OPIOIDS

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Objectives

- **Opioid Classification**
- **Site of action and mechanism of opioids**
- **Clinical application**
- **Adverse Effects of opioids**

Nomenclature

- **OPIUM**
  - **The dried powdered(poppy seeds) 20^{+} alkaloids**
- **OPIATE**
  - **Any agent extracted from opium**
  - **Analgesic action: Morphine, Codeine**
- **OPIOID**
  - **All substances (synthetic and semi-synthetic) with morphine-like properties : work at opioid receptors**

Opioid Classification

By Synthesis

- Natural
- Semisynthetic
- Synthetic

By Action

- Agonist
- Partial Agonist
- Mixed Agonist-Antagonist
- Antagonist

By WHO

- Weak
- Strong

By Synthesis

- **Natural (Alkaloid) :**
  - Morphine, Codeine
- **Semi-Synthetic : modified morphine functional groups**
  - Diacetylmorphine(Heroin)
  - Thebain derivatives (Oxycodone, Oxymorphone)
- **Synthetic:**
  - Morphine Series (Levorphanol, Butorphanol)
  - Diphenylproplyamines (Methadone)
  - Phenylpiperidine derivatives (Meperidine, Fentanyl)

World Health Organization

Weak opioids

- Codeine
- Dihydrocodeine
- Dextropropoxyphene
- Tramadol

Strong opioids

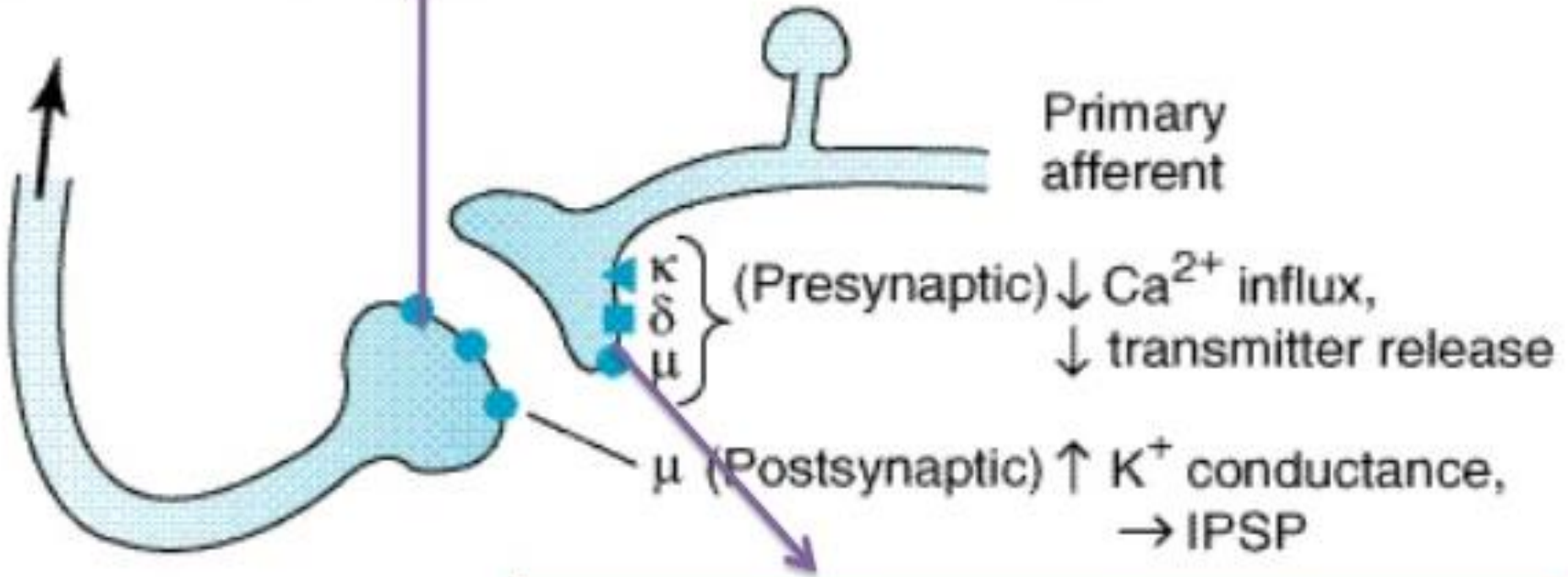
- Morphine
- Methadone
- Fentanyl
- Hydromorphone
- Pethidine
- Oxycodone

By Action

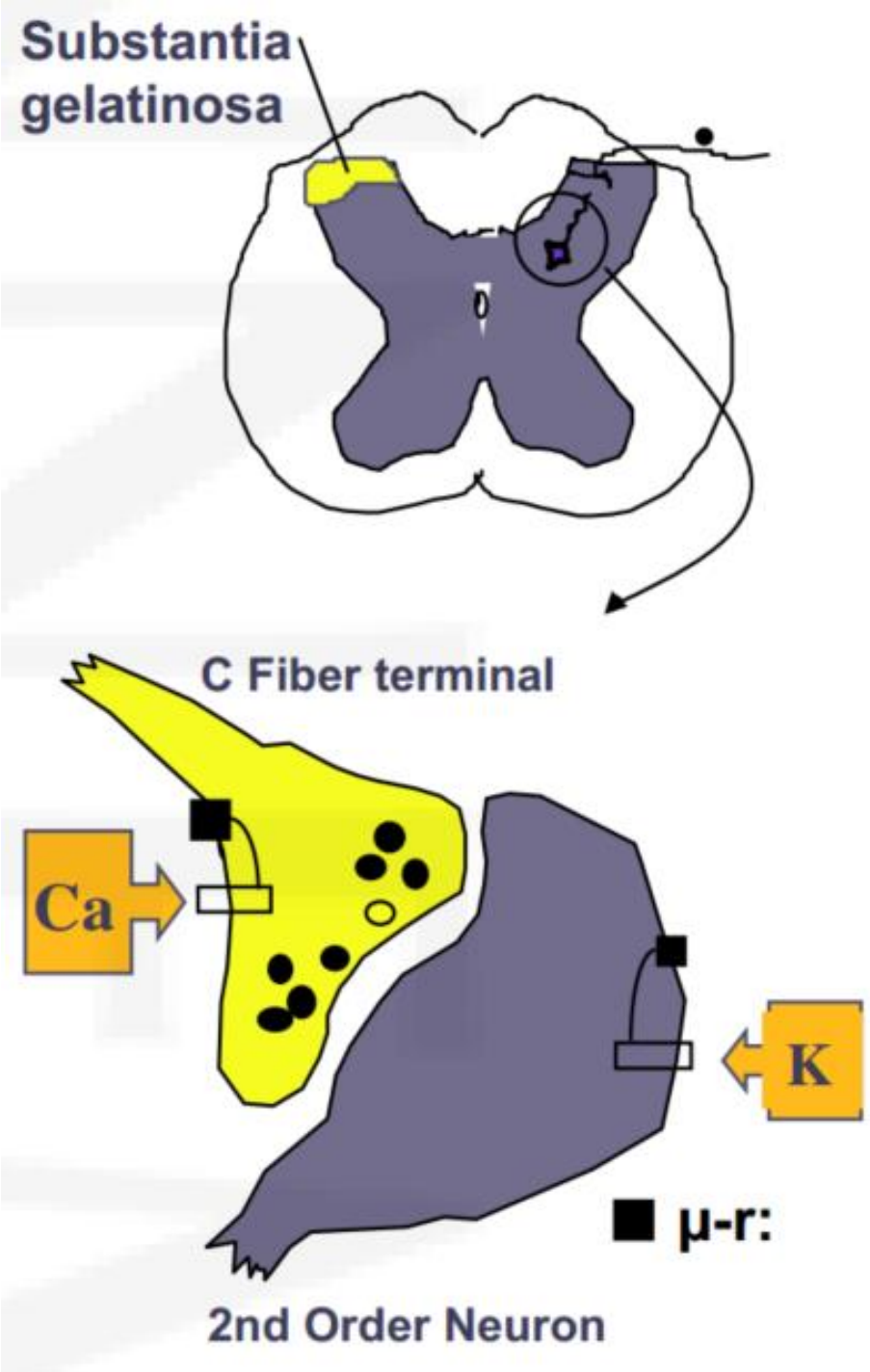
	μ (Mu)	K (Kappa)	δ (Delta)	σ (Sigma)
Agonist				
- Morphine	Agonist	Weak Agonist	-	-
- Meperidine	Agonist	-	Agonist	-
- Fentanyl	Agonist	-	-	-
- Methadone	Agonist	-	-	-
Partial agonist				
- Buprenorphine	P. Agonist	-	-	-
Agonist-Antagonist				
- Nalbuphine	Antagonist	P.Agonist	Agonist	-
- Pentazocine	Antagonist	Agonist	Agonist	-
- Butorphanol	Antagonist	Agonist	Agonist	-
Antagonist				
- Naloxone	Antagonist	Antagonist	Antagonist	Antagonist
- Naltrexone	Anatgonist	Antagonist	Antagonist	Antagonist

Receptor	Clinical Effect
Mu 1	- Supraspinal analgesia
Mu 2	- Spinal analgesia - Sedation - Respiratory depression - Nausea/vomiting
Kappa	- Spinal analgesia without concomitant respiratory depression - Dysphoria - Psychotomimetics - Diuresis - Sedation
Delta	- Supraspinal and spinal analgesia - Respiratory depression - Physical dependence - Constipation - Urinary retension
Sigma	- No analgesia - Dysphoria - Hallucination - Vasomotor stimulation : tachycardia, hypertension, mydriasis

hyperpolarize
second-order pain transmission neurons by increasing K+ conductance, evoking an inhibitory postsynaptic potential



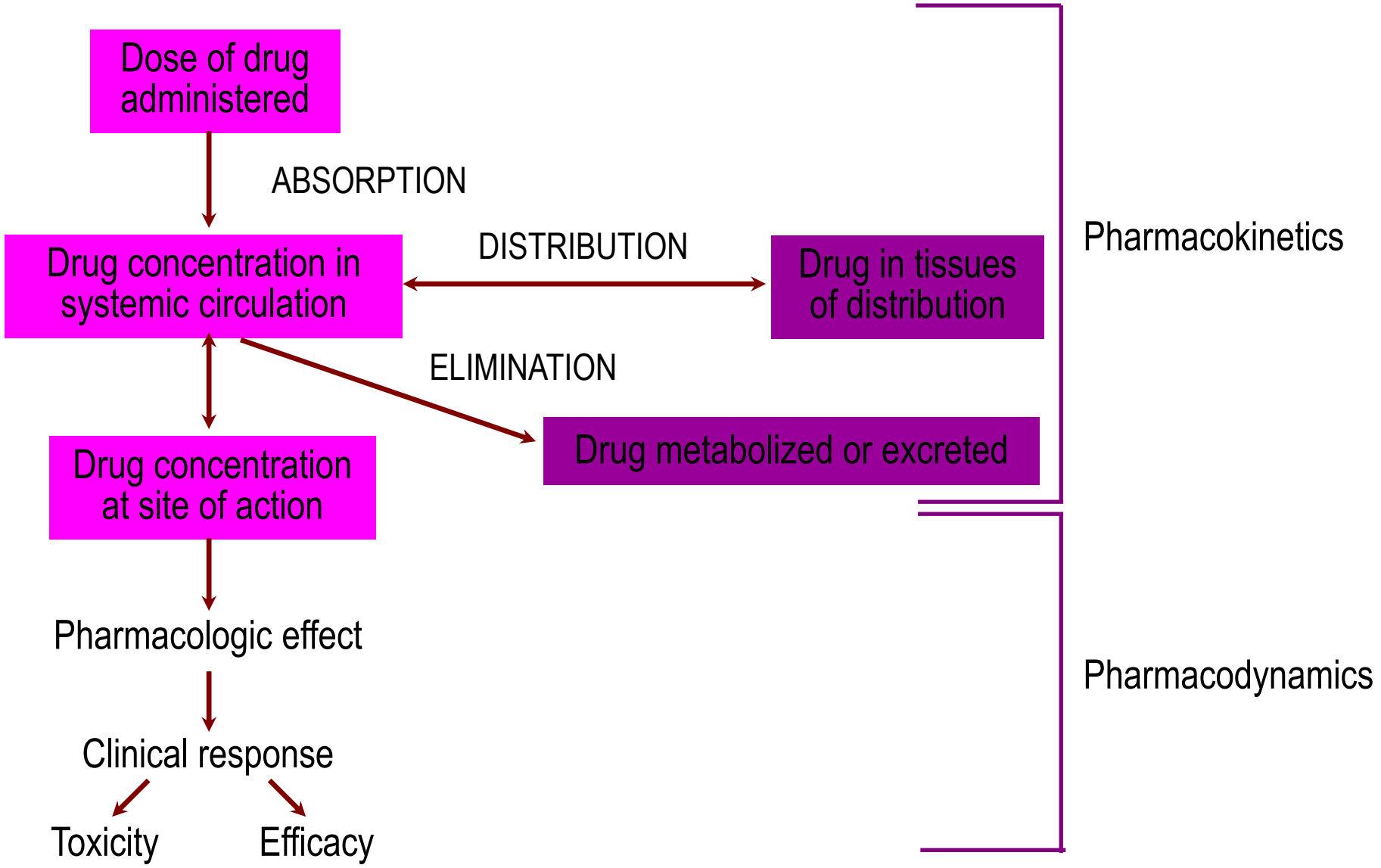
reduce transmitter release
from presynaptic terminals of nociceptive primary afferents



Spinal Opiate Analgesia Mechanism

- Opioid receptors on terminals of sensory C fibers
- Presynaptic: ↓Ca channel activation
  - ↓release transmitters
- Post-synaptic:↑K channel permeability
  - hyperpolarization
  - ↓glutamte &sub P

Pain Medicine & Management Just the facts. 2015: 134-141.



The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components.

CYP P3A4

- Enzyme Inhibitor
  - Cimetidine
  - Antiviral: Ritonavir
  - Antibiotic: Erythromycin,clarithromycin
  - Antifungal: Itraconazone,ketoconazone
  - Antiarrthymic: Verapamil,diltiazem,amiodarone
- Enzyme inducer
  - Rifampicin,Glucocorticoid,Barbiturate,Ethanol
  - Anticonvulsant: Phenytoin,Carbamazepine

Duragesic® (fentanyl transdermal system) US prescribing information (Jul 2009)

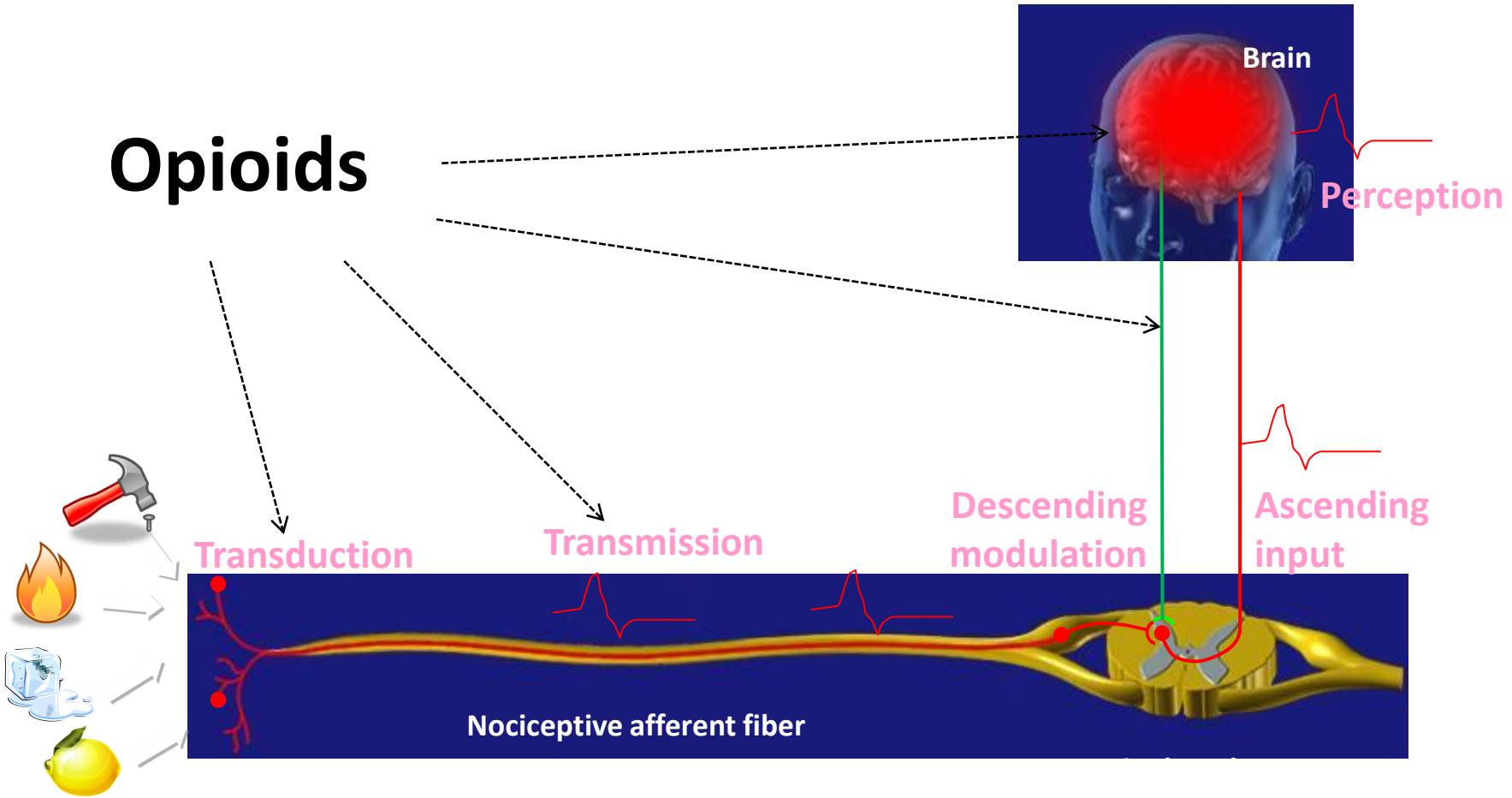
CYP 2D6
(Oxycodone, Tramal, Codeine)

- Enzyme inhibitor
  - Cimetidine
  - SSRI(fluoxetine, setraline)
  - SNRI
- Enzyme inducer
  - Rifampicin
  - Dexamethasone

Metabolic Pathways of Opioids

- **Phase 1**
  - **Metabolism mainly involves CYP3A4 & CYP2D6**
- **Phase 2**
  - **Glucuronidation**
    - **Catalyzed by uridine diphosphate glucuronosyltransferse (UGT enzymes)**

How Opioids Affect Pain



Excretion

- Most opioid metabolites is excreted via the **kidneys**
- Methadone is primarily excreted in the **feces**

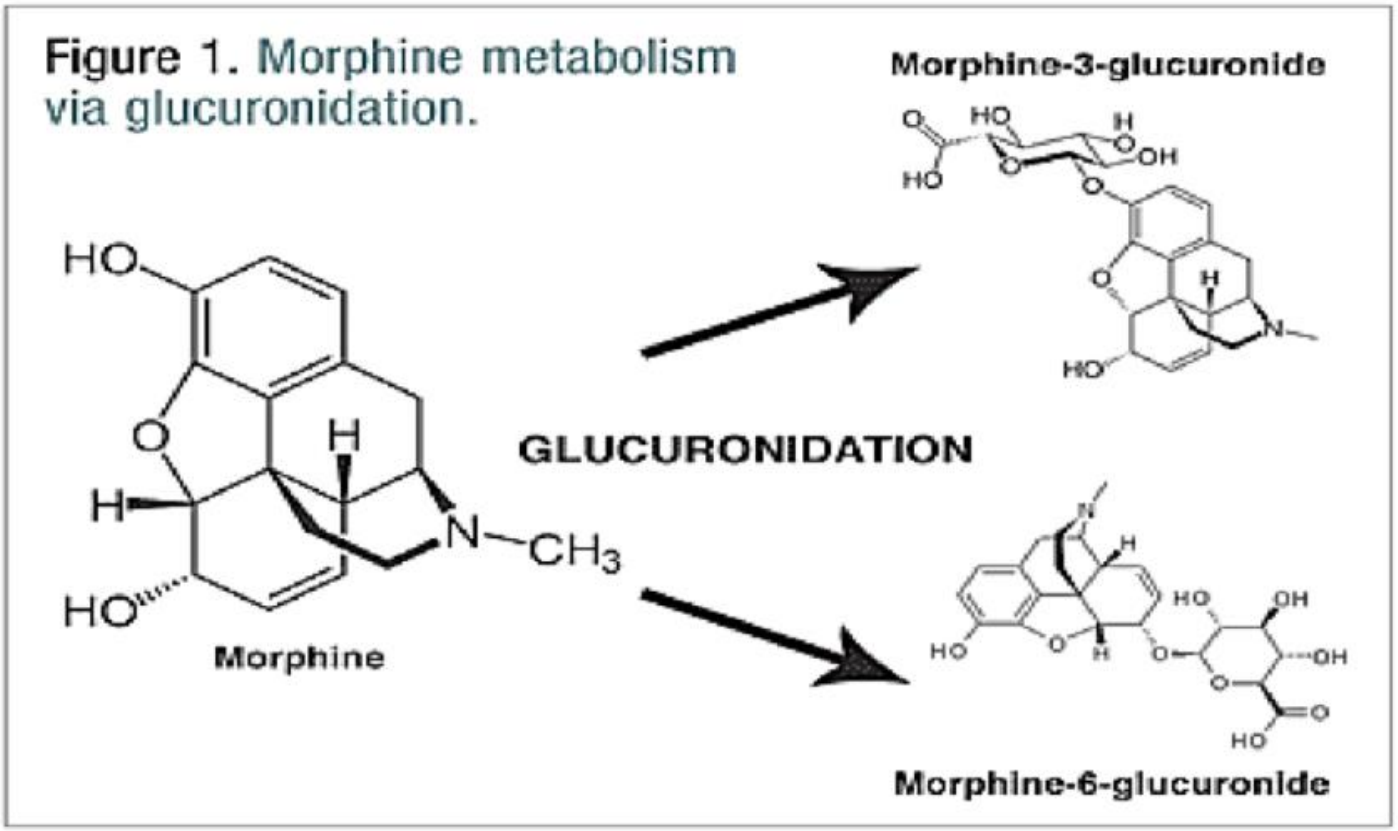
Pharmacology of Specific Opioids

- Morphine
- Fentanyl
- Meperidine
- Oxycodone
- Methadone
- Codeine
- Tramadol

Morphine

- **Half-life of morphine is:**
  - **2-4 hours in adults**
  - **6-8 hours in neonates**
  - **15 hours in elderly (individual)**
- **Oral bioavailability 20- 40% (30%)**
  - Dose oral 3X dose IV
- **Hydrophilic** nature, **delaying onset** of action
- **After 3 months of age, renal clearance and respiratory depression is same as adults.**

Morphine



- **Metabolized**
  Glucuronidation
- **Excreted by kidney**
  Caution in patients with renal impairment

Dialysis Implications of morphine

- Caution patients with renal impairment
- Both parent drug or metabolite
  - Completely removed with dialysis from plasma

Morphine

M6G

- 5-15% : more active
- μ (higher affinity) and delta agonist
  - Analgesic
- Accumulate in renal insufficiency patients
  - Prolong effect morphine

M3G

- 50% (major metabolite)
- Anti-analgesic actions
  - Allodynia
  - Hyperalgesia
- Myoclonus, seizures
- Tolerance

Morphine Controlled Release Tablet

Morphine Controlled Release Tablet **60** MG

Morphine Controlled Release Tablet **30** MG

Morphine Controlled Release Tablet **10** MG

Morphine sustained release tablets

Morphine Sulfate controlled release	Strength	Onset	Duration	Note
Tablet 	10 mg 30 mg 60 mg	2-4 hr	12 hr	• Tablets must be swallowed intact • Not permitted to be cut, broken, chewed, crushed, or dissolved.
Capsule 	20 mg 50mg 100 mg	2-4 hr	24 hr	• Gelatin capsule • Pellets can be fed by NG. • Pellets must not be chewed or crushed. • Do not disperse pellets in warm water.

TASP : Clinical Practice Guideline for Cancer Pain (2013)
Kapanol PI

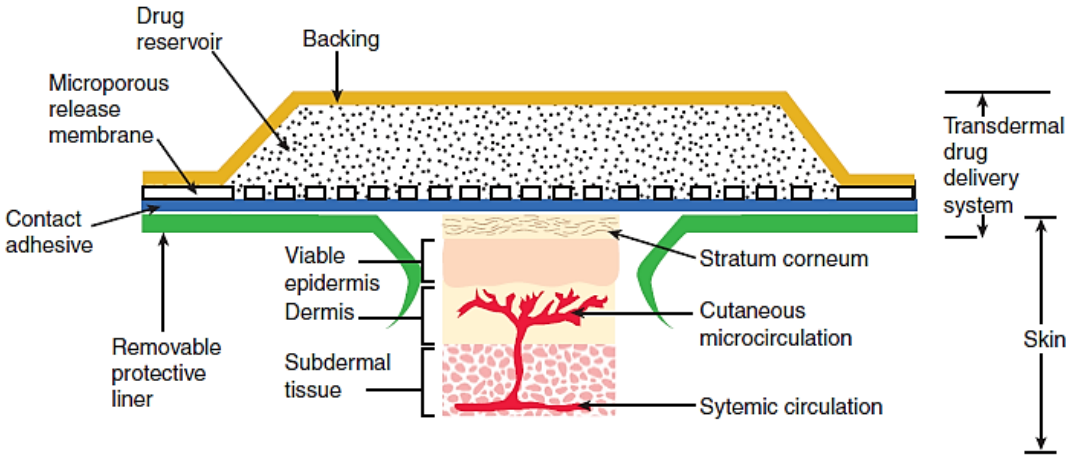
Equianalgesic dose in different routs

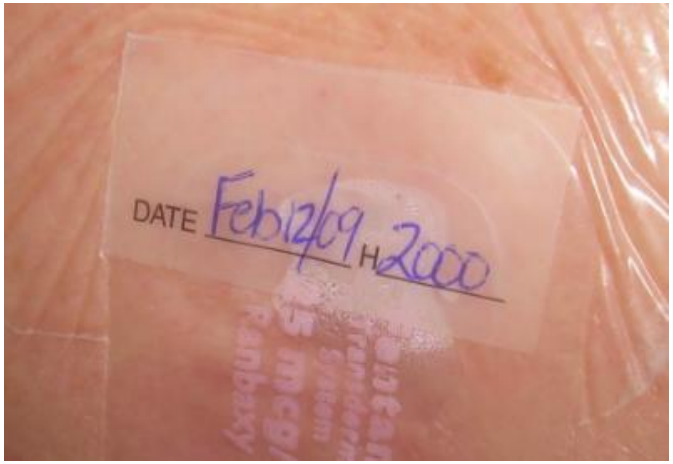
Oral	Intravenous	Epidural	Intrathecal
30	10	1	0.1

Fentanyl

- **Multiple preparations**
  - Oral, transdermal,intravenous
- **Onset** of transdermal is **8-24 hours**
- **Absorption : function of cutaneous blood flow**
- **Metabolize at liver**

Transdermal opioids

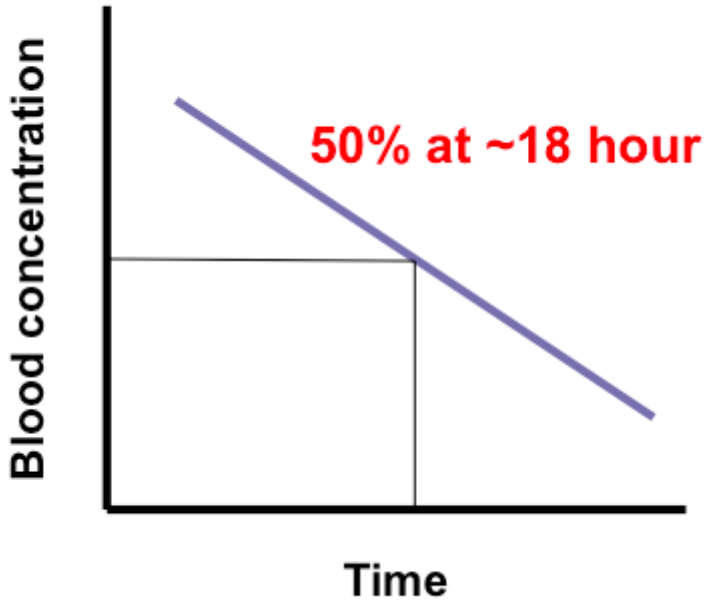


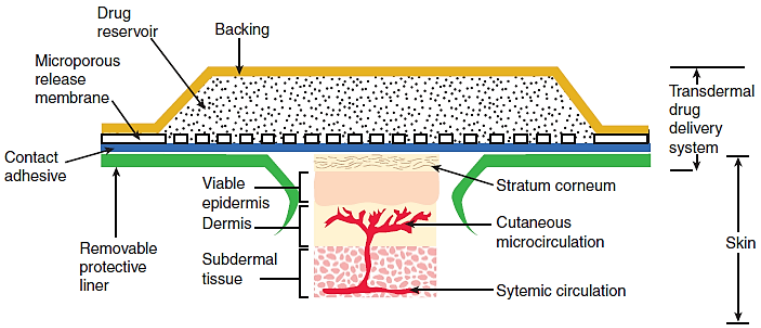


- Stable control
- No need for swallowing
- Suitable for renal impairment

Kitzmiller JP, et al. Ther Deliv 2015; 6(4):419-22; Ahn JS, et al. J Pain Res 2017; 10:1963-72.

Fentanyl transdermal system





- Fentanyl diffuses from the patch to subcutaneous fat.
- Delaying onset [2]
- Peak blood levels ranges from 17 – 48h
- Serum fentanyl concentration to drop by 50% after patch is removed ~ 18 hours[1]
- Prolong adverse effects may take many hours after patch removal

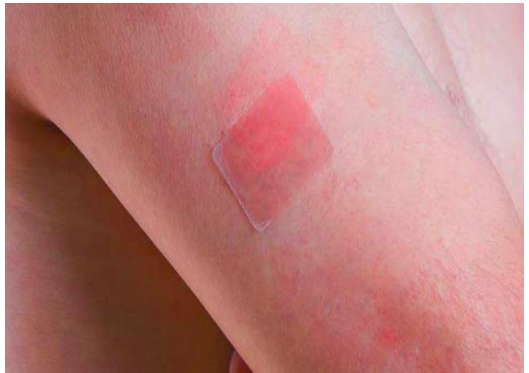
1. Duragesic® (fentanyl transdermal system) US prescribing information (Jul 2009); 2
2. Kornick CA, Santiago-palma J, Moryl N, Payne R, Obbens E. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. Drug safety 2003; 26(13): 951-973.

Transdermal opioids- disadvantages

Example of Calculation for Breakthrough Medications During Titration Phase

Transdermal Fentanyl	Oral Morphine[a]	Oral Oxycodone[a]
25 µg/h	15 mg q3-4h	7.5 mg q3-4h
50 µg/h	30 mg q3-4h	15.0 mg q3-4h
75 µg/h	45 mg q3-4h	22.5 mg q3-4h
100 µg/h	60 mg q3-4h	30.0 mg q3-4h

[a]Dose of breakthrough medication proposed is 25% of dose used prior to conversion to transdermal fentanyl.



- Difficult to titrate dose
- **Over**/under treatment in transitional period
- **Unsuitable for acute or unstable**
- Skin irritation

Vithlani and Baranidharan. Rev Pain 2010; 4(2):8-13.
Ahn JS, et al. J Pain Res 2017; 10:1963-72.

Potential Disadvantages Transdermal opioid

- In patients with a temp ≥ 40°C/104°F, the serum fentanyl concentration could increase[1]
- Drug interaction with CYP 3A4 inhibitor and inducer

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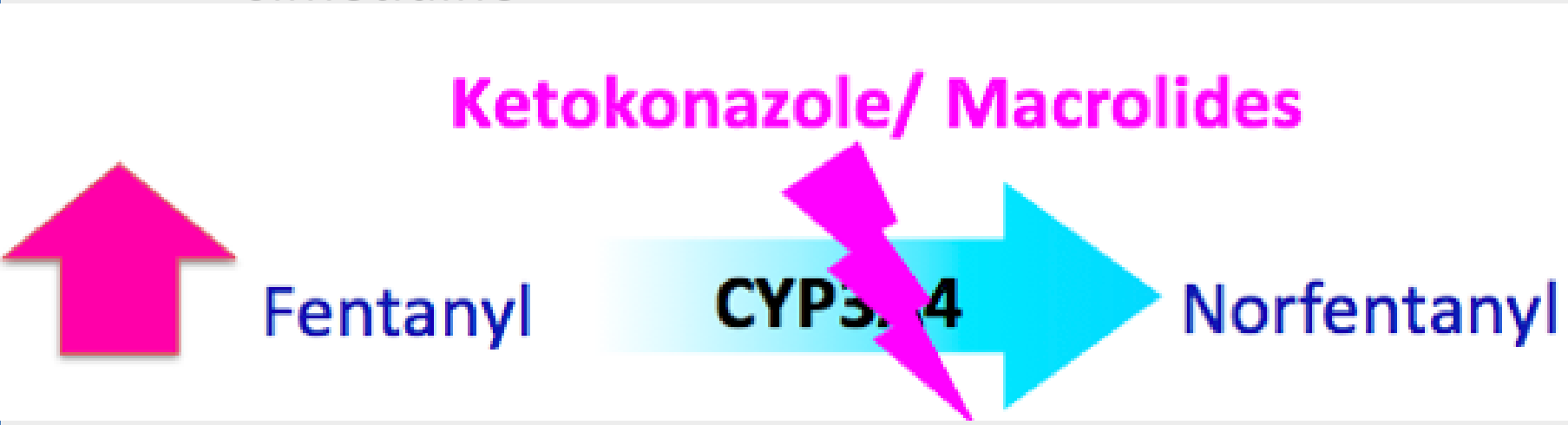

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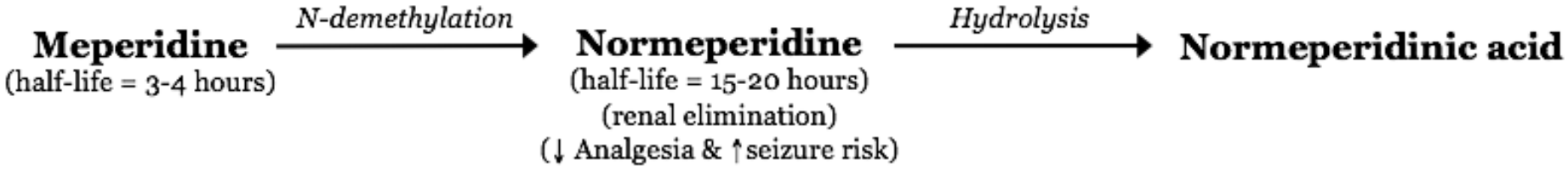
Meperidine

- High lipophilicity
- 8–10 times less potent than morphine
- Metabolized to normeperidine
  - Respiratory depression & excitatory neurotoxicity
  - Not reversible by naloxone



EBM CONSULT®

Meperidine

- Blocks reuptake of NE and HT
- Serotonin syndrome
- Structure similar to Atropine
- Not recommend for chronic pain :Typical drug-seeking behavior
- Limit to use less than 48 hrs or 600 mg per day

The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent Canadian nonprofit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

The Healthcare Insurance Reciprocal of Canada (HIROC) is a member-owned expert provider of professional and general liability coverage and risk management support.

Volume 4, Issue 8

ISMP Canada Safety Bulletin

August, 2004

Meperidine (Demerol®): Issues in Medication Safety

3. Restrict the use of parenteral meperidine to:
   a. The prevention and treatment of drug-induced or blood product-induced rigors (e.g., amphotericin B, platelets)
   b. Treatment of postoperative shivering
   c. Short term pain management in individuals with normal renal, hepatic and CNS function **where alternative opioids are contraindicated** (e.g. drug allergy), and
      i. Do not exceed 600 mg/24 hours,
      ii. Limit the duration of use to 48 hours.

Avoid using…

- **Chronic pain**
- **Continue > 48 hrs**
- **CKD**

Oxycodone

- **Oxycodone (14-hydroxy-7,8 dihydrocodeinone)**
  - Semisynthetic derivative of thebaine
- Activity at **multiple opiate receptors** : **kappa** receptor
- **Oral bioavailability** of oxycodone : **60-80%**
- Available as pure drug, combined with Acetaminophen/NSAID, and continuous release
- **Do not crush the ER version** to mix with juices/applesauce, tube feeds for sustained release products

Oxycodone

- **Metabolized**
  - To **oxymorphone** via Hepatic **CYP450 : 2D6**
    - **Drug–drug interactions : 2D6 inhibitors**
  - To **noroxycodone** via glucuronidation
    - <1% analgesia potency of oxycodone
- **Excreted Renally** after hepatic Glucuronidation
- **$T_{1/2}$ 3-4.5 hours**
- **Analgesic** : not a pro-drug
  - Parent compound : **oxycodone** → analgesia
  - **Oxymorphone** : active metabolite : analgesia

Oxycodone Hydrochloride CR Tablets (Oxycontin)	
Dosing Interval	Every 12 hours
Key instructions	• Opioid-naïve patients: initiate treatment with 10 mg every 12 hr • Titrate using a minimum of 1 to 2 d intervals • **Hepatic impairment: start with ⅓-½ usual dosage** • **Renal impairment** (creatinine clearance <60 mL/min): start w/ ½ usual dosage • Consider other analgesics in patients w/ difficulty swallowing or underlying GI disorders that predispose to obstruction. Swallow tablets whole (do not chew, crush, or dissolve) • Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth
Drug Interaction	• **CYP3A4 inhibitors** may increase oxycodone exposure • **CYP3A4 inducers** may decrease oxycodone exposure
Opioid-tolerant	• Single dose >40 mg or total daily dose >80 mg for use in opioid-tolerant patients only
Product Specific Safety Concerns	• Choking, gagging, regurgitation, tablets stuck in throat, difficulty swallowing tablet • Contraindicated in patients w/ GI obstruction
Relative potency: oral morphine	• Approximately 2:1 oral morphine to oxycodone oral dose ratio

Methadone

- Racemic mixture of 2 enantiomes
- R form is more potent: 10X higher affinity opioid receptor
- S-methadone is the NMDA antagonist, inhibits reuptake of serotonin and norepinephrine : SSRIs and TCAs
- High absorption and a threefold bioavailability compared with morphine

Methadone

- Metabolism;
  - CYP3A4 to inactive metabolite
  - Other CYP such as CYP2D6,CYP2C9 play a minor role
- The alpha elimination phase 8-12 hours
- The beta elimination phase 30-60 hours and is difficult for withdrawal symptoms
- Eliminated via the feces
- Very small fraction excreted in urine

Methadone Hydrochloride Tablets	
Dosing Interval	Every 8 to 12 h
Key Instructions	• Initial dose in opioid non-tolerant patients: 2.5 to 10 mg • Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose & death. • High inter-patient variability in absorption, metabolism, & relative analgesic potency. • Opioid detoxification or maintenance treatment only provided in a federally certified opioid (addiction) treatment program • *Titrate Slowly, with dose increases no more frequent than every 3-5 days. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days)
Drug Interaction	• Pharmacokinetic drug-drug interactions w/ methadone : complex – CYP 450 inducers may decrease methadone levels – CYP 450 inhibitors may increase methadone levels – Anti-retroviral agents have mixed effects on methadone levels • Potentially arrhythmogenic agents may increase risk for QTc prolongation & torsade de pointe • Benzodiazepines may increase respiratory depression
Opioid Tolerant	Refer to full PI
	• QTc prolongation & torsade de pointe • Peak respiratory depression occurs later & persists longer than analgesic effect • Clearance may increase during pregnancy • False-positive UDT possible
Relative Potency	• Varies depending on patient's prior opioid experience

Methadone

Table 7. *Oral Morphine to oral methadone conversion.*

Oral morphine dose	Morphine: methadone ratio
<100 mg	3:1
101 -300 mg	5:1
301-600 mg	10:1
601-800 mg	12:1
801-1000 mg	15:1
> 1000 mg	20:1

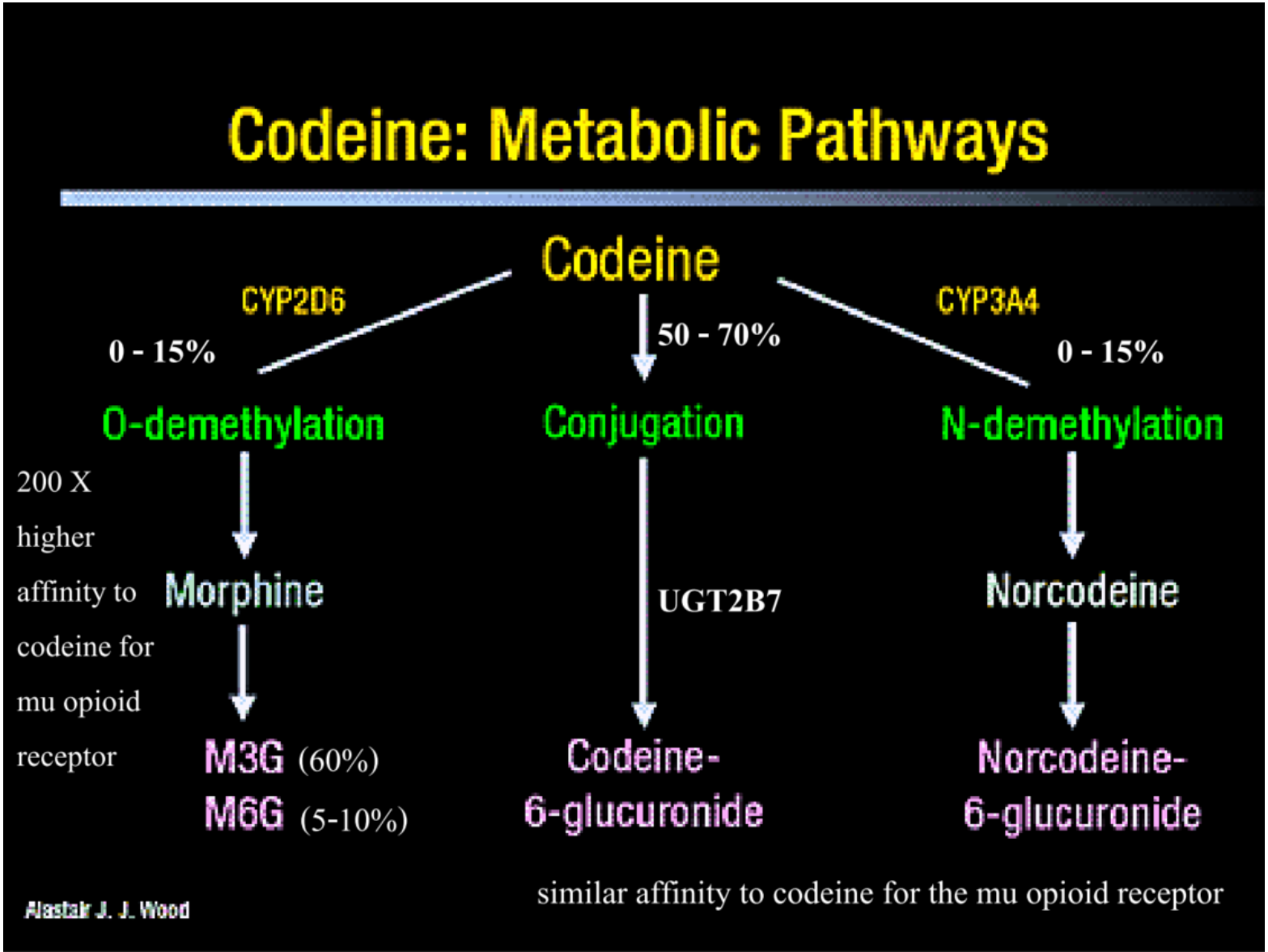
Codeine

- Analgesic potency : 50% of morphine
- Affinity to the μ opioid receptor
  - 300 X lower than morphine
- Oral bioavailability ~90%
- Dose : 15 - 30 mg every 4 - 6 hours
- Max dose 240 - 360 mg/day

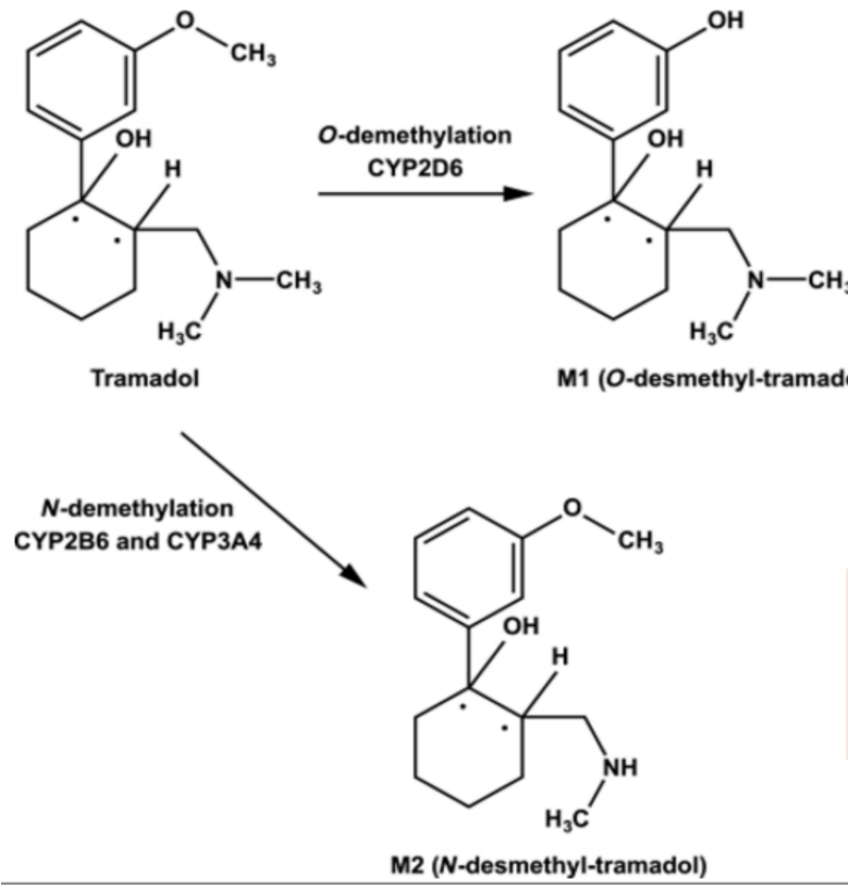
Codeine

- Onset of analgesia at 30 - 60 minutes
- Metabolism
  - Hepatic via UGT2B7, CYP2D6, CYP3A
- Half-life of 2.5 to 3 hours
- 90% drug excreted by kidney within 24 hours

Codeine


Codeine: Metabolic Pathways
Codeine
CYP2D6
0 - 15%
50 - 70%
CYP3A4
0 - 15%
O-demethylation
Conjugation
N-demethylation
200 X higher affinity to codeine for mu opioid receptor
Morphine
UGT2B7
Norcodeine
M3G (60%)
M6G (5-10%)
Codeine-6-glucuronide
Norcodeine-6-glucuronide
similar affinity to codeine for the mu opioid receptor
Alastair J. J. Wood

Tramadol



Mechanism of action

1. **Centrally acting Mu1 agoinst (30%)**

   Weak affinity : 6,000X weaker than morphine

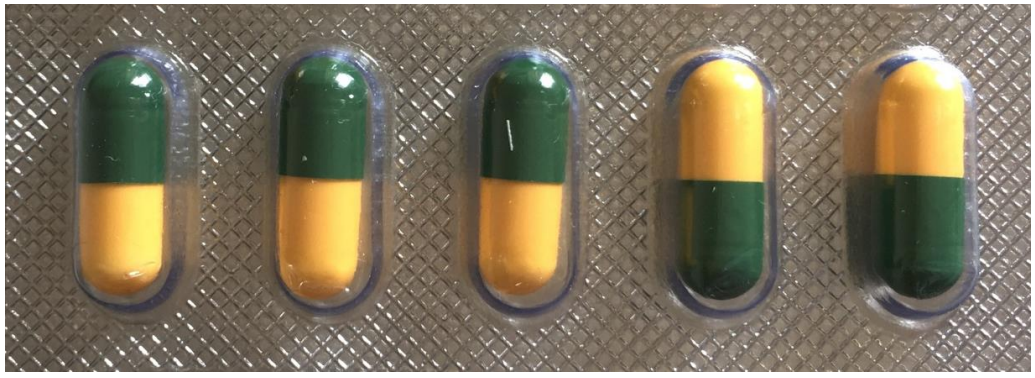
2. **SNRI (70%)**

   Inhibitory effect on central neuronal norepinephrine (NE) and serotonin (5-HT) reuptake systems

   Risk of serotonin syndrome/seizures

Tramadol

- **Oral tramadol**
  - High bioavailability in the range of 80–90%
  - Onset 30 min to 1 hour : Peak concentration 2 hours
  - **Dose-dependent analgesic efficacy**



Tramadol

- Max dose 400 mg/day
  - Initial 50 mg oral q 6 - 12 hours
- Dosing adjustment in renal impairment, hepatic failure and in geriatric patients
- Maximum recommended dose in geriatric patient is not exceed than 300 mg/day

CYP 2D6
(Oxycodone, Tramal, Codeine)

- Enzyme inhibitor
  - Cimetidine
  - SSRI(fluoxetine, setraline)
  - SNRI
- Enzyme inducer
  - Rifampicin
  - Dexamethasone

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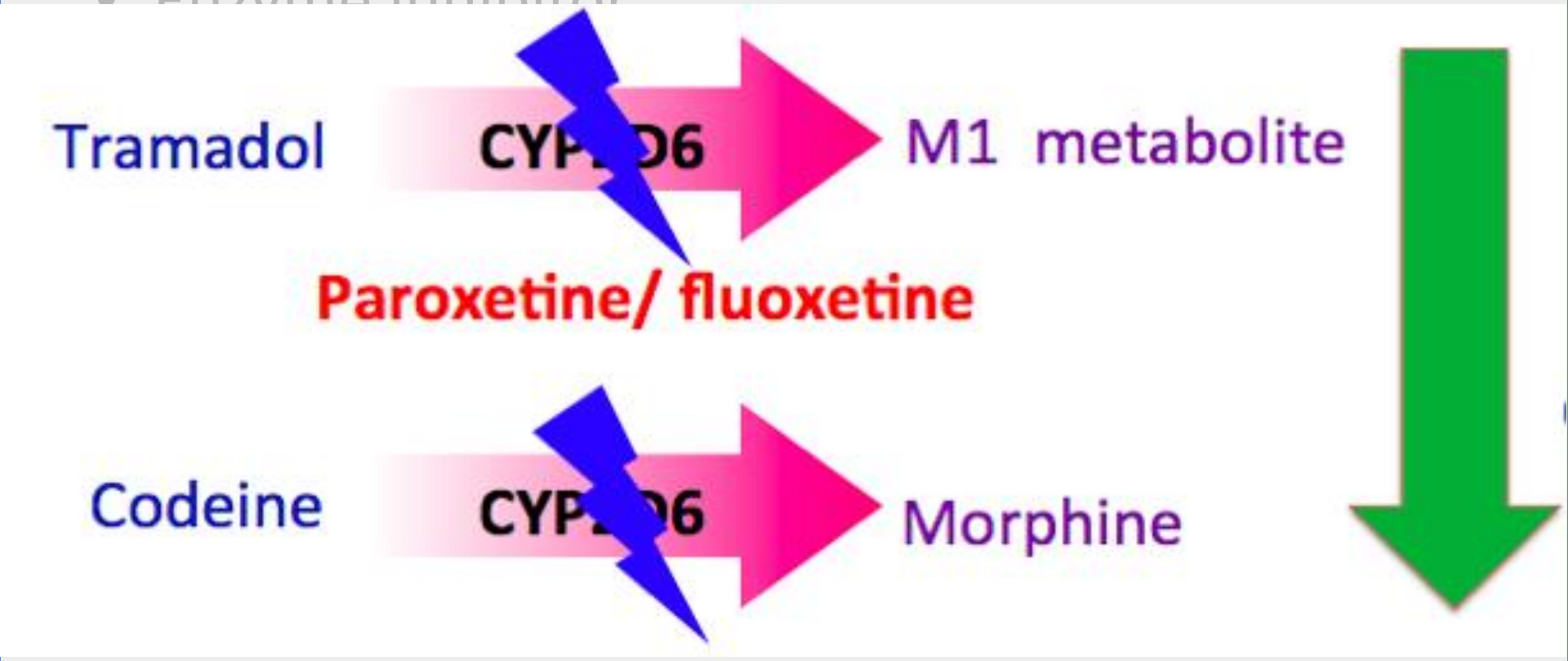


Adverse Effect of Opioids

Common	Occasional	Rare
• Nausea • Vomiting • Constipation • Sedation • Drowsiness • Cognitive impairment • Miosis • Cough suppression • Urinary retention	• Hallucinations • Mood changes • Anxiety • Pruritus • Myoclonus • Rigidity • Dry mouth • Gastric stasis • Bronchoconstriction	• Respiratory depression • Delirium • Seizures • Hyperalgesia • Allodynia • Biliary spasm • Pulmonary edema • Tolerance • Physical dependence • Addiction

CNS Effects

- **Found in both acute and chronic**
  - Dizziness
  - Lightheadedness
  - Sedation and Drowsiness
    - Miosis of pupil(activation of mu receptor at Edinger-Westpal nucleus of CN VI)

Respiratory Depression

- **2 Components**
  1. **Reduced drive to breathing with decreased respiratory rate (less than 8 breaths/minute)**
     - Shallow/apneustic breathing
     - CO_2 retention leads to increased risk of sedation
  2. **Occlusion upper airway**
     - Direct suppress neurons in brainstem maintaining upper airway muscle tone
     - Loss muscle tone due to sedation

Respiratory Depression

- **Treatment : Naloxone (0.4 mg/ml)**
  - **Competitive MOR antagonist**
    - All Receptor antagonist but greater affinity with Mu
  - Blood-effect site equilibrium half life 6.5 min
    - **Rapid onset (2-5 min)**, but **short plasma half life** (30 min)
    - Duration of action 30-120 minutes (depends on route)
  - Doses
    - 40-100 mcg IV, repeated q 2-3 min as needed, up to 10 mg
    - Continuous infusion 2-4 mcg/hour : dilution 2 mg of naloxone in 500 ml of NSS or 5%DW to a concentration of 0.004 mg/ml
  - **Renarcotinization**
  - **Adverse Effects :** Withdrawal reaction, cardiac arrest, ventricular fibrillation, dyspnea, pulmonary edema, abdominal cramps, diarrhea
    - **Large dose is reserved for known overdose and respiratory arrest**
  - Abrupt reversal : N/V, sweating, tachycardia, hypertension

CVS Effects

- **Central Effects**
  - Stimulate Vagal Nuclei
  - Depress Vasomotor centers in brainstem
- **Peripheral Effects**
  - High dose : direct myocardial depression
  - Arterial and venous dilatation
  - Orthostatic hypotension
  - Bradycardia
  - ↓SVR, PVR

Histamine release

- **Histamine release from mast cells**
- **Symptoms**
  - Itching, redness
  - ↓SVR, PVR

Nausea - Vomiting

- **Mechanism**
  - Chemoreceptor Trigger Zone (CTZ)
    - Vomiting center at Medulla
  - Direct GI tract : Decreased pyloric tone
  - ↑ Sensitivity Vestibular system
  - Nausea that is not associated with movement
    - Droperidol, ondansetron, hydroxyzine, prochlorperazine

GI effects

Pharmacologic Action	Clinical Effect
↓ Gastric motility & emptying	↓Appetite, ↑Gastroesophageal reflux
Inhibition small and large bowel movement	Delayed absorption of medications Straining, Bloating, Abdominal distension Incomplete evacuation, Constipation
↑Anal sphincter tone	Incomplete evacuation

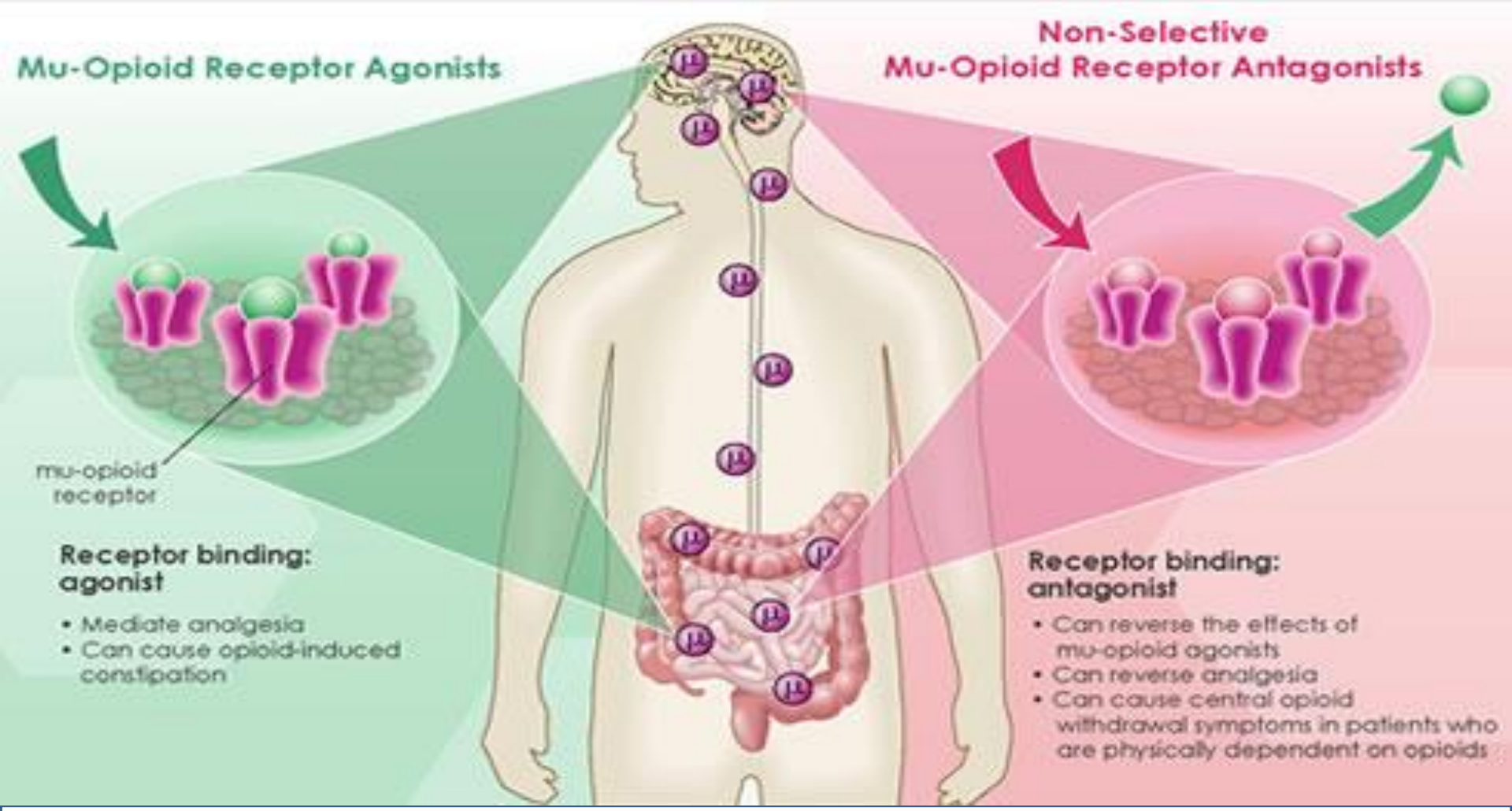
Opioid and biliary colic

- This is based on belief that morphine may increase pain by causing spasm of sphincter of Oddi, where pethidine dose not have not this effect
- This is based on intraoperative manometry studies & there is **not statistically clinical significant.**

. Am J Gastroenterol 2001; 96:1266-1272.

Opioid induce constipation

- OIC is seen even with single dose administration
- Lower dose or weak opioids is not prevent OIC
- No tolerance ;even repeated dose



Mechanism of OIC to be **decreased gastric motility** related to opioid binding to opioid receptors located in the antrum of the stomach and the proximal small bowel

Treatment of OIC

- Active laxative(1st Line)
  - Senna, Bisacodyl
  - Lactulose(Hypernatremia,lactic acidosis)
  - Magnesium salt product
- Passive laxative(Bulk forming agent)
  - Inappropriate for low fluid intake, intestinal obstruction or palliative care patient
- Naloxone
- Methylnaltrexone : IV : peripheral action

Urinary retension

Most common after intrathecal or epidural administration.

Relax detrusor muscle with a corresponding increase in maximum bladder capacity.

Ann Fr Anesth Reanim. 1995;14(4):340-351

Pruritus

- **NOT histamine-related**
- The most likely cause is via a **direct central effect activates opioid receptors throughout the brain and spinal cord** (substantia gelatinosa)
- Intrathecal or intravenous morphine who have significant pruritus that is **unresponsive to antihistamines**
  - low dosages of nalbuphine(a μ-receptor antagonist and k-receptor agonist) may effectively reduce pruritus without reversing analgesia
- Reversible:
  - Small doses of naloxone

Miller R, et al. Miller's Anesthesia 8th edition. 2015;864-913.

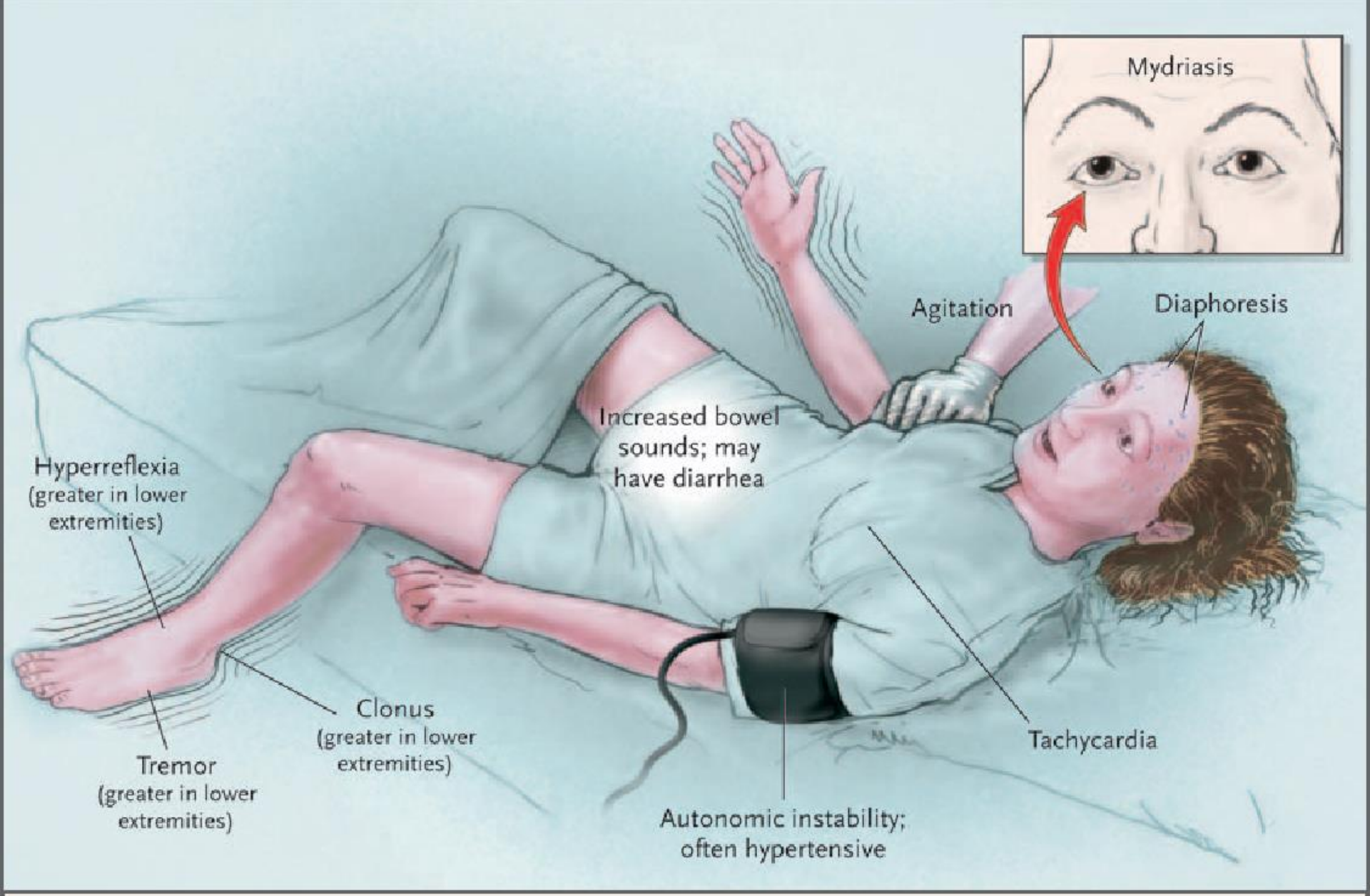
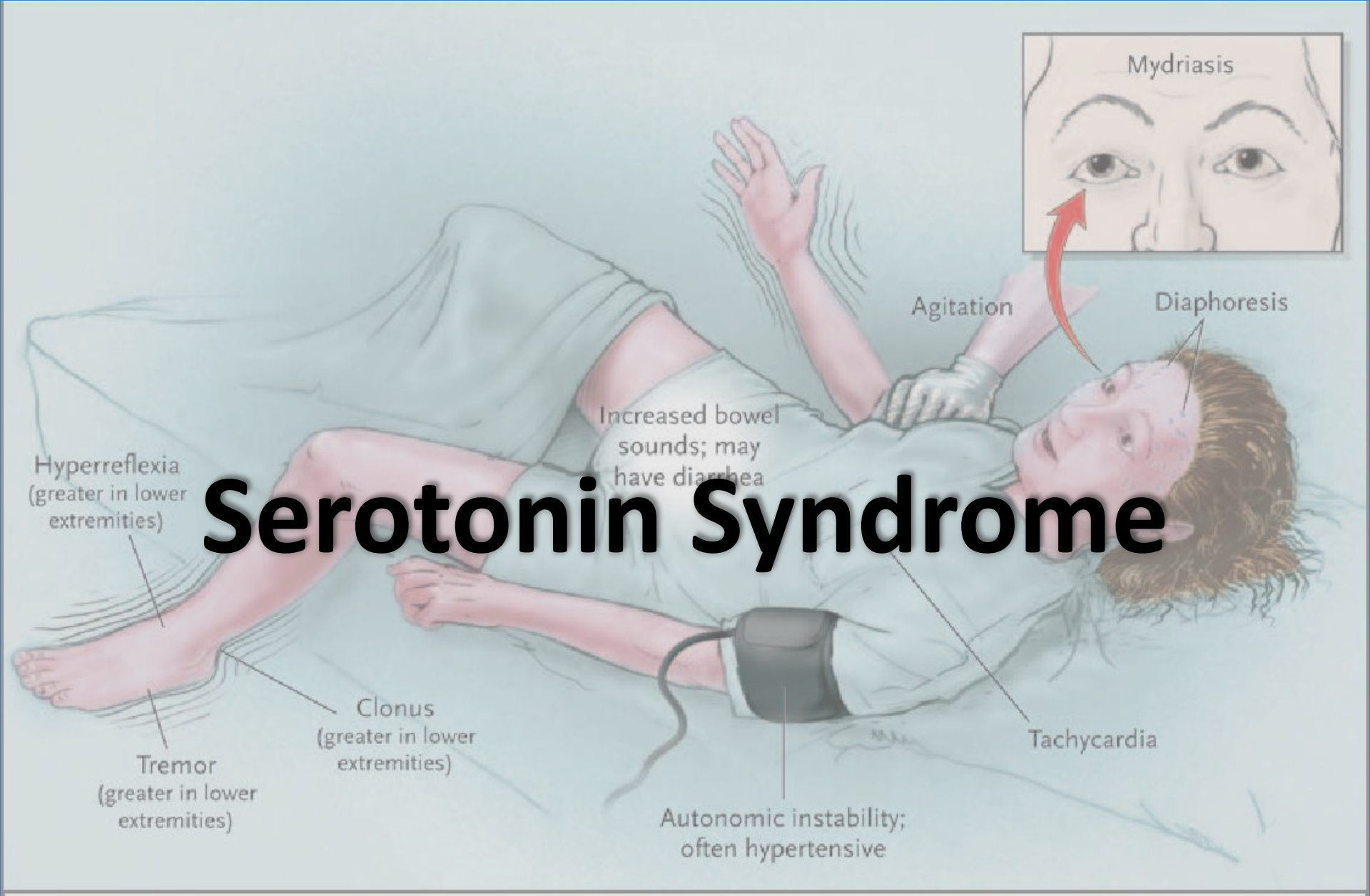


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.



Serotonin Syndrome

Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

Triad of Serotonin Syndrome

- 1.Cognition and behavior abnormality
- 2.Autonomic nervous system (ANS) abnormality

  e.g. diaphoresis, hypertension ,tachycardia, high grade fever

- 3. Neuromuscular abnormality

  e.g. myoclonus, hyperreflexia, muscle rigidity ,muscle rigidity

Serotonin Syndrome

- Certain agents prevent the reuptake of serotonin at the neuromuscular junction
  - Selective Serotonin Reuptake Inhibitors (**SSRI**)
  - Serotonin Norepinephrine Reuptake Inhibitors (**SNRI**)
  - **Tramadol**
  - **Pethidine**
  - **Methadone**
  - Herbal Agent : **St. John's Wort**

Physical Dependence

- **Withdrawal syndrome**
- Produced by **abrupt cessation**, **rapid dose reduction** or administration of an **antagonist**.

Addiction

- P**sychological dependence**
- Characterized by **compulsive behavior** to obtain a drug in order to experience its **psychic effects (euphoric effect)**, despite full knowledge of its harmful effects

Addiction 5C

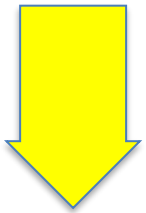
- Chronic usage & Impaired control over drug use
- Compulsive use
- Control impaired
- Craving
- Continued use despite harm

Pseudo-Addiction

- Iatrogenic syndrome of behavioral change similar to addiction
- **Inadequate pain management**

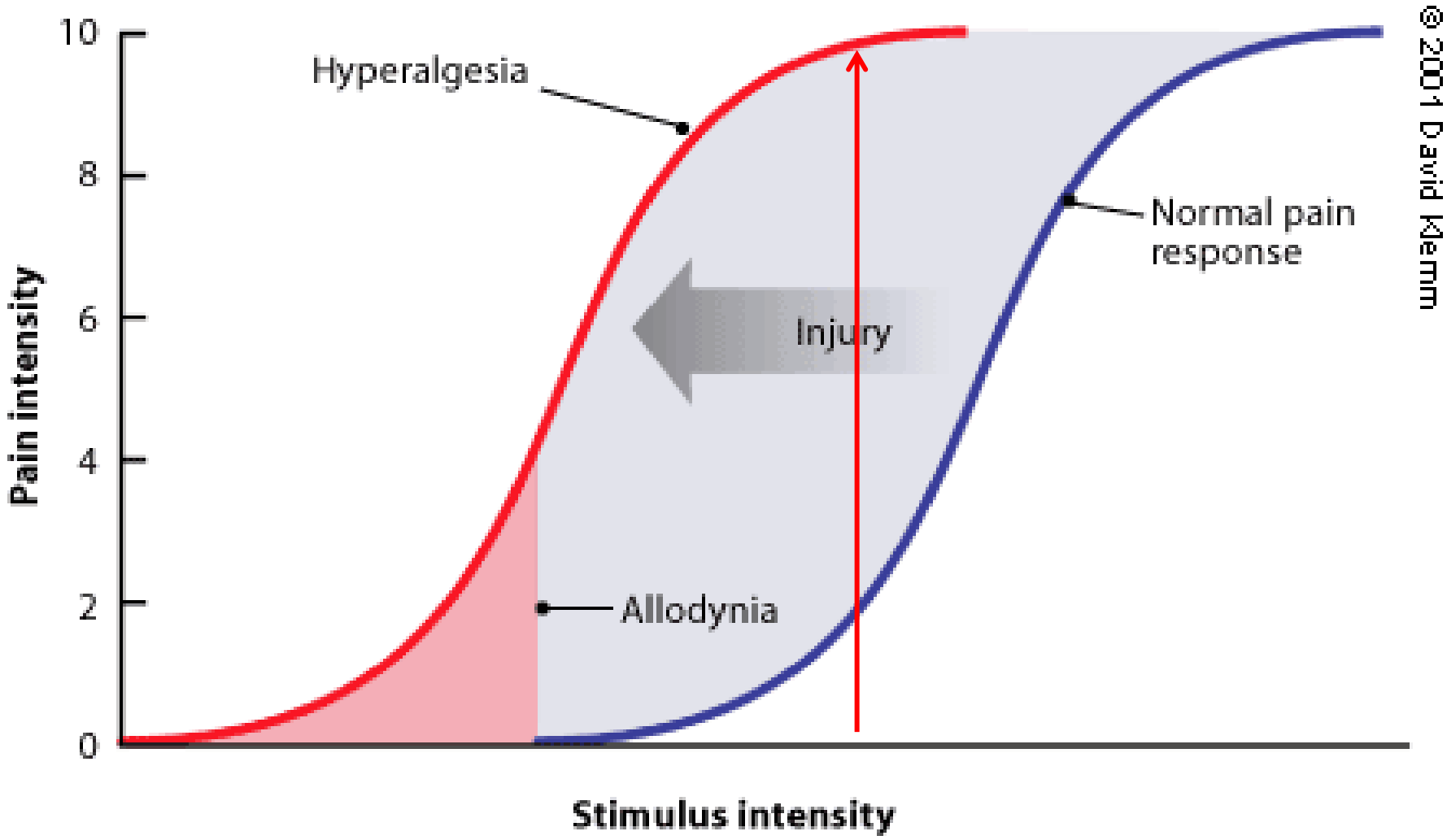
Tolerance

Increased dose of opioid



Progressive lack of response

Hyperalgesia



Opioid induced hyperalgesia

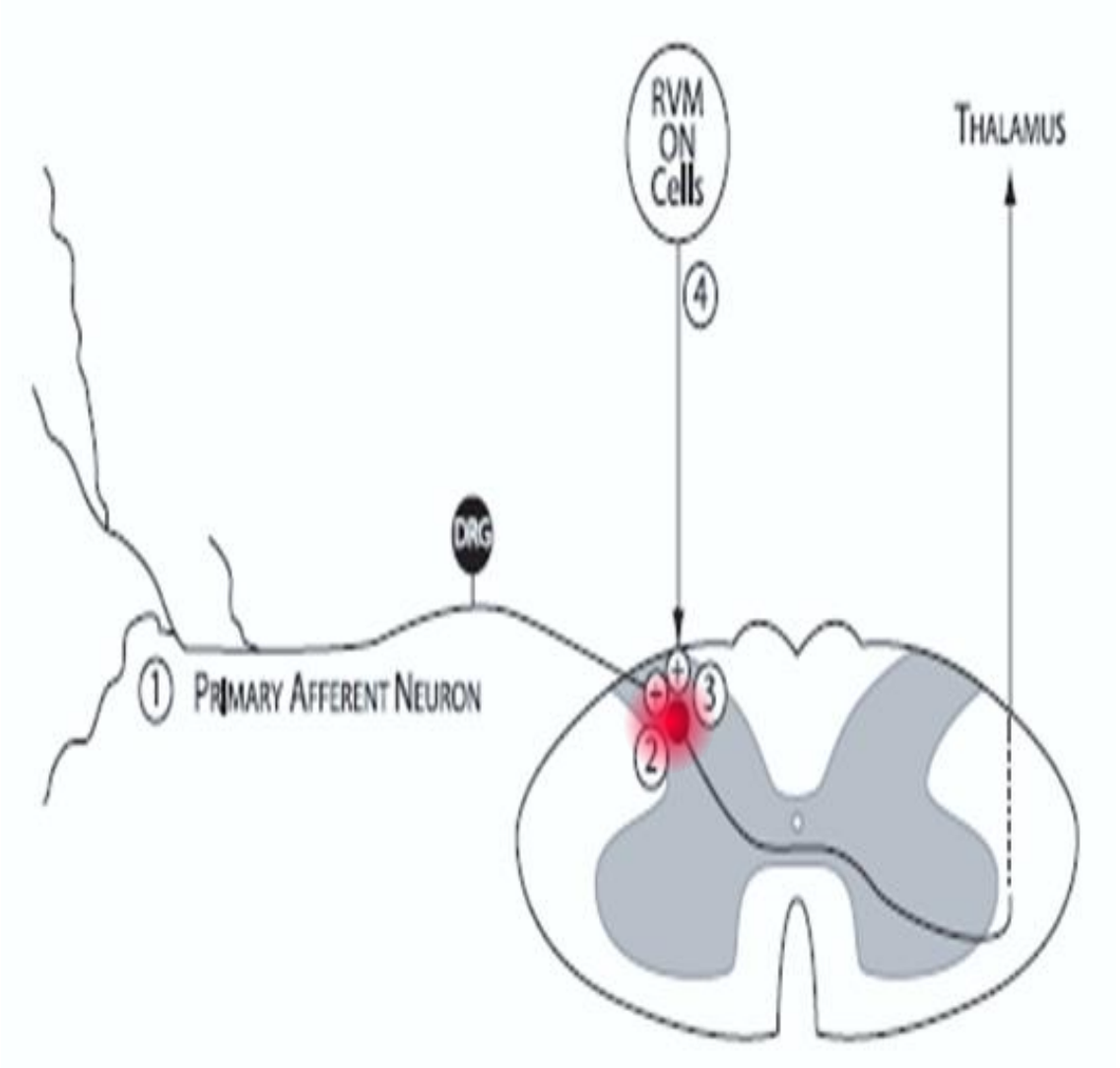
- State of nociceptive sensitization of opioids
- Paradoxical response of opioids

Tolerance vs OIH

less response to opioids

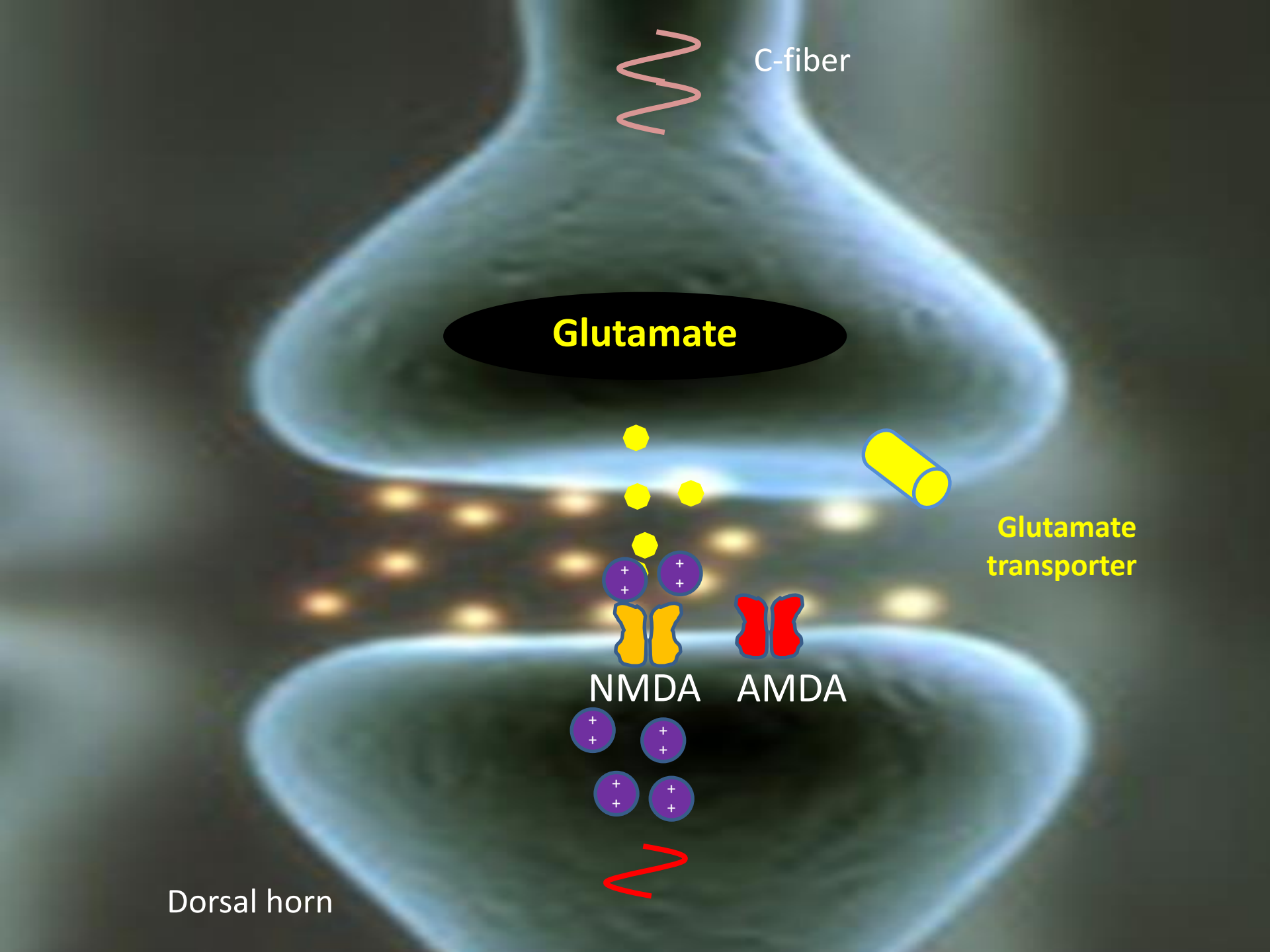
	Tolerance	OIH
Increased dosage	Improved pain	Worsen pain
Pain	Decreased efficacy when increasing dose	Improved by reducing or stop opioids

Mechanism

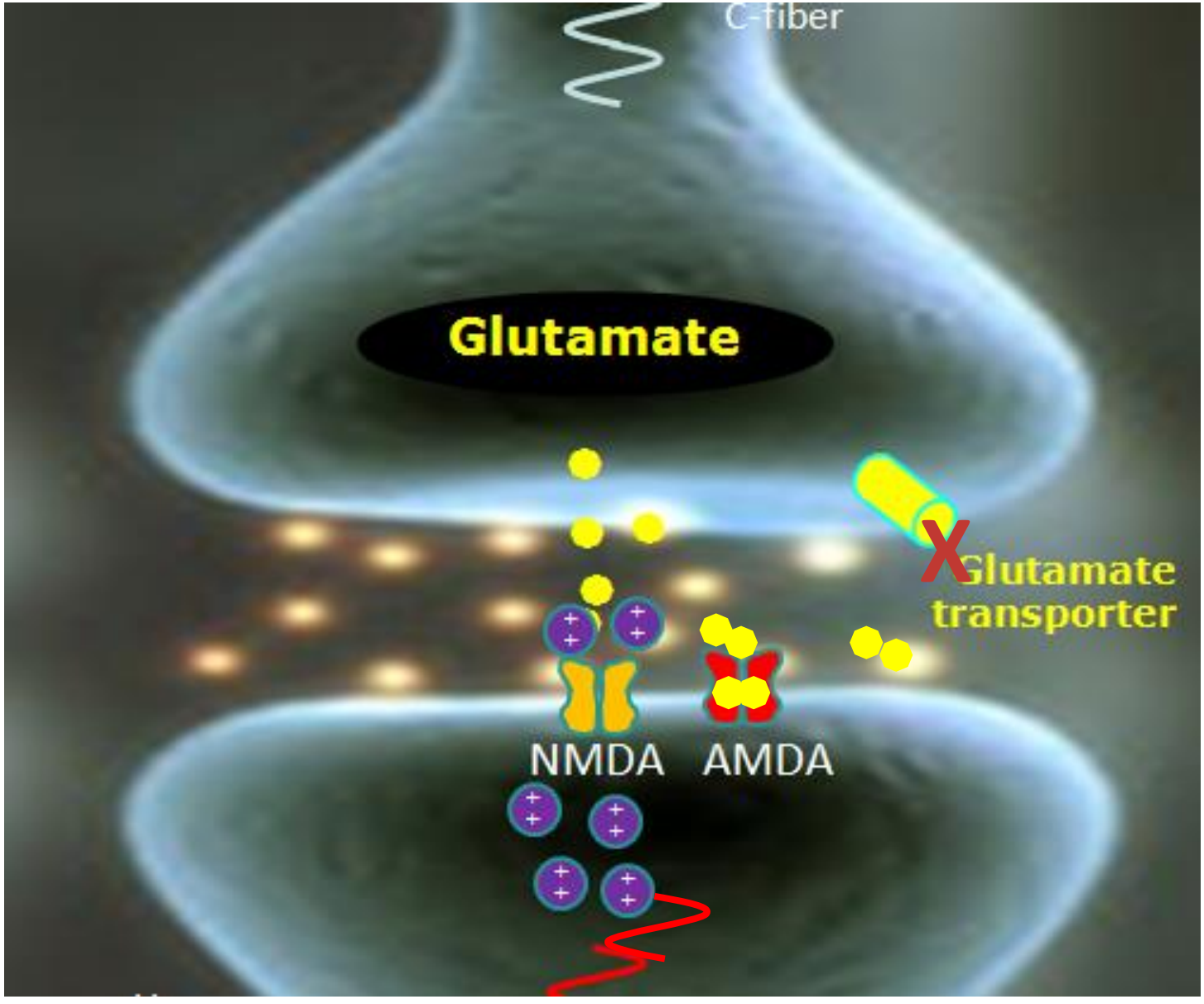


- Central glutaminergic system
- Inhibited glutamate transporter system

Pain Physician 2011; 14:145-161 • ISSN 1533-3159


C-fiber
Glutamate
Glutamate transporter
NMDA
AMDA
Dorsal horn

Inhibited glutamate transporter system



Summary of Treatment of OIH

- Reduce or discontinue the current opioid
- Consider opioid switching
- Add non-opioid medications such as acetaminophen and NSAIDs

Journal of Pain & Palliative Care Pharmacology. 2011;25):219-230

Summary of treatment Appoarch of OIH

- Add a NMDA receptor antagonists
  - such as ketamine
- Consider other pharmacological agent
  - such as antidepressant, anticonvulsant, and skeletal muscle relaxants to treat pain
- Consider regional/local anesthesia

Journal of Pain & Palliative Care Pharmacology. 2011;25):219-230

Guidelines for Opioid Rotation

Calculate equianalgesic dose of new opioid from EDT

Reduce calculated equianalgesic dose by 25%-50%*

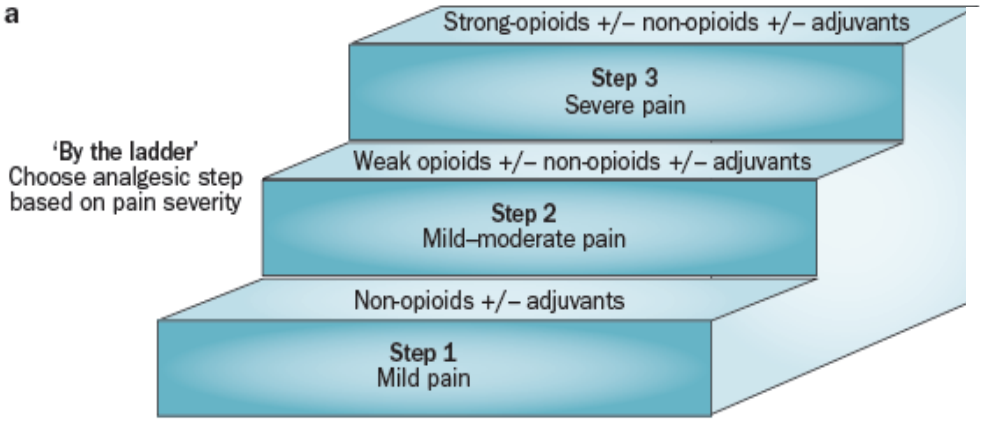
Select % reduction based on clinical judgment

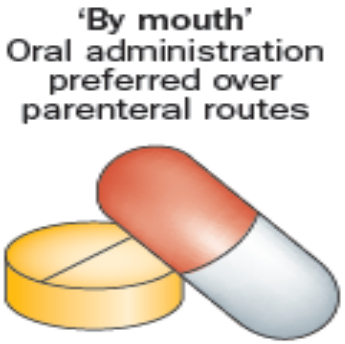
Closer to 50% reduction if patient is	Closer to 25% reduction if patient
• Receiving a relatively high dose of current opioid regimen • Elderly or medically frail	• Does not have these characteristics • Is switching to a different administration route of same drug

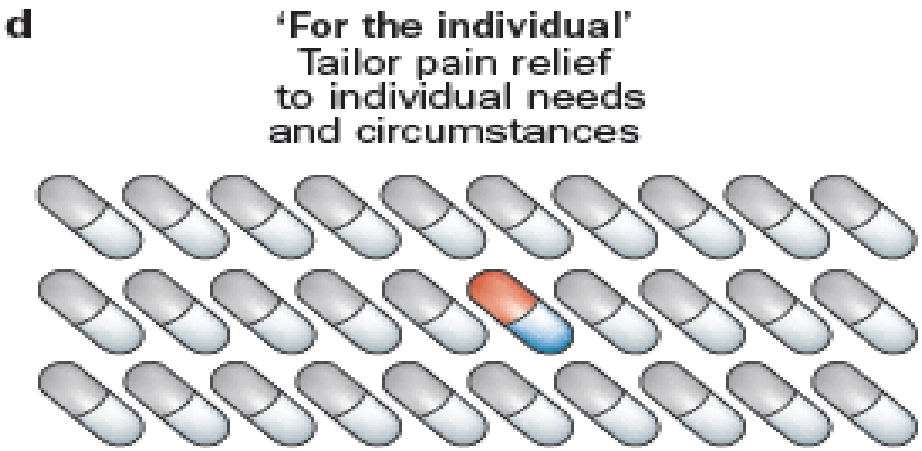
***75%-90% reduction for methadone**

Fine PG, et al. *J Pain Symptom Manage*. 2009;38:418-25.

WHO principles







World Health Organization (WHO). Cancer pain relief: With a guide to opioid availability. 2nd ed. Geneva: WHO; 1996

Thank you for all your attention