surface, infiltration a. b/ analgesics- antipyretics
2) Block of nerve conduction a/ local anesthetics – nerve block anesthesia
3) Block of pain transmision on spinal colum level a/ local anesthetics – spinal a. b/ opioid analgesics
4) Effect on thalamo-cortical level a/ opioid analgesics
5) Effect on hypothalamo-limbic area a/ opioid analgesics b/ neuroleptics

Terminology

- “opium” is a Greek word meaning “juice,” or the exudate from the poppy which has been used for social and medicinal purposes for thousands of years, as an agent to produce euphoria, analgesia and sleep, and to prevent diarrhoea

- “opiate” is a drug extracted from the exudate of the poppy

True opiate – morphine, codeine

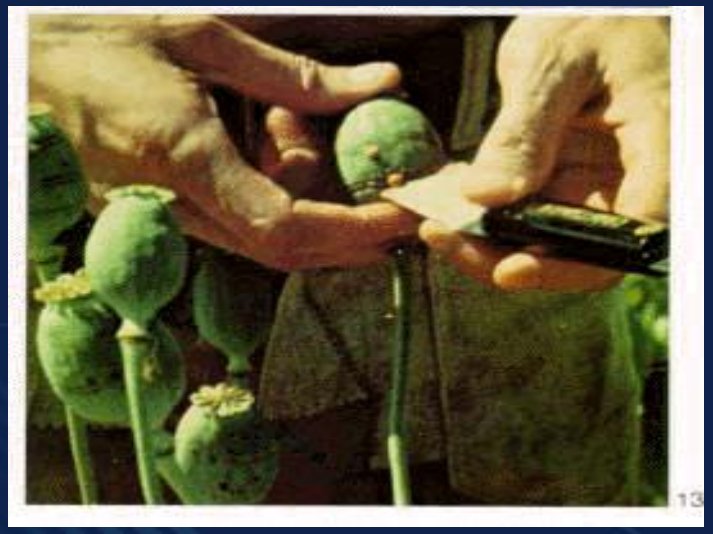
- “opioid” is a natural or synthetic drug that binds to opioid receptors producing agonist effects

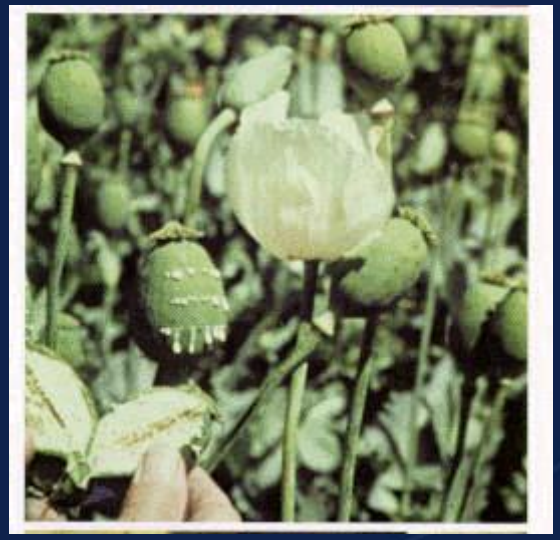
Classification of opioids

Natural opium alkaloids:
- morphine
- codeine

Semisynthetic opiates:
- diacetylmorphine (heroin)
- hydrocodone • hydromorphone •
- oxycodone • oxymorphone

Synthetic opioids:
- pethidine (meperidine)
- fentanyl, alfentanil, sufentanil, remifentanil
- methadone
- dextropropoxyphene
- tramadol





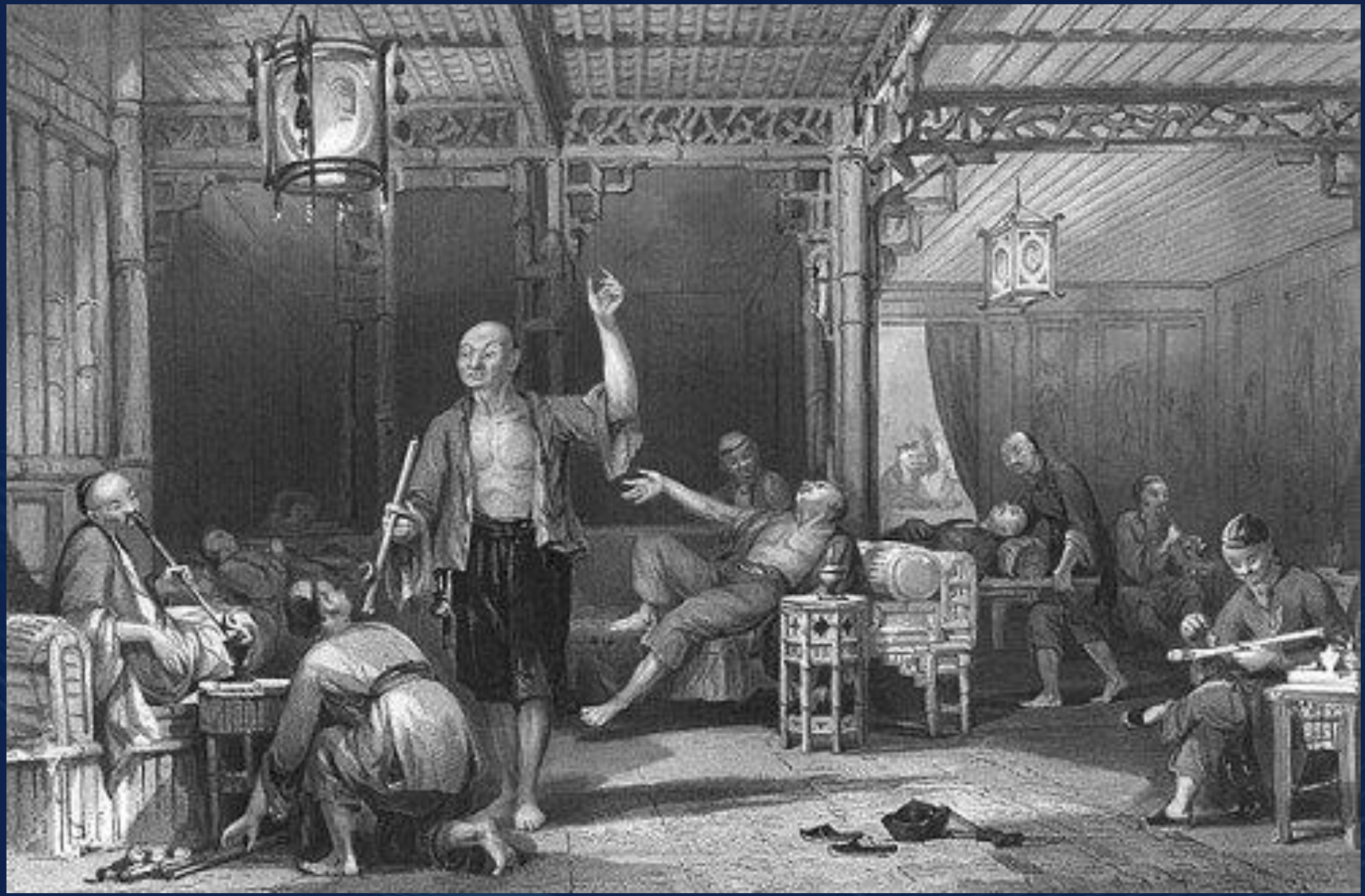
History of opioids

- Opium, the milky latex sap of *Papaver somniferum*, referred to as early as 3000 *B.C.* and found in Spanish burial sites dated 4200 *B.C.*

- Greeks and Romans used opium to produce constipation, sleep

More history...

- opium use spread from its origins in Turkey with the expansion of Islam
- Arab traders took it to India and China
- in Persia, Avicenna (Ibn-Sina, 980-1037) recommended opium for eye disease and diarrhea
- in 1644, the Chinese emperor banned tobacco smoking; Chinese switched to smoking opium
- the Opium Wars (1841, 1856-58, 1860)



"Chinese Opium Smokers" by Thomas Allom

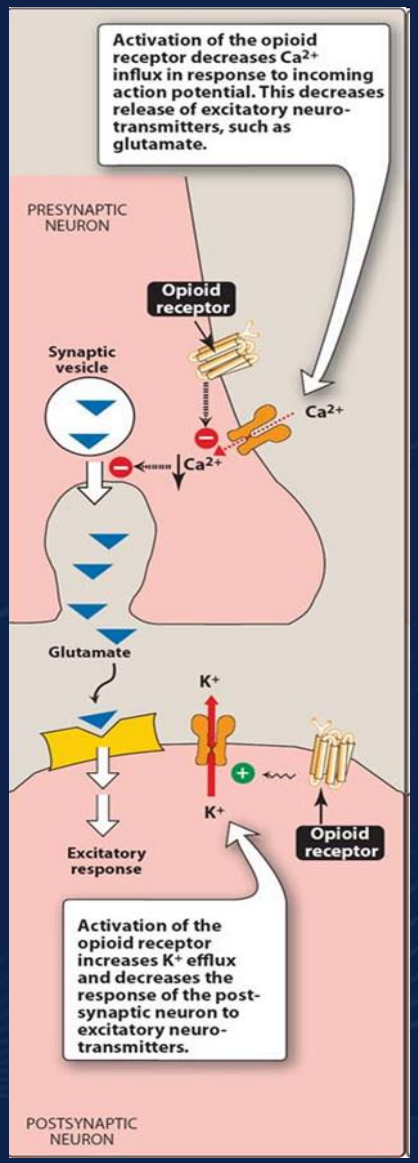
History cont'd

- Opium and laudanum (opium combined with alcohol) were used to treat almost all known diseases
- Morphine was isolated from opium in the early 1800's (1804 Friedrich Sertürner) and since then has been the most effective treatment for severe pain
- 1874 C.R. Wright – discovers "Heroin" or diacetylmorphine by boiling morphine

Morphine pharmacodynamics

- o p i o i d receptors : there are 3 main receptor subtypes.
- they belong to the family of G-proteins-coupled receptors

- their stimulation:
  - inhibits adenylyl cyclase - ↓ cAMP content
  - exerts effects on ion channels through a direct G-protein coupling to the channels:
    - promote the opening of K^+ channel
    - and inhibit the opening of voltage-gated Ca^{2+} channels



Consequences

decrease in:

- neuronal excitability (since the increased potassium conductance causes hyperpolarization of the membrane)
- transmitter release (due to inhibition of calcium entry)

At the spinal level, morphine **i n h i b i t s:**

- transmission of nociceptive impulses through the dorsal horn
- release of **substance P** from dorsal horn neurons

Three Opioid Receptors

- Mu (μ)
- Kappa (κ)
- Delta (δ)

Mu-Receptor: Two Types

- Mu-1
  - Located outside spinal cord
  - Responsible for central interpretation of pain
- Mu-2
  - Located throughout CNS
  - Responsible for respiratory depression, spinal analgesia, physical dependence, and euphoria

Kappa Receptor

- Only modest analgesia
- Little or no respiratory depression
- Little or no dependence
- Dysphoric effects

Delta Receptor

- It is unclear what delta's responsible for.
- Delta agonists show poor analgesia and little addictive potential
- May regulate mu receptor activity

Mu (μ)1	Mu (μ) 2	Kappa (κ)	Delta (δ)
analgesia (supraspinal & spinal)	analgesia (spinal)	analgesia (supraspinal & spinal)	analgesia (supraspinal & spinal)
euphoria	resp.dep.	dysphoria	resp.dep.
miosis	phy. dep	sedation	phy.dep
bradycardia	constipation	miosis	constipation(minimal)
hypothermia		diuresis	urinary retention
urinary retention			

Endogenous opiates

endorphins (α, β, γ) – hypophysis, hypothalamus; the most potent is β-endorphin (high affinity to μ_1-receptors, moderate to μ_2- a δ-receptors and low affinity to κ-receptors)

enkephalins – Met-enkephalin, Leu-enkephalin; neurotransmitters

dynorphins (A, B) – the highest affinity to κ-receptors; CNS transmitters

Receptor Activity

- Agonists – activate one or more opioid receptors (e.g. morphine)
- Antagonists – occupy receptors and prevent agonist binding (e.g. naloxone)
- Mixed agonist-antagonists – agonist activity at one type of receptor and antagonist activity at another type of receptor (e.g. buprenorphine)

Classes of opioids

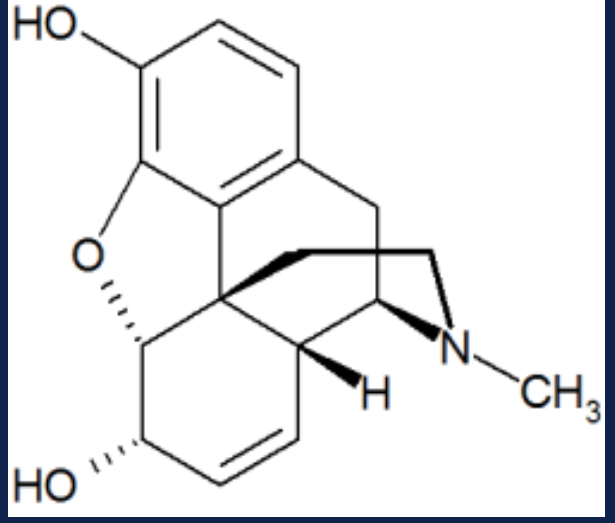
- full agonists
  - morphine (SA)
  - hydromorphone (SA)
  - fentanyl (SA)
  - codeine (W/MA)
  - oxycodone(W/MA)
  - hydrocodone (W/MA)
  - methadone (SA)
- partial antagonists
  - buprenorphine

SA – strong agonists, W/MA – weak/moderate agonists, PA – partial agonists

- mixed agonist-antagonists
  - pentazocine
  - nalbuphine
  - butorphanol
- suppress μ-receptors, activate κ-receptors

- full antagonists
  - naloxon
  - naltrexon

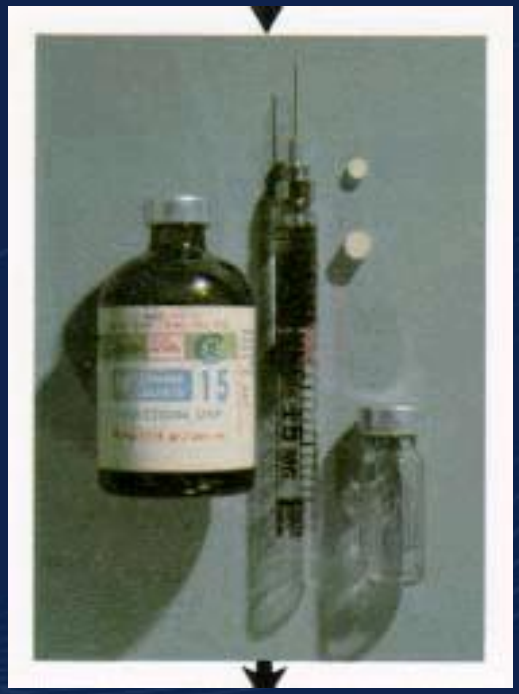
Morphine



- morphine is the golden standard among opioid analgesics to which the structure and strengths of all other drugs are compared
- it is the primary ingredient in opium and was isolated in 1804
- morphine has strong binding affinity for the μ and δ opioid receptors and some weak affinity for the κ receptor

Morphine – *cont.*

- morphine is administered in subcutaneous, intravenous or epidural injections or orally in the form of a solution (however this form is far less potent).
- morphine acts extremely fast and crosses the blood brain barrier quickly but is not as fast acting lipid-soluble opioids such as codeine or heroin



Morphine metabolism

- once morphine is administered about one third of it become bound to proteins in the plasma

- the major pathway for the metabolism of morphine is conjugation with **glucoronic acid**

- two metabolites are formed from this conjugation which cross the blood brain barrier
  - **morphine-6-glucuronide** seems to be the metabolite responsible for the associated interactions of morphine with the opioid receptors
  - morphine-3-glucuronide is inactive

Effects of opioids

A. CENTRAL EFFECTS

1. analgesia
2. euforia
3. sedation
4. respiratory depression
5. depression of cough reflex
6. miosis (except Meperidine)
7. nausea and vomiting
8. muscle rigidity

Analgesia

- pain consists of both sensory and affective (emotional) components.

- opioid analgesics reduce both aspects of the pain experience, especially the affective aspect.

- in contrast, nonsteroidal anti-inflammatory analgesic drugs have no significant effect on the emotional aspects of pain.

Euphoria

- intravenous drug users experience a pleasant floating sensation with lessened anxiety and distress (DA release in nucleus accumbance).

- however, dysphoria, an unpleasant state characterized by restlessness and malaise, may sometimes occur.

Sedation

- drowsiness
- clouding of mentation
- little or no amnesia
- no motor incoordination
- sleep is induced in the elderly (can be easily aroused from this sleep)

Respiratory Depression

- by inhibiting brainstem respiratory mechanisms.

- alveolar PCO_2 may increase, but the most reliable indicator of this depression is a depressed response to a carbon dioxide challenge.

- in individuals with increased intracranial pressure, asthma, chronic obstructive pulmonary disease, or cor pulmonale, this decrease in respiratory function may not be tolerated.

Cough Suppression

- codeine in particular
- however, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

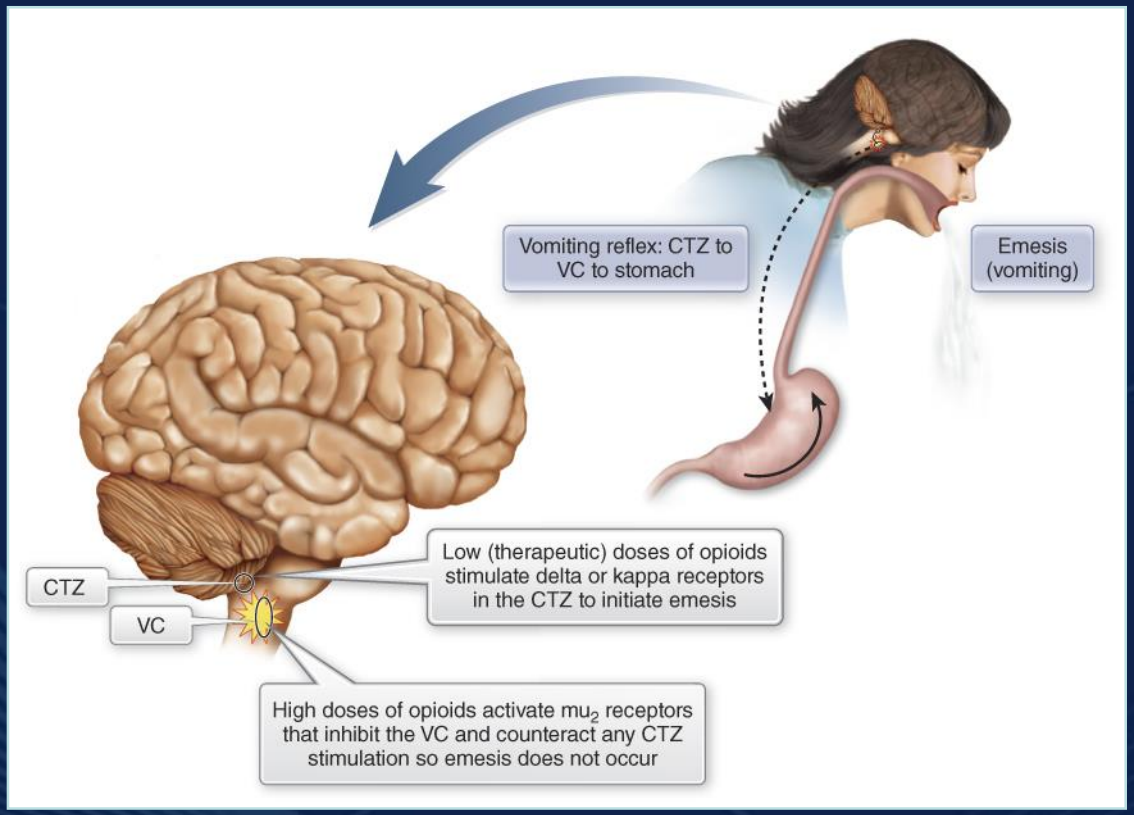
Temperature regulating centre depression

- chances of hypothermia

Vasomotor centre depression

- Fall in BP

Nausea and vomiting



Miosis

- constriction of the pupils
- By stimulating Edinger Westphal nucleus of III nerve
- miosis is a pharmacologic action to which little or no tolerance develops
- valuable in the diagnosis of opioid overdose.

Truncal rigidity

- Truncal rigidity reduces thoracic compliance and thus interferes with ventilation.

- Truncal rigidity may be overcome by administration of an opioid antagonist, which of course will also antagonize the analgesic action of the opioid.

- Preventing truncal rigidity while preserving analgesia requires the concomitant use of neuromuscular blocking agents.

Effects of opioids

B. PERIFERAL EFFECTS

1. cardiovascular system
2. gastrointestinal tract
3. biliary tract
4. urogenital tract
5. neuroendocrinne effects
6. others (histamine, immunosupression)

Cardiovascular System

- Bradycardia

  Meperidine is an exception (can result in tachycardia)

- Hypotension - due to
  - peripheral arterial and venous dilation
  - depression of vasomotor centre
  - release of histamine.

- Increased PCO_2 leads to cerebral vasodilation associated with a decrease in cerebral vascular resistance, an increase in cerebral blood flow, and an increase in intracranial pressure.

Gastrointestinal Tract

Constipation

- no tolerance
- Oopioid receptors exist in high density in the gastrointestinal tract
- constipating effects of the opioids are mediated through an action on the enteric nervous system as well as the CNS
- gastric secretion of hydrochloric acid is decreased
- propulsive peristaltic waves are diminished
- tone is increased
- this delays passage of the fecal mass and allows increased absorption of water, which leads to constipation
- so used in the management of diarrhea

Biliary Tract

- sphincter of Oddi may constrict
- contract biliary smooth muscle
- result in biliary colic

Renal

- renal function is depressed by opioids
- decreased renal plasma flow
- enhanced renal tubular sodium reabsorption
- ureteral and bladder tone are increased
- increased sphincter tone may precipitate urinary retention
- ureteral colic caused by a renal calculus is made worse by opioid-induced increase in ureteral tone

Uterus-

- may prolong labor
- both peripheral and central actions of the opioids can reduce uterine tone

Pruritus-

- CNS effects and peripheral histamine release may be responsible for these reactions
- pruritus and occasionally urticaria (when administered parenterally)

Neuroendocrine effects

- inhibit the release of gonadotropin-releasing hormone (GnRH) and corticotropin-releasing factor (CRF), thus decreasing circulating concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), ACTH, and β- endorphin
- as a result of the decreased concentrations of pituitary trophic hormones, the concentrations of testosterone and cortisol in plasma decline
- secretion of thyrotropin is relatively unaffected.

Morphine effects on various smooth muscles

- **biliary tract**
  - marked increase in the pressure in the biliary tract
  - increase due to contraction of Sphincter of Oddi
- **urinary bladder**
  - tone of detrusor muscle increased
  - feel urinary urgency
  - have urinary retention due to increased muscle tone where sphincter closed off
- **bronchial muscle**
  - bronchoconstriction can result
  - contraindicated in asthmatics, particularly before surgery

Effects of selected opioids

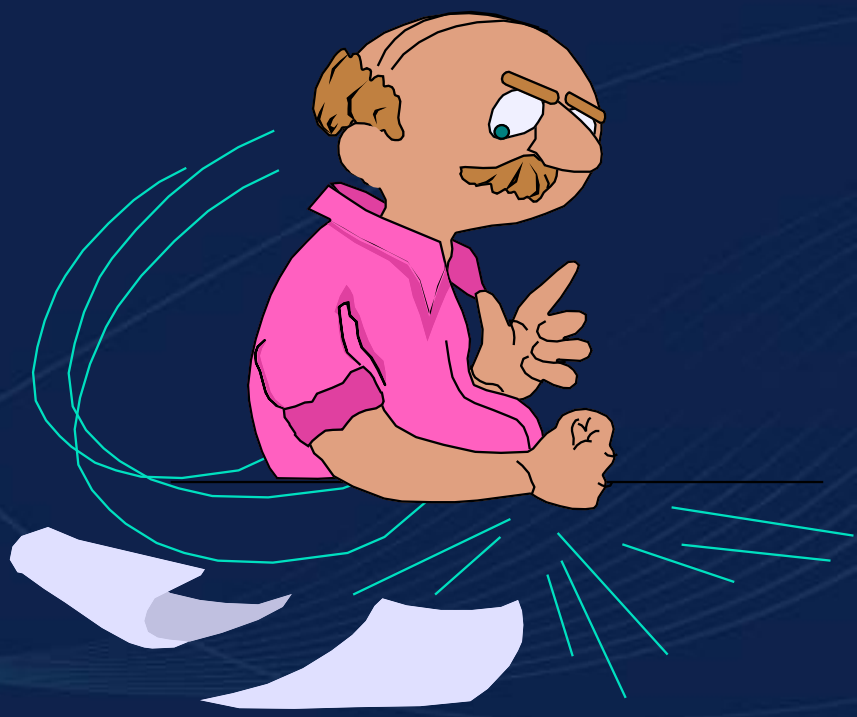
DRUG	ANALG.	ANTITUS.	OBSTIPA.	RESP. DEP.	DEPEND.
butorphanol	++/+++	–	±	++/+++	±
codeine	+	++	++	+	±
heroin	+++	++	+++	+++	++++
hydromorphone	+++	++	++	+++	+++
meperidine	++/+++	–	±	+++	++
methadone	+++	++	++	+++	++
morphine	+++	++	+++	+++	+++
oxycodone	++	++	++	++	+++
pentazocine	++/+++	–	±	++/+++	+
propoxyphene	+	–	±	+	+

Therapeutic uses of opioids

- relief of pain
- terminal illness
- preoperative medications
- postoperative medications
- open heart surgery
- acute pulmonary edema
- constipating effect
- cough
- obstetrical analgesia

Opioid adverse effects

- constipation
- urinary retention
- sedation
- respiratory depression
- nausea
- confusion
- myoclonus
- orthostatic hypotension
- itching, urtica,
- bronchoconstriction



Contraindications or *use with caution*

- Head injury or craniotomy
- Acute pancreatitis
- Bronchial asthma
- Acute alcohol intoxication
- Hypovolemic shock - use i.v.
- Hypothyroidism
- Convulsive disorders
- Hepatic failure

Drugs interactions of opioids

- phenothiazines, - ↑CNS depressant effects of opioid narcotics
- lower dose needed with CNS depressants

- small doses - amphetamines, antihistamines, - ↑ effects of morphine analgesia

- meperidine + MAO inhibitors: excitation, delirium, hyperpyrexia, convulsions, or severe respiratory depression

Definitions

- **Addiction:** psychological dependence with compulsive drug use, and craving for opioids for effects other than pain relief

- **Tolerance:** when increased doses of a drug is needed to produce the same pharmacological effect

- **Withdrawal:** a cluster of physiological signs and symptoms, which occur after sudden ceasing of some drugs

- **Dependency:** when sudden absence of an opioid produces physical withdrawal syndrome

Opioid tolerance

High	Medium	Minimal
analgesia	bradycardia	miosis
euphoria, dysphoria		constipation
physical dependence		convulsion
sedation		
respiratory depression		
antidiuresis		
nausea, vomiting		
antitussic effect		

Toxicity

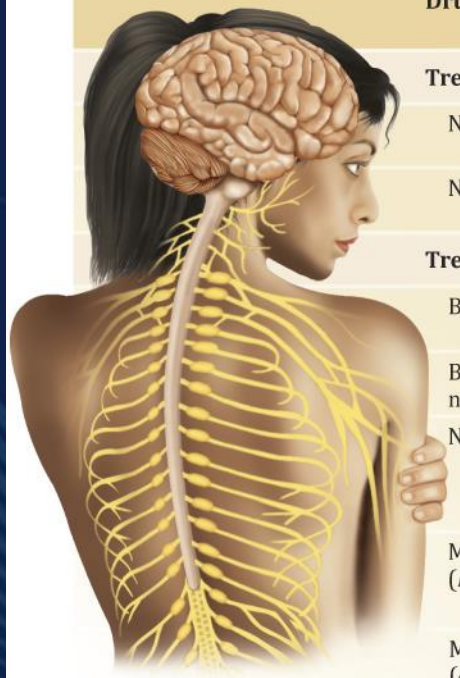
Acute (naloxon)

Chronic (methadone, buprenorphine, L-α -acetyl methadol (LAAM))

- tolerance (ability of the body to alter its response (to adapt) to drug effects so that the effects are minimized over time).

- dependence (drug required to prevent onset of withdrawal symptoms)

Opioid Antagonists Used to Treat Opioid Analgesic Respiratory Depression or Addiction



Drug (*Trade Name*)	Type of antagonist	Adult dose
Treatment of respiratory depression		
Naloxone (*Narcan*)	Pure	0.4–2 mg repeated at 3-min intervals IM, SC, IV
Nalmefene (*Revex*)	Pure	Individualized dose by weight
Treatment of addiction		
Buprenorphine (*Subutex*)	Partial	12–16 mg maintenance dose PO, sublingual
Buprenorphine and naltrexone (*Suboxone*)	Partial, pure	12–16 mg PO maintenance dose, 0.5 or 2 mg dose sublingual
Naltrexone (*ReVia*)	Pure	Only after the patient has been opioid-free for 7–10 days; maintenance dose 50 mg every 24 hr
Methadone (40 mg) (*Intensol*)	—	15–20 mg PO initially; 40 mg for those dependent on high opioid doses
Methadone diskettes (40 mg)	—	2.5–10 mg PO, IM, SC every 3–4 hr
Levomethadyl (*Orlaam*)	—	Maintenance dose 60–90 mg three times a week

Treatment options

- **Best treatment option is <u>PREVENTION!</u>**

- **Counseling & Behavioral Therapies**
  - Individual and group counseling
  - Inpatient and residential treatment
  - Intensive outpatient treatment
  - Case or care management
  - Recovery support services
  - 12-step fellowship
  - Peer supports

- **Medication Assisted Treatment**
  - Buprenorphine
  - Methadone
  - Naltrexone

"Treatment for Substance Abuse Disorders." *SAMHSA*. N.p., 8 Sept. 2016. Web. 26 Jan. 2017. Available at: https://www.samhsa.gov/treatment/substance-use-disorders

Acute morphine poisoning

- **TRIAD**: coma, miosis, cyanosis (🡻 respiration)
- asphyxia, pupils dilate
- biliary spasms, G.I. smooth muscle spasm
- pulmonary edema
- muscle twitches, peripheral vasodilation, hypotension, shock
- **RESPIRATORY FAILURE - DEATH 2-4 hrs!!**

Opiate overdose treatment

- first one must monitor and support respiration with oxygen, if necessary
- next is the administration of an **opioid antagonist** such as naloxone.
- **naloxone**, given iv, has a **very short duration** of action (1-4 hours)
- **monitoring of the patient is critical** due to the short duration of action - several opiates have durations of action that are longer than that of naloxone
- **naltrexone** is an opiate antagonist which has a **relatively long duration** of action of 24 hours

Dependence on opioids

- **The euphoria** that individuals feel can lead to an **uncontrollable need to continue taking the drug**
- it is reinforced by the **physical dependence** that results in taking opiates
- if the drug is stopped then **withdrawal symptoms** occur
- **duration and severity of the withdrawal is dependent on the opiate's half life**, **a short $T_{1/2}$ like in the case of heroin (0.5hrs) leads to severe withdrawal symptoms, while methadone with long half life has a milder withdrawal symptoms**.

Withdrawal Reactions

Acute Action	Withdrawal Sign
• Analgesia	• Pain and irritability
• Respiratory Depression	• Hyperventilation
• Euphoria	• Dysphoria and depression
• Relaxation and sleep	• Restlessness and insomnia
• Tranquilization	• Fearfulness
• ⇩blood pressure	• ⇧ blood pressure
• Constipation	• Diarrhea
• Pupillary constriction	• Pupillary dilation
• Hypothermia	• Hyperthermia
• Drying of secretions	• Lacrimation, runny nose
• Reduced sex drive	• Spontaneous ejaculation

Withdrawl symptoms

Time (hours)	Symptoms
6-12	anxiety, lacrimation, rhinorhea, sweating
12-24	insomnia, iritability, tremor, mydriasis, anorexia. piloerection
24-72	depression, nausea, vomiting, GIT-cramps, diarhea, several aches, tachycardia, ↑ BP, involuntary leg and arms movement, dehydratation, electrolyte dysbalance
72-	insomnia, decrease intenzity of above mentioned symptoms, 7-10 days – physical symptoms largely disappear; strong craving for the drug

Why do people abuse opioids?

- Predisposition:
  - psychopathological basis for euphoria
  - deficient endorphin systems
  - painful emotional states
- Maintenance:
  - avoid withdrawal
  - experience euphoria
  - alleviate painful emotional states
  - damaged endorphin system need opioids

Fear of addiction

- Fear of creating addiction in patients contributes to the **under use** of opioid analgesics (Ferrell BR et al, J Pain & Sympt Manage, 1992)

- The risk of addiction for patients having opioids for medical reasons is **low**

- Tolerance to an opioid **does not** mean the patient has an addiction

Tramadol

- synthetic opioid
- weak agonist of μ-receptors in CNS
- stimulation of serotonin release
- inhibition of noradrenaline re-uptake
- therapy of acute or chronic pain (moderate to severe)
- painful diagnostic or therapeutic intervention
- postsurgery pain
- cancer pain (II. step in pain treatment)

Tramadol

- p.o. - rapid and good resorption
- T_{max} - 2 hours after administration
- bioavailability after rectal administration - 70 %
- plasma protein bound - 20%
- placentar barrier - 80%

Tramadol

- biotransformation in liver - demetylation

  O-demetyltramadol - pharmacologically active - affinity to μ receptors - cca 200x higher than in tramadol

- "First pass metabolism" - 30%
- more than 90 % of tramadol is excreted by urine (70 % as metabolites)

Tramadol
contraindications and side effects

- acute intoxication with alcohol, hypnotics, opioids, or another CNS-depresive compounds (A)
- co-administration of MAO inhibitors (A)
- I. trimester of gravidity (R)
- hypersensitivity to other opioid analgetics (R)

- weak respiratory and cardiovascular depresssion
- nausea and vomiting
- minimal risk of dependence

Tramadol

Analgetic effect

- 1 mg/kg equal to:
  - 0.1 mg/kg of morphin
  - 0.00 1mg/kg of fentanyl
  - 0.1 mg/kg methadon
  - 1.0 mg/ kg of mepridine

Analgetic effect of tramadol in daily dose of 250 mg is comparable to combination codeine/paracetamol in doses 150/1500 mg

Tapentadol

- FDA approval – 21 November 2008
- Potency between morphine and tramadol

Mechanism of action

- Agonist at μ receptor
- Inhibitor of noradrenaline uptake
- Modify sensory and affective aspects of pain
- Inhibit pain pathways at spinal cord and brain

Pharmacokinetics

- Administered orally
- Bioavailabilty - 32%
- Peak plasma concentration after ~ 0.83 hrs.
- Metabolism in liver – Phase II glucouronidation
- No active metabolite

Uses

- In moderate to severe pain
- In pts of end stage joint disease, pts with dental pain
- Provided acceptable pain relief

Contraindications

- ↑ ICP
- Impaired consciousnesss
- Coma
- Caution in
  - head injury
  - Pancreatic, biliary and hepatic disease
  - Elderly
  - Pts with respiratory compromise- COPD, asthma, cor-pulmonale,sev.obesity,sleep apnea syndrome(resp. depression)
  - Patients with risk of abuse

Adverse effects

- Nausea,
- Vomitting
- Somnolence
- Headache

Fentanyl

- **Fentanyl** is an opioid analgesic introduced into medical practice in the 1960s
- analgesic potency of about 80-100 times that of morphine
- It is extensively used for anesthesia and analgesia, most often in the operating room and intensive care unit.
- fentanyl transdermal patch is used in chronic pain management
- patches work by releasing fentanyl into body fats, which then slowly release the drug into the blood stream over 72 hours, allowing for long lasting relief from pain.

New fentanyl derivatives

Sufentanil

- 10x more potent than fentanyl
- high affinity to μ-receptors
- great therapeutic index
- cardiovascular surgery

Alfentanil

- 1/4 - 1/3 of fentanyl activity
- short acting
- analgesia after 1 min.

New fentanyl derivatives – *cont.*

Carfentanil

- 100x more potent than fentanyl
- imobilisation of animals (6 t elephant - 10 mg i.m.)
- It is intended for animal use only as its extreme potency makes it inappropriate for use in humans.

Iofentanil

- 50x more potent than fentanyl
- difficult to antagonize
- in experiments

Carfentanil

- It is thought that in the 2002 Moscow theater hostage crisis, the Russian military made use of an aerosol form of carfentanil to subdue Chechen hostage takers. Its short action, easy reversibility and therapeutic index (10600 vs. 300 for fentanyl) would make it a near-perfect agent for this purpose.

Carfentanil

- Wax *et al.* surmise from the available evidence that the Moscow emergency services had not been informed of the use of the agent, and therefore did not have adequate supplies of naloxone or naltrexone to prevent complications in many of the victims.

- Assuming that carfentanil was the only active constituent (not verified by the Russian military), the primary acute toxic effect to the theatre victims would have been opioid-induced apnea; in this case mechanical ventilation and/or treatment with opioid antagonists would have been life-saving for many or all victims.

Pethidine (meperidine)

- 1/10th in analgesic potency
- Spasmodic action on smooth muscles is less
- Tachycardia (**antimuscarinic** action)- it is related to atropine, even acts on opioid receptors
- Safer in asthmatics (less histamine release)
- Uses- analgesia, preanaesthetic medication
- Preferred opioid analgesic during labour (less neonatal respi depression)

Methadone

- slow & persistant action
- sedative & subjective effects are less intense
- less abuse potential
- use- as substitute therapy for opioid dependence
- 1mg methadone for 4 mg morphine.

Moderate opioid receptor agonists: codeine

- About **10% of codeine** (methylmorphine) is **converted to morphine**
- **Less respiratory depression, less dependence and less euphoria than morphine**
- Used for **moderate pain** and as an **antitussive**

- Up to 10% of population are poor metabolizers – little or no analgesia from codeine
- Max. analgesia = 12-15% that of morphine
- At high doses causes CNS stimulation

Pentazocine (κ analgesic)

- It has agonistic actions and weak opioid antagonistic activity
- elicit dysphoric and psychotomimetic effects
- increase in blood pressure and heart rate

Uses-

- moderate to severe pain
- as a preoperative medication and
- as a supplement to anesthesia

Mixed Agonist-Antagonists

Opioid	*Receptor Type*			
	μ	κ	σ	δ
Buprenorphine	partial			
Butorphanol	antagonist	agonist	agonist	-
Nalbuphine	antagonist	partial	agonist	-
Pentazocine	antagonist	agonist	agonist	-

Opioid antagonists

Naloxone

- Non- selective antagonist at all 3 opioid receptors
- Short duration of action-30-45 min

Uses

- reversal of opioid-induced vent. depression
- vent. depression in neonates after maternal opioid adminstration
- opioid overdose
- detect physical dependence
- S/E- nausea, vomitting,CVS stimulation, ↑sympathetic activity

Naltrexone:

Similar to naloxone, but longer duration of action (24 hrs)

Nalmefene

Analogue of naltrexone

Equipotent to naloxone

Longer $t1_{/2}$- 6.8 hrs

WHO 3-step ladder

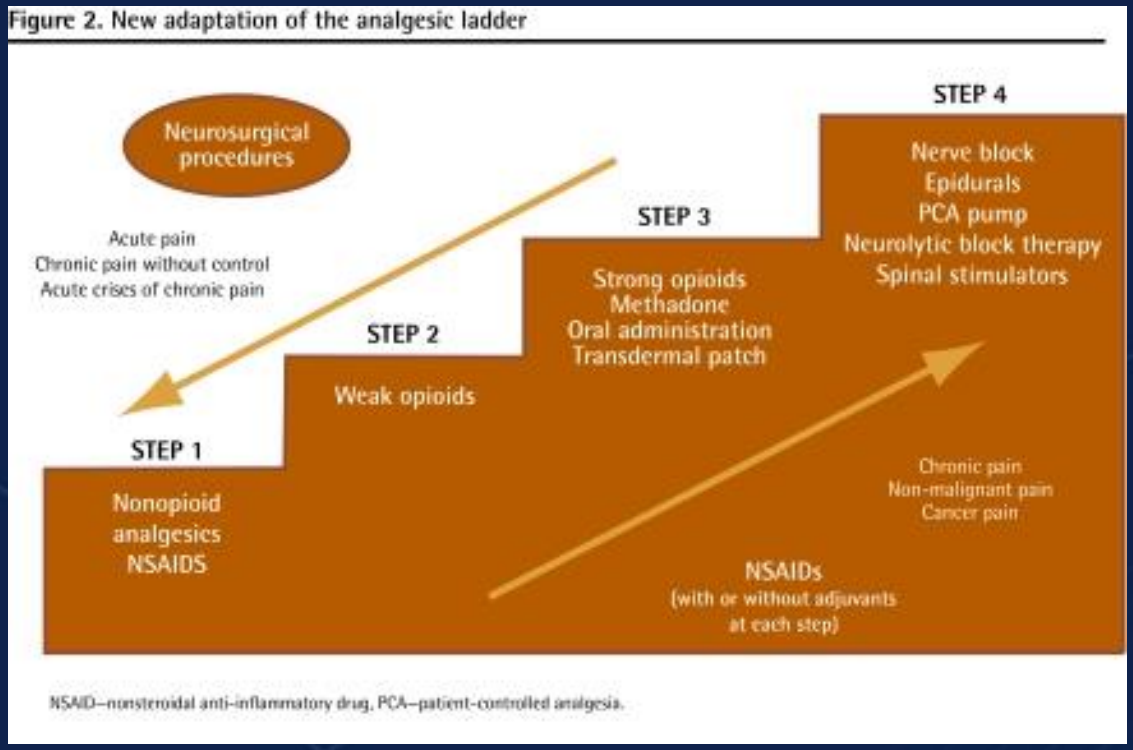
Pain

Step 1: Non-opioid
± Adjuvant

Step 2: Opioid
± Adjuvant
± Non-opioid

Step 3: Stronger Opioid
± Adjuvant
± Non-opioid

Pain Free



Acute: step down

Chronic: step up

I.step

ASA

paracetamol

NSAID

± *Adjuvants*

antidepressants

neuroleptics

anxiolytics

anticonvulsants

II. step

codeine, hydrocodone

oxycodone, tramadol

dihydrocodeine

± *I.step analgesics*

± *Adjuvants*

III. step

morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone

± *I.step analgesics; ± Adjuvants*

Opioids used in cancer pain

Drugs	Dose (mg) equianalgesic to morphine 10mg IM/IV			
	PO	IM/IV	Half-life (h)	Duration (h)
Morphine (morphine syrup (immediate release)	20-30	10	2-3	2-4
Morphine controlled release	20-30	10	2-3	8-12
Morphine sustained release	20-30	10	2-3	24
Hydromorphone	7.5	1.5	2-3	2-4
Oxycodone	20		2-3	3-4
Oxycodone CR	20		2-3	8-12
Methadone	20	10	8->120	4-12
Fentanyl	–	–	7-12	–
Fentanyl TS	–	–	16-24	48-72

Opiophobia

- The fear of prescribing opioid pain medications is known as "opiophobia”

- *Goodman and Gillman’s Pharmacological Basis of Therapeutics* insists that although physical dependence and tolerance may develop, this should not in any way prevent physicians from fulfilling their primary obligation to ease the patient’s discomfort

Finally…

Optimal pain management is the right of **all** patients and the responsibility of **all** health professionals