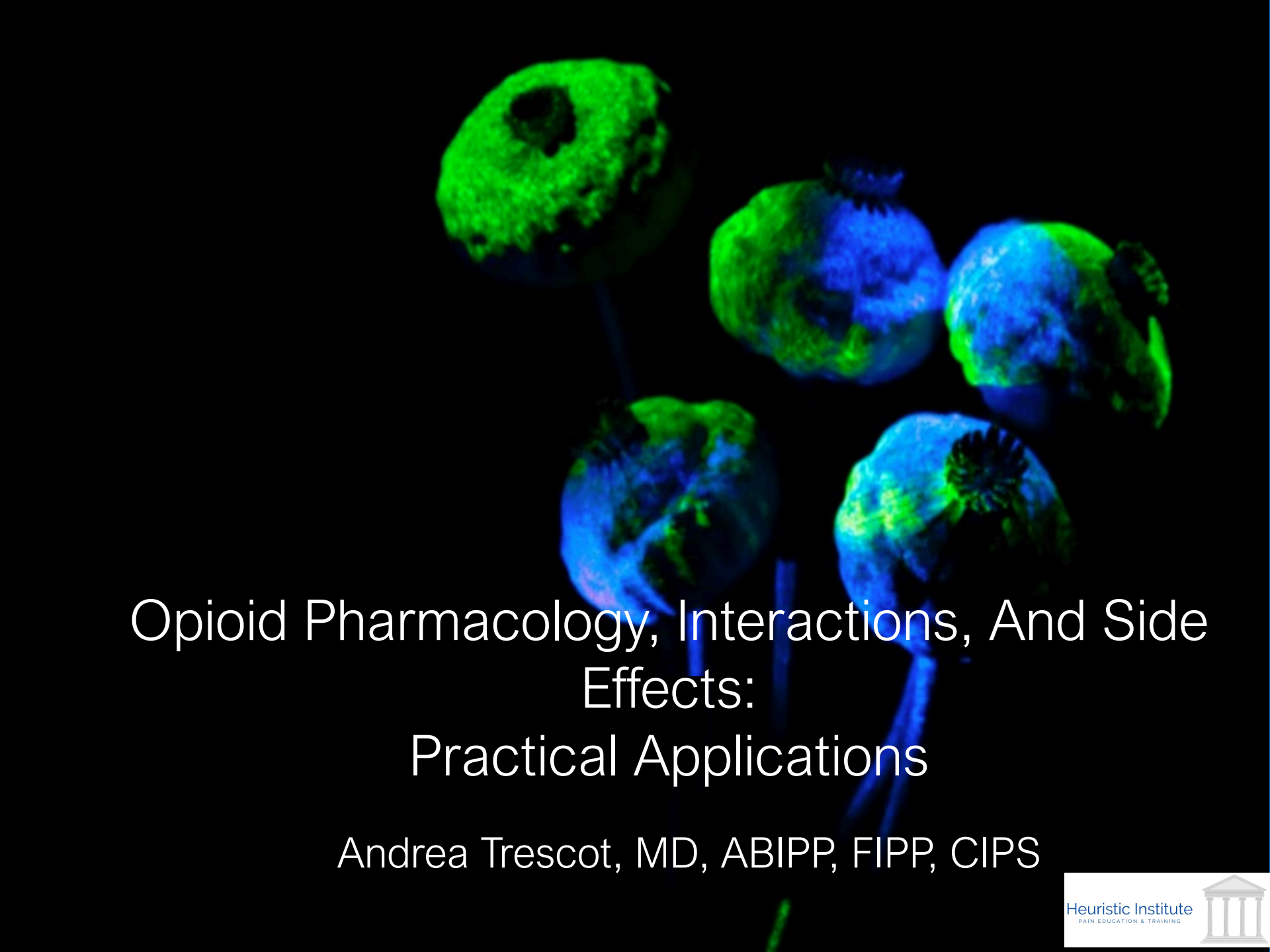

Opioid Pharmacology, Interactions, And Side Effects: Practical Applications

Andrea Trescot, MD, ABIPP, FIPP, CIPS

Heuristic Institute
PAIN EDUCATION & TRAINING

Disclosure

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- Affiliate Assistant Professor, WWAMI School of Medical Education, University of Alaska
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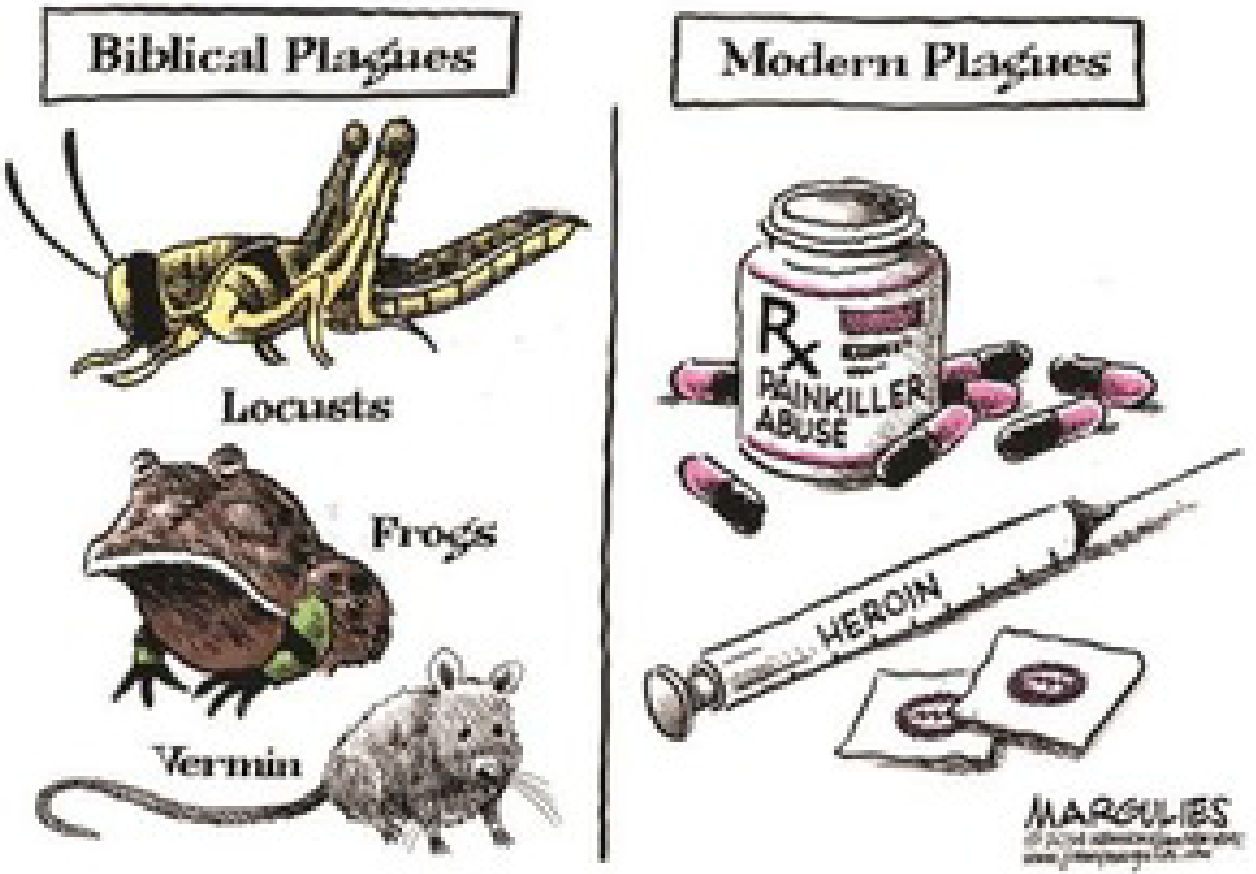
- Former Director, Pain Fellowship Program, University of Washington and University of Washington
- Past President, American Society of Interventional Pain Physicians
- Past President, Florida and Alaska Societies of Interventional Pain Physicians
- Past Chair, Education Committee, World Institute of Pain
- Chief Medical Officer - Stimwave

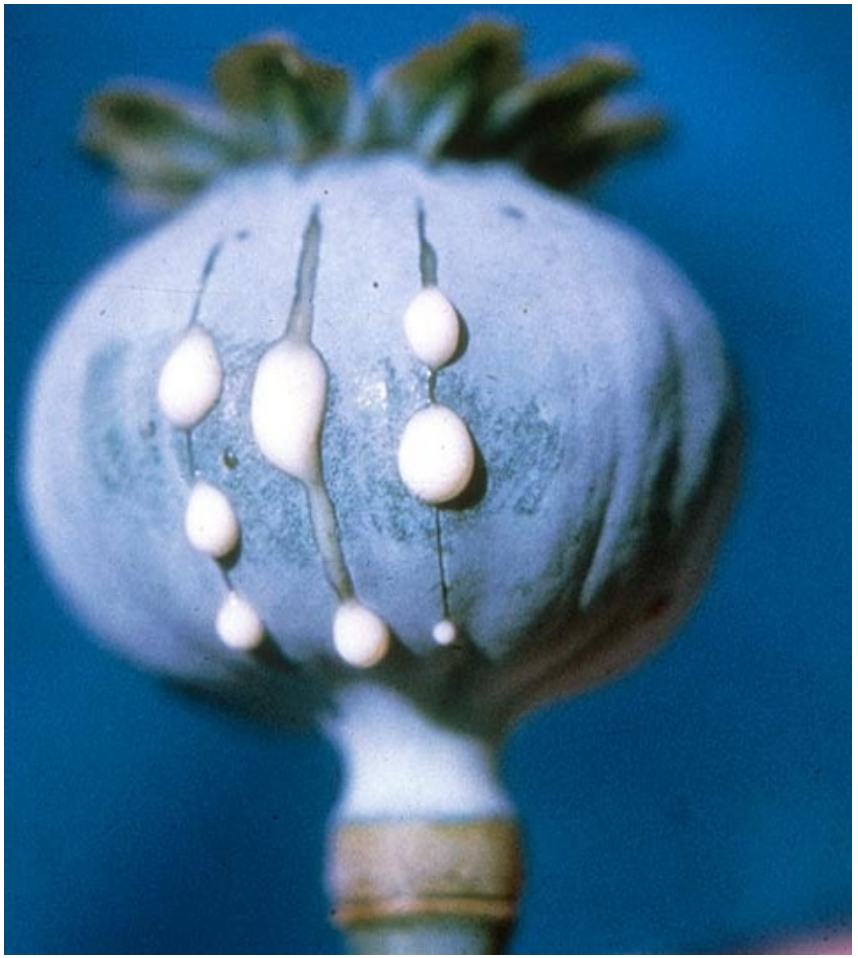

Biblical Plagues
Locusts
Frogs
Vermin
Modern Plagues
Rx
PAINKILLER ABUSE
HEROIN
MARGULIES

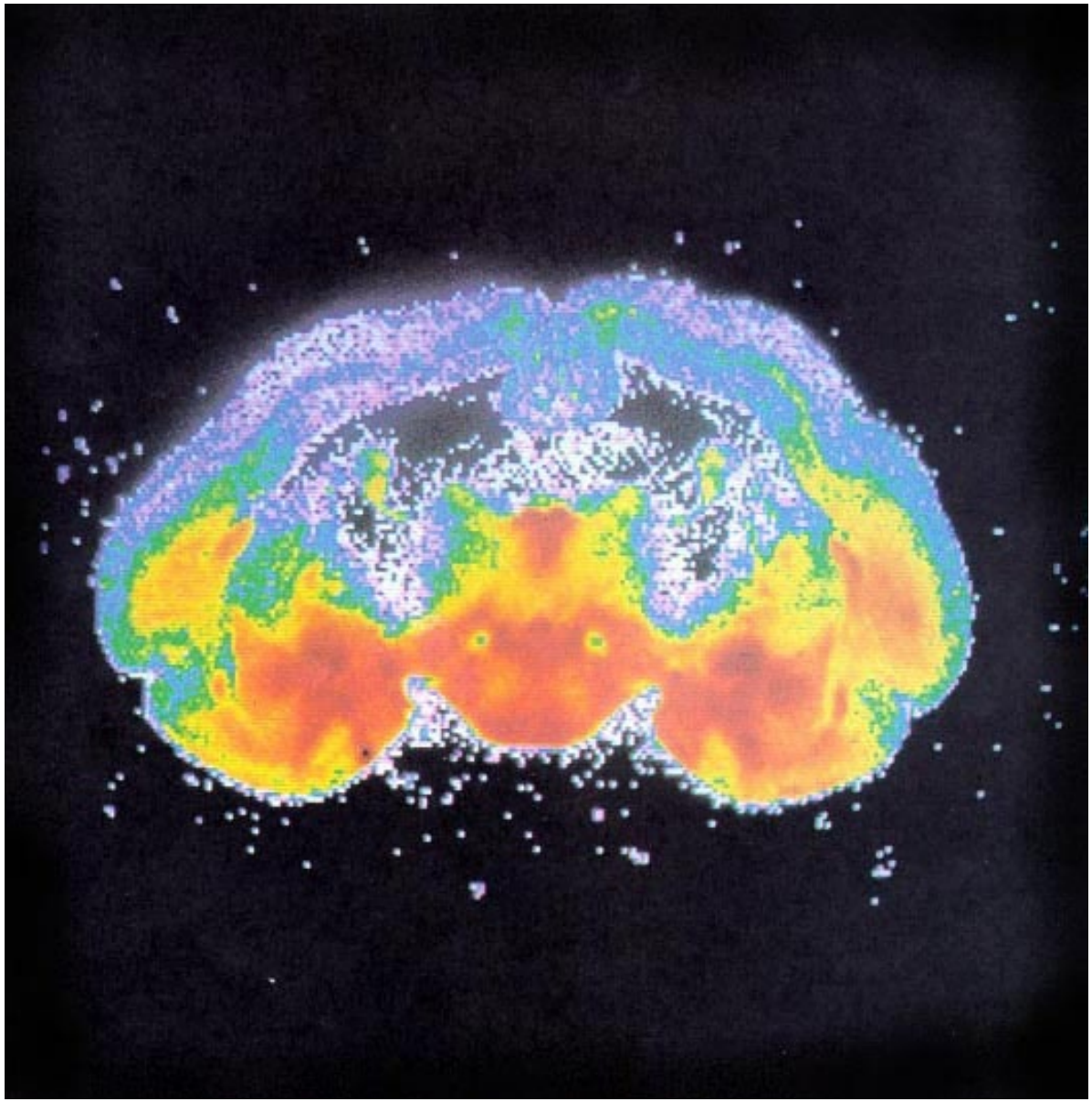
Opioids

- Opioids are extremely useful but potentially dangerous broad-spectrum analgesics
- Understanding the pharmacology, metabolism, and genetics of opioids may help predict effectiveness and potential side effects of opioids
- Effective management of side effects is necessary to preserve opioid efficacy

Terminology

1. *Opium:* a mixture of alkaloids from the poppy seed
2. *Opiate*: a naturally occurring alkaloid such as morphine or codeine
3. *Opioid*: refers broadly to all compounds that work at the opioid receptors
4. *Narcotics*: derived from the Greek word for stupor.
   - Once used to describe medications for sleep
   - Then used for opioids
   - Now a ***legal*** term for drugs that are abused





Opioid Receptors

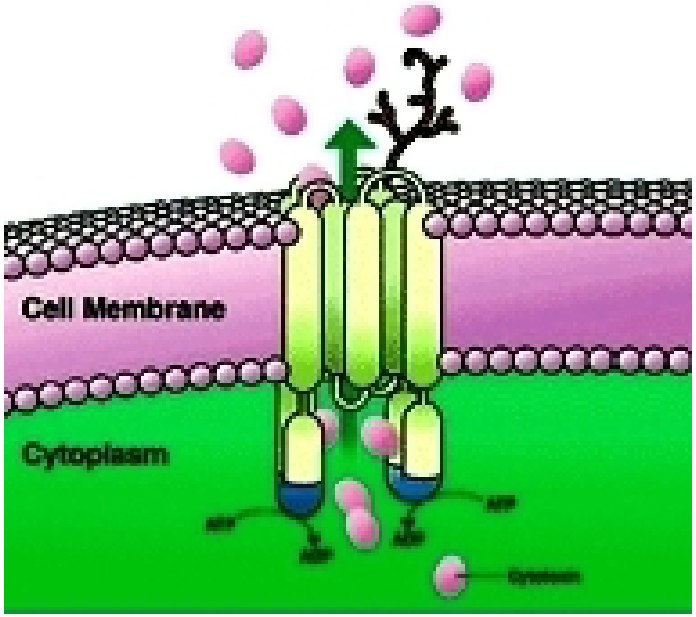
RECEPTOR	PROPOSED LOCATION	PROPOSED EVENTS
Mu_1 (μ)	Supraspinal, peripheral analgesia, spinal cord, substantia gelatinosa, periductal gray, locus ceruleus	Analgesia
Mu_2	Spinal trigeminal nucleus, limbic area, reticular activating system, medullar raphe nucleui	Sedation, pruritis, prolactin release, vomiting, urinary retention, respiratory depression, euphoria, miosis, dependence, anorexia, decrease GI motility, histamine release
Kappa	K_1 spinal cord K_2 poorly defined K_3 supraspinal	Spinal analgesia, dyspnea, resp depression, miosis, sedation, diuresis (lower ADH release), dependence, endocrine events
Delta	D_1 spinal, supraspinal D_2 frontal cortex, limbic area, olfactory tubercle, spinal	
Sigma		Psychomimetic effects, dysphoria

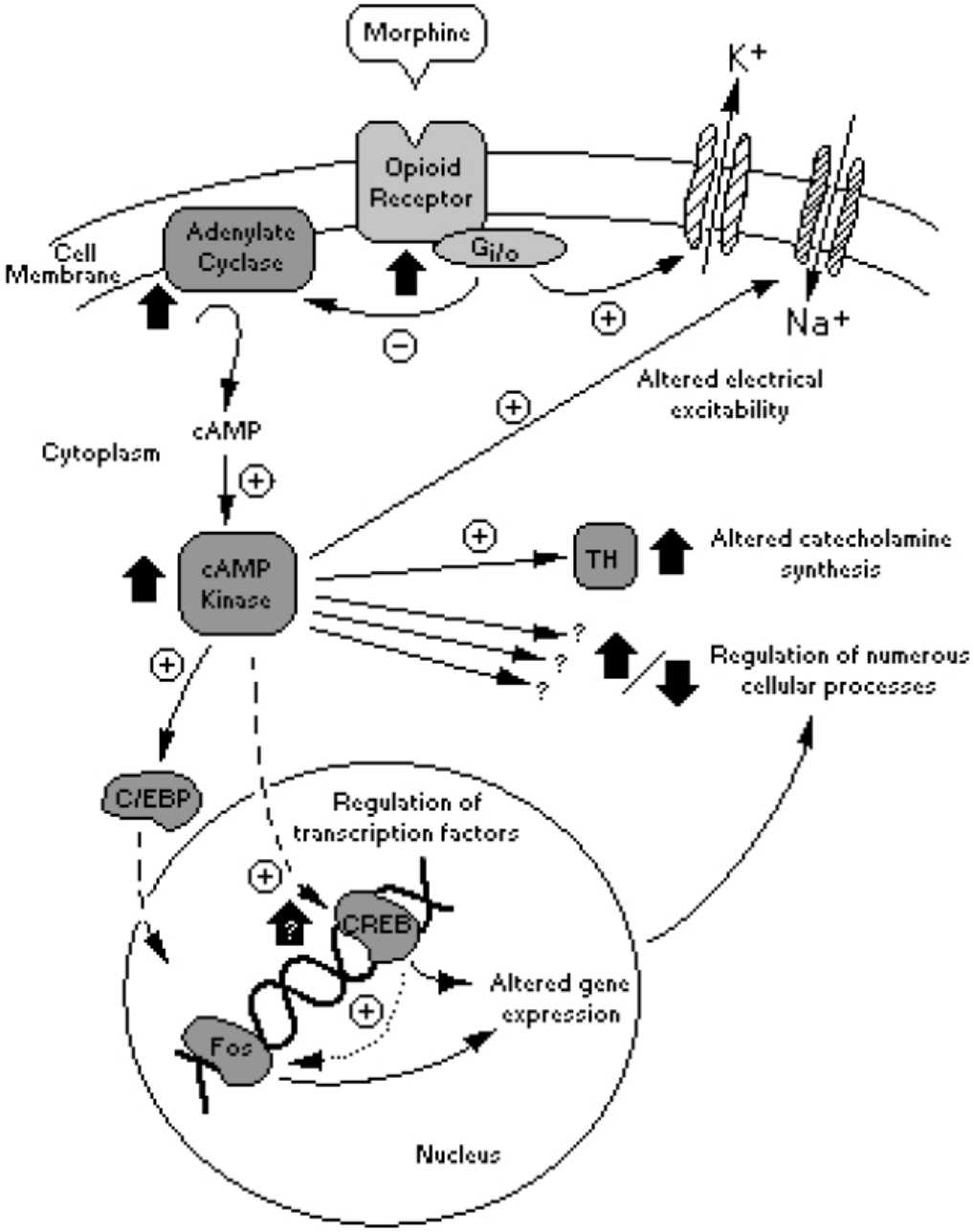
Opioid Receptors

Function	Receptor				
	μ	κ	σ	δ	ε
Analgesia cerebral	+	-	-	-	+
Spinal	+	+	+	-	-
Vigilance	-	↓	-	↑	-
Respiratory drive	↓	-	-	↑	-
Heart rate	↓			↑	-
Cardiovascular tonus	-	↓	↓	-	-
Endocrine effects	+	-	+	-	-
Diuresis	↓	↑	-	-	-
Constipation	+	-	-	-	-
Euphoria	+	-	-	-	-
Dysphoria	-	+	+	+	-
Pupil size	↓	↓	-	↑	-
Nausea	+	-	-	+	-
Muscular rigidity	↑	↓		↑	-

Opioid Receptors

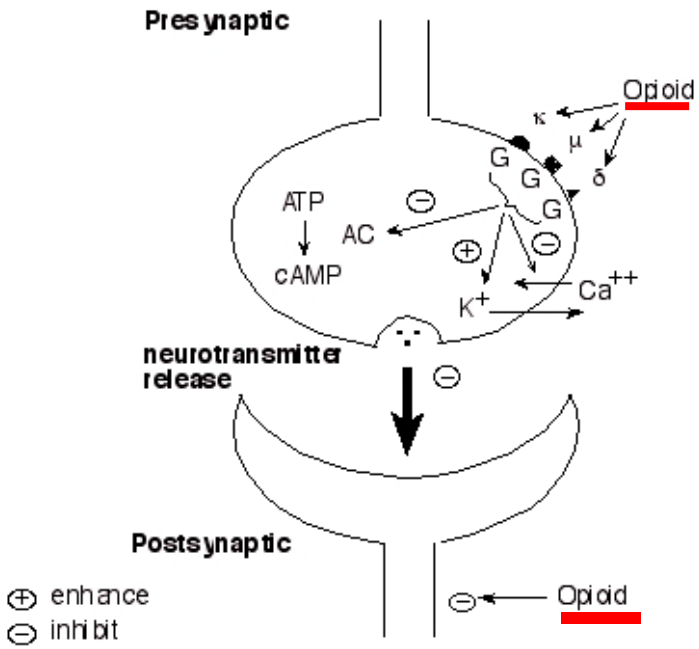
- Inhibitory G protein-linked receptors embedded in the plasma membrane of neurons
- Once the receptor is bound, a portion of the G protein is activated
  - Diffuses within the membrane until it reaches its target
    - Enzyme or ion channel
  - Alters protein phosphorylation via cyclic AMP (short term) or gene transcription (long term)





Opioid Site of Action

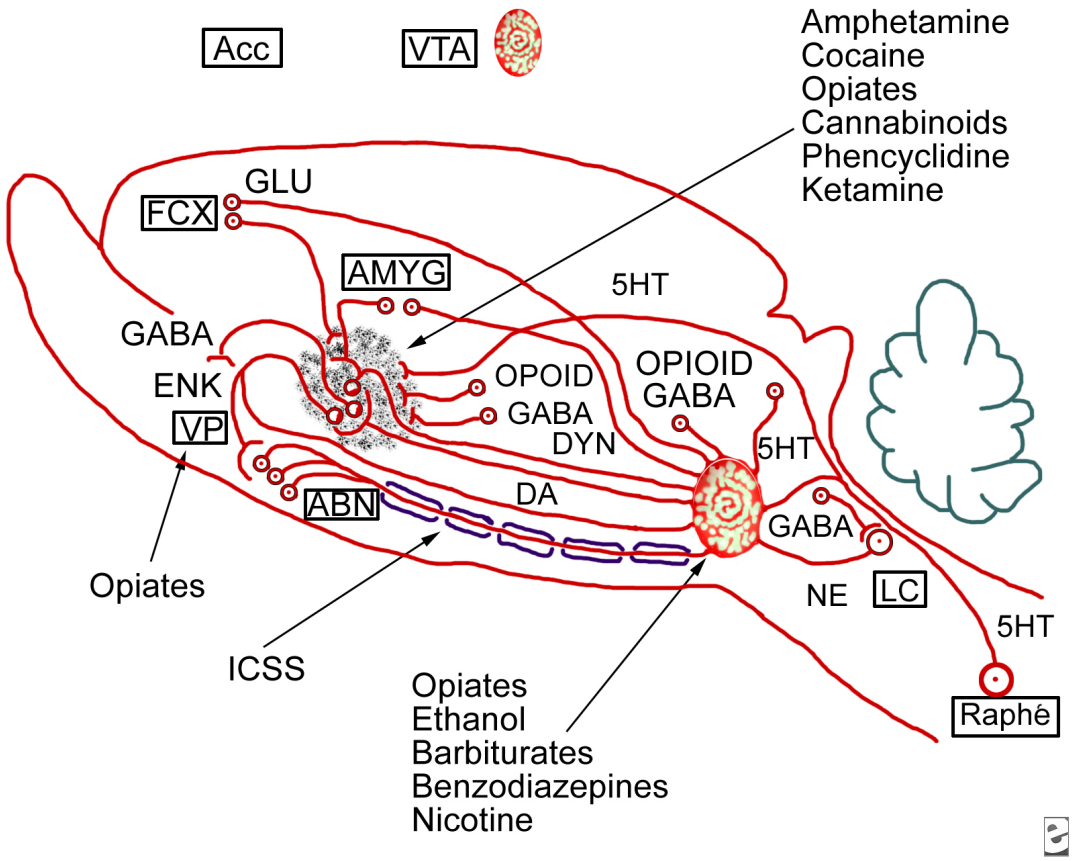
- Presynaptic receptors inhibit neurotransmitter release
  - Acetylcholine, norepinephrine, serotonin, substance P
  - May produce inhibition of inhibition which produces excitation
- Postsynaptic receptors are usually inhibitory



Clinical Activity

- Dopaminergic mesolimbic system originates in the ventral tegmental area (VTA) of the midbrain.
  - Projects to the nucleus accumbens and the frontal cortex
    - Natural rewards of food and water
    - Action of abusive drugs.
- GABA usually inhibits dopaminergic neurons
  - Opioid and endorphins activate the presynaptic receptors on GABA neurons
    - Inhibits release of GABA in the VTA
    - Allows dopaminergic neurons to fire more vigorously
    - Intensely pleasurable

Brain Pathways



Opioids are Divided into 5 groups:

- Strong (full) agonists
- Partial agonists
- Mixed agonist/antagonists
- Antagonists
- Special use opiates

Full Agonists

- Bind to the opioid receptors
- Some opioids bind to some receptors more than others
  - Morphine is a μ agonist
  - Oxycodone is a μ and a κ agonist

Opioid Agonist-Antagonists

- Two types
  - Partial agonist at μ receptor
    - Buprenorphine has high affinity but low efficacy at μ receptor
  - Antagonist at μ/partial agonist at κ receptor
    - Nalorphine, pentazocine, nalbuphine, butorphanol
    - Act as κ agonists but competitive μ antagonists

Opioid Antagonists

- Naloxone
  - Pure, competitive antagonist at μ, κ, and δ receptors
  - Rapidly reverses opioids but short lived, therefore the potential for "renarcotizing"
- Naltrexone
  - Competitive antagonist at μ and κ receptors (long lasting)

Special Use Opioids-

Decrease the activity of myenteric plexus, via mu-receptors, in the intestine, slowing GI motility.

Diphenoxylate - Lomotil^{R}

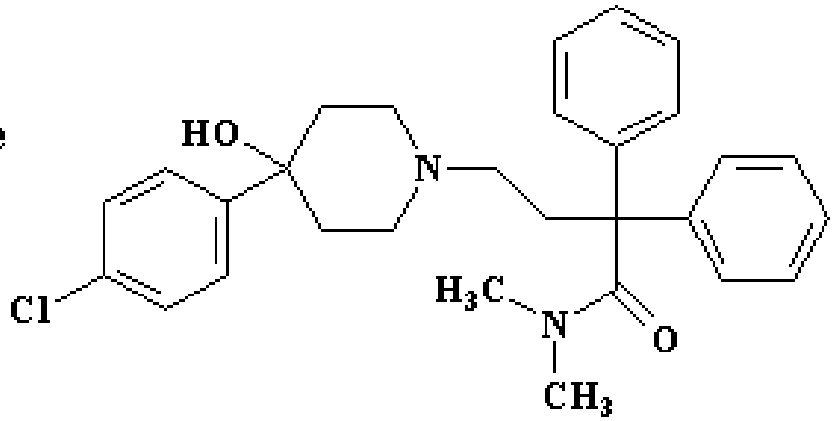
Loperamide - Immodium^{R}

poorly absorbed from gut

low abuse potential

Loperamide

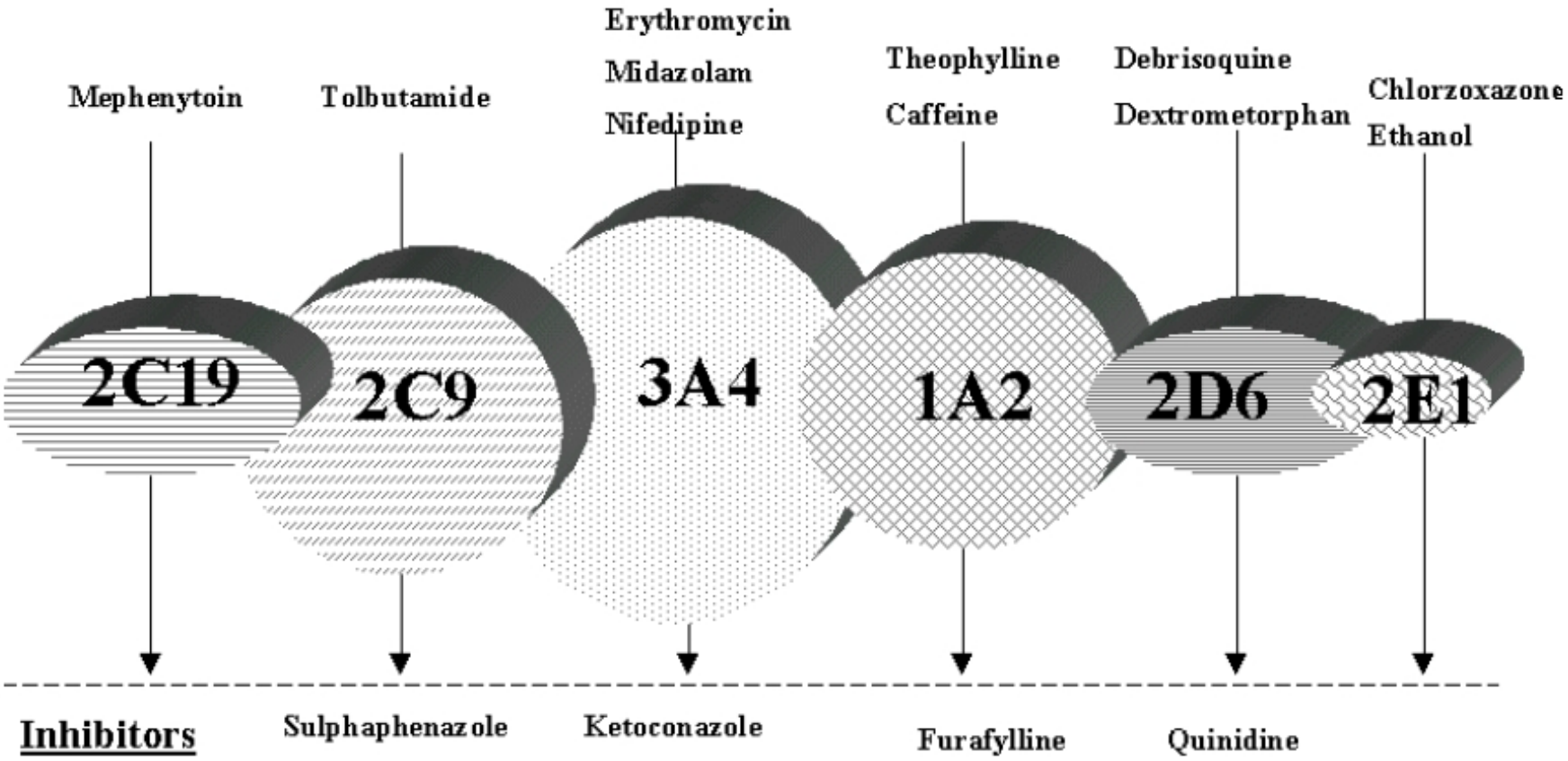
$C_{29}H_{33}ClN_2O_2$



"If it were not for the great variability among individuals medicine might as well be a science and not an art"

William Ostler (1892)

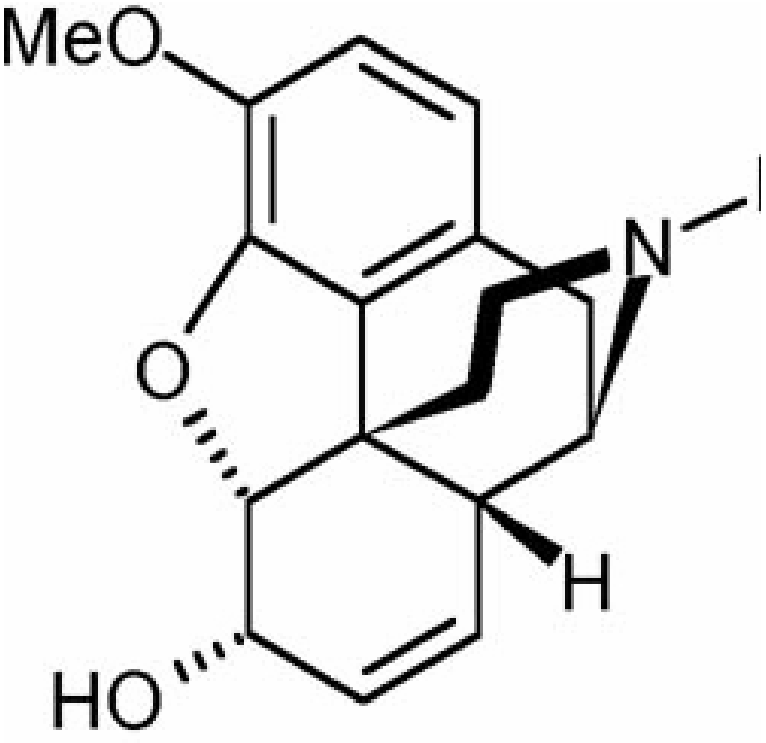
Cytochrome P450 System



Schematic presentation of human CYP450 enzymes with model substrates and selective inhibitors (Breimer 1994)

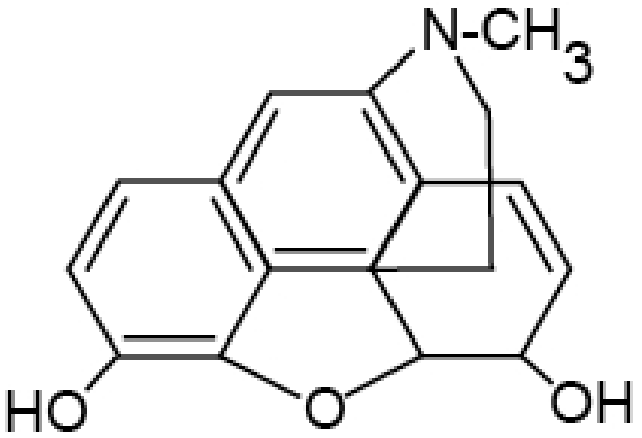
Codeine Metabolism

- Pro-drug
- Metabolized by CYP2D6 and by glucuronidation to **morphine**
- Multiple drug interactions
- Low doses cause nausea



Morphine Metabolism

- Glucuronidation to Morphine-3-glucuronide (M3G) and Morphine-6-glucuronide (M6G) and normorphine
- M6G adds to analgesia
- M3G is hyperalgesic
- Small amounts may be metabolized to hydromorphone



MORPHINE

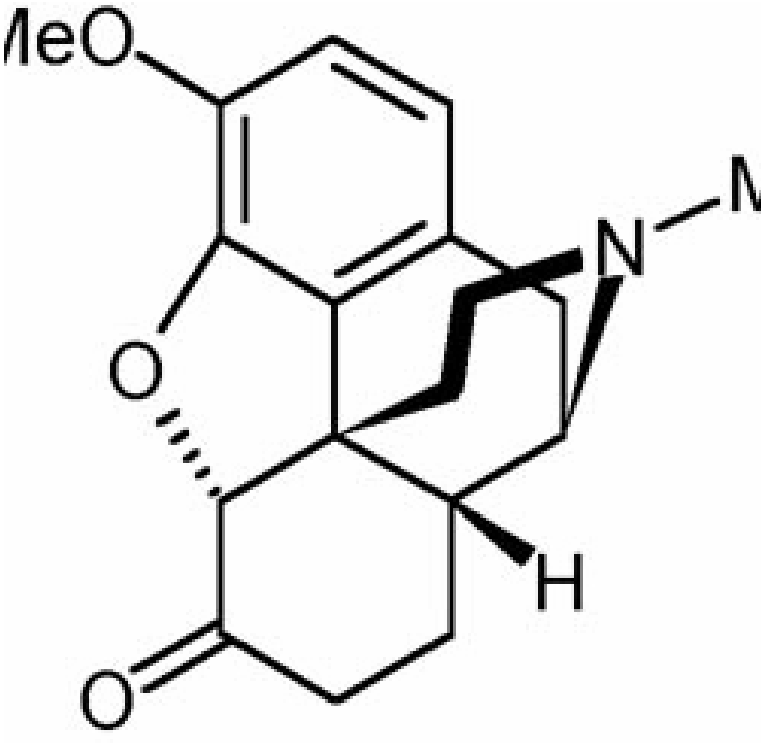
Interpreting Urine Drug Tests: Prevalence of Morphine Metabolism to Hydromorphone in Chronic Pain Patients Treated with Morphine

- Retrospective case-control study of urine toxicology results in pain patients taking only morphine
- Hydromorphone was present in 21/32 cases (66%), none with aberrant drug behavior
  - Positives were predominately female, taking higher daily doses, with higher urine morphine concentrations
  - Quantitatively only about 2% of morphine dose, therefore positive in doses of 100-200mg morphine per day or more

Wasan A, et al. Reg Anesth Pain Med 2006;30(3):A-7

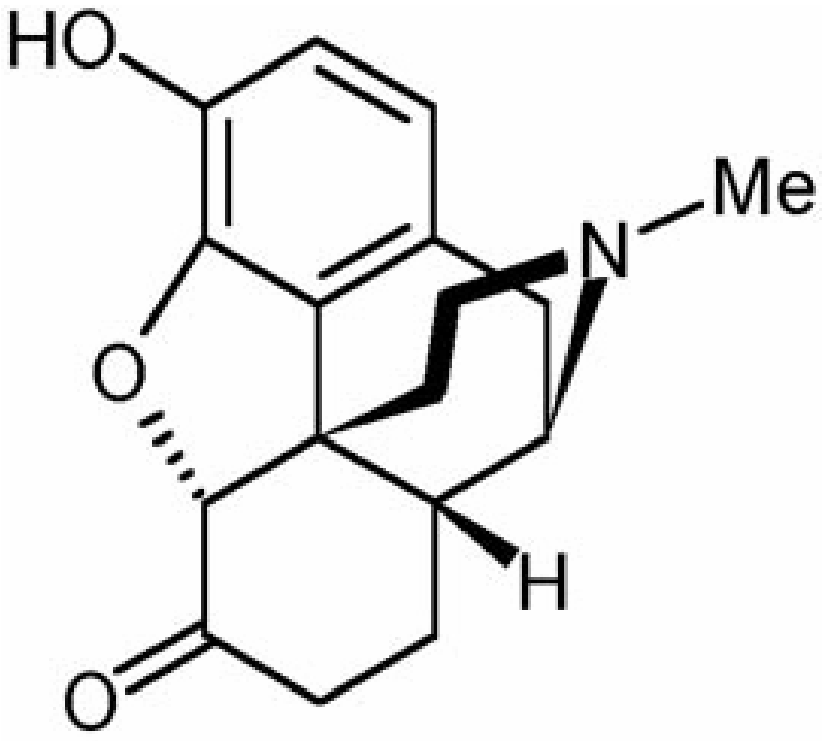
Hydrocodone Metabolism

- Metabolized by CYP2D6 to hydromorphone
- Metabolized by CYP3A4 to norhydrocodone
- Available with APAP, ibuprofen, or time released



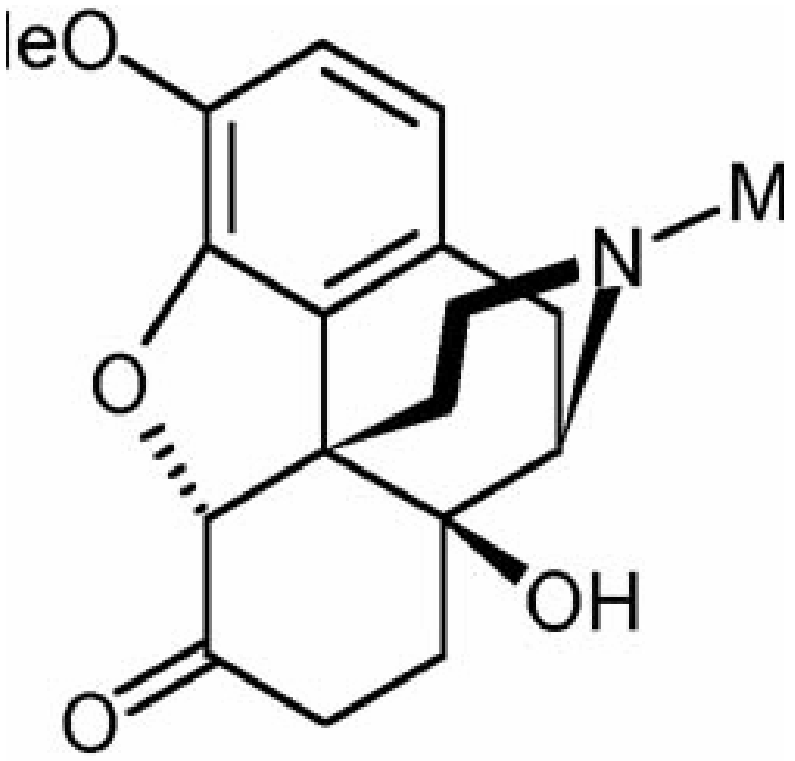
Hydromorphone Metabolism

- About 5 times more potent than morphine
- Very water soluble which allows for very concentrated solutions
- Available po, ER, IV



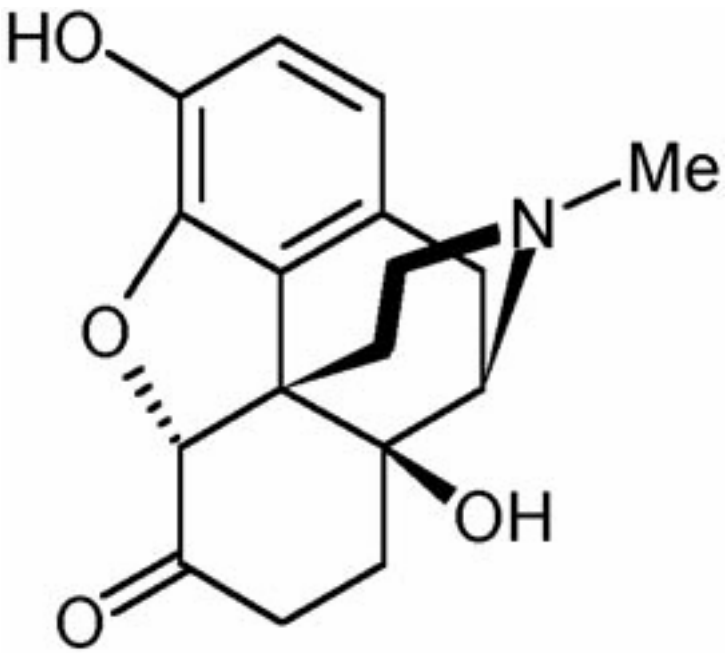
Oxycodone Metabolism

- Metabolized by CYP3A4 to noroxycodone (inactive)
- Metabolized by CYP2D6 to oxymorphone (active)
- Oxycodone has activity at multiple receptors
- “perky Percocet”



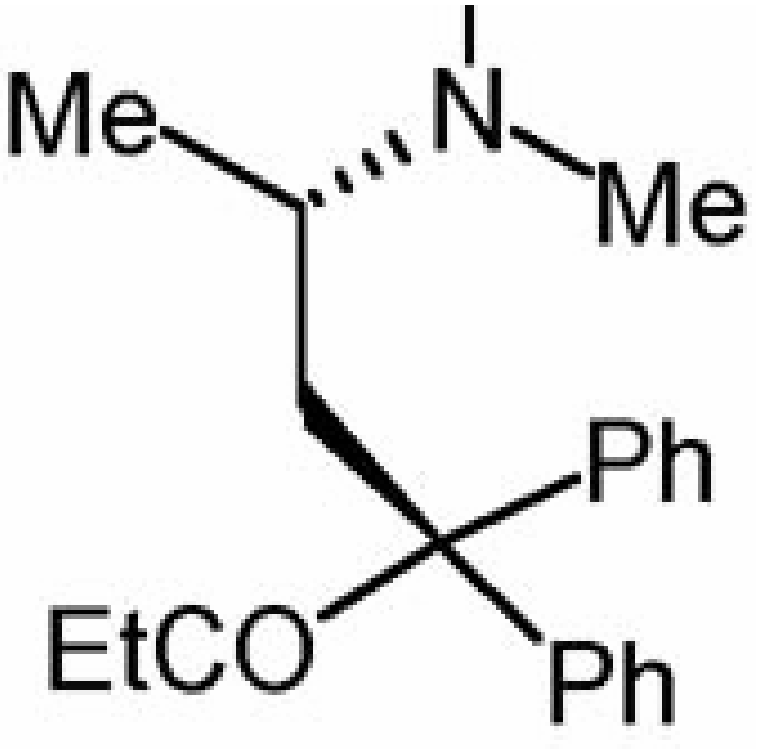
Oxymorphone Metabolism

- Oxymorphone has a very high affinity for the μ receptor
- Oxycodone CR to oxymorphone ER (2:1)
- 1mg oxymorphone is equivalent to 10mg morphine
- Extensively metabolized by liver, but not affected by CYP2D6 or 3A4 metabolism



Methadone Metabolism

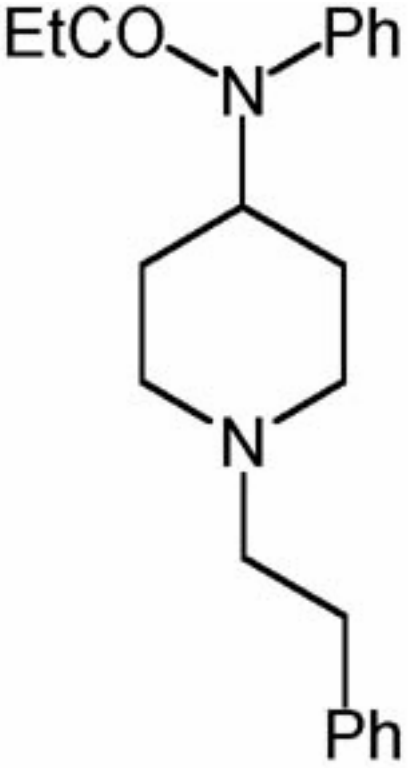
- Metabolized by 3A4 primarily and 2D6 secondarily
- EDDP inactive metabolite
- L-isomer is the opioid. D-isomer affects the NMDA receptors
- Slow onset of action (half life from 12 to 150 hrs; average 23 hours)
- Cheap



P450 Enzymes Metabolizing Methadone	
CYP3A4	Primary enzyme (can also be induced by methadone during the start-up phase of MMT).
CYP2D6	Secondary role (methadone can inhibit this enzyme in same cases).
CYP1A2, CYP2C9, CYP2C19	Possibly involved (clinical significance is still under investigation).
CYP2B6	Newly proposed as important methadone metabolizer.
Borg and Kreek 2003; Eap et al. 2002; Gerber 2002; Leavitt et al. 2000; Moolchan et al. 2001; Wu et al. 1993	

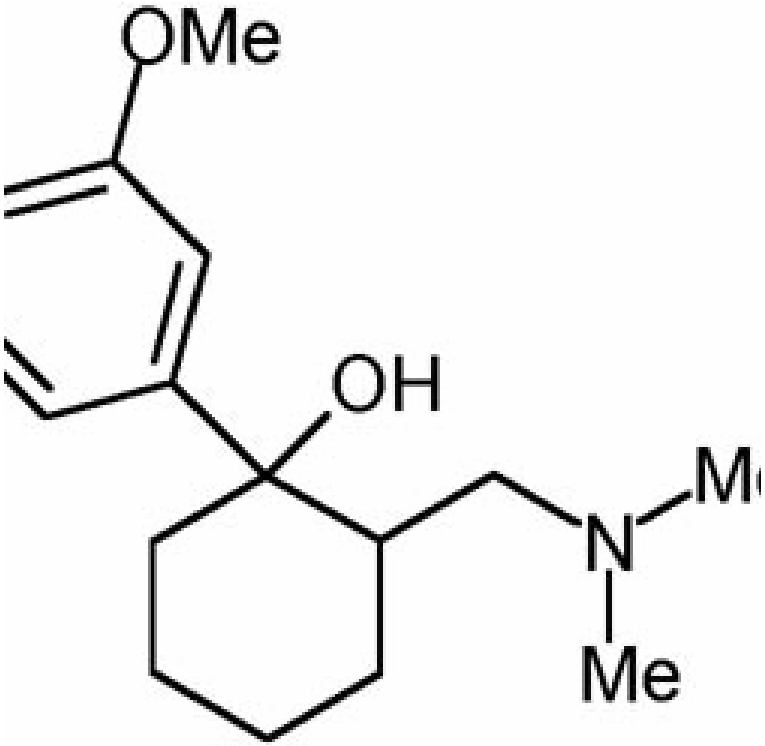
Fentanyl Metabolism

- Extremely lipophilic with rapid crossing of blood-brain barrier
- Lowest histamine release, highest μ affinity
- Metabolized by CYP3A4 to inactive norfentanyl
- IV, transdermal, intranasal, transoral



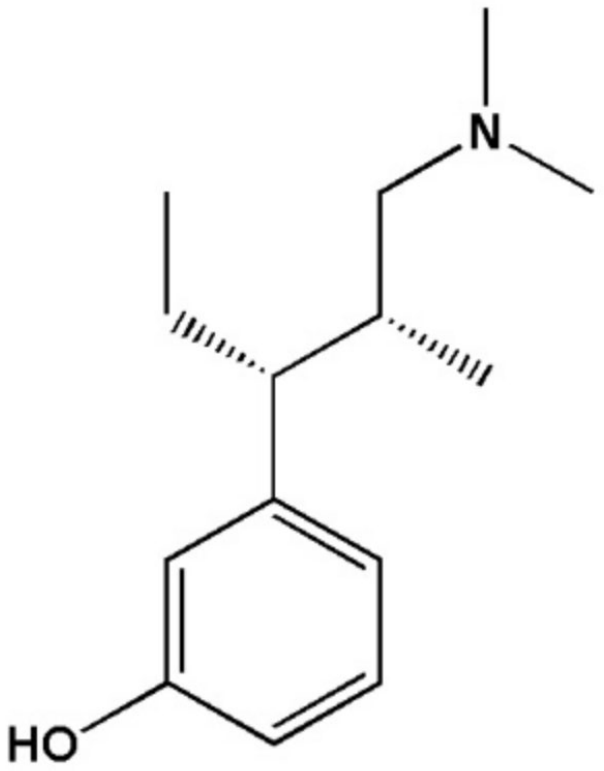
Tramadol Metabolism

- Synthetic analogue of codeine
- Metabolized by CYP2D6 to M1 metabolite (O-dimethyl tramadol) which is more active than parent compound
- Toxic amounts cause seizures



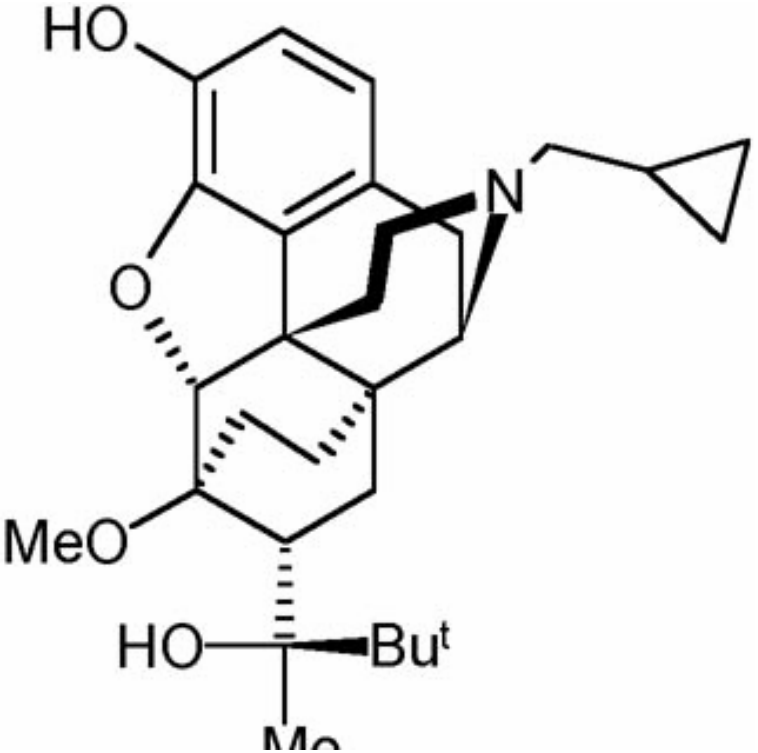
Tapentadol Metabolism

- Ist new opioid in 25 years
- Centrally-acting analgesic with a dual action
  - μ agonist
  - Norepinephrine reuptake inhibitor
- Not as weak as tramadol but not as strong as morphine
  - IR and ER formulations
- Inactive metabolites



Buprenorphine Metabolism

- Partial agonist at μ (antagonist at κ and δ)
- Sublingual (Subutex®)
- Sublingual with naloxone (Suboxone®)
- IV or IM (Buprenex®)
  - 0.3mg = 10mg MSO4
- Patch (Butrans®)
- Metabolized by CYP3A4 to norbuprenorphine (active)



Opioid Metabolism

- As we discussed earlier, many opioids are potentially prodrugs that require metabolism to a more active compound
  - Codeine to morphine (CYP2D6)
  - Hydrocodone to hydromorphone (CYP2D6)
  - Oxycodone to oxymorphone (CYP2D6)
  - Tramadol to more potent M1 metabolite (CYP2D6)
- Therefore, anything that interfers with CYP2D6 can have significant effects on analgesia

CYP450 Inhibition *in vitro*

	3A4	2D6	1A2	2C19	2C9
Escitalopram (Lexapro®)	0	0	0	0	0
Citalopram (Celexa®)	0	+	+	0	0
Fluoxetine (Prozac®)	++	+++	+	++	++
Paroxetine (Paxil®)	+	+++	+	+	+
Sertraline (Zoloft®)	+	+	+	++	+
Duloxetine (Cymbalta®)		++			

Greenblatt DJ, et al. Poster presented at Annual Meeting of the Society of Biological Psychiatry May 2001

Population Frequency of CYP Genotypes

Gene	PM	IM	EM	UM
CYP2D6	10%	35%	48%	7%
CYP2C9	2-4%	>35%	~60%	N/A
CYP2C19	2-20%	24-36%	14-44%	30%

Urine Drug Toxicology

TEST	TEST METHOD	TEST OUTCOME	MEASURED RESULTS*	CREATININE NORMALIZED**	CUTOFF*
NATURAL AND SEMI-SYNTHETIC OPIOIDS					
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
Hydrocodone	LC-MS/MS	Neg		-	50.00
Norhydrocodone	LC-MS/MS	Neg		-	50.00
Hydromorphone	LC-MS/MS	Neg		-	50.00
Oxycodone	**LC-MS/MS**	**POS**	**15,646**	**12,437**	**50.00**
Noroxycodone	**LC-MS/MS**	**POS**	**9,010**	**7,162**	**50.00**
Oxymorphone	**LC-MS/MS**	**POS**	**9,881**	**7,855**	**50.00**

Urine Drug Toxicology

TEST	TEST METHOD	TEST OUTCOME	MEASURED RESULTS*	CREATININE NORMALIZED**	CUTOFF*
NATURAL AND SEMI-SYNTHETIC OPIOIDS					
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
Hydrocodone	LC-MS/MS	Neg		-	50.00
Norhydrocodone	LC-MS/MS	Neg		-	50.00
Hydromorphone	LC-MS/MS	Neg		-	50.00
Oxycodone	**LC-MS/MS**	**POS**	**15,782**	**18,991**	**50.00**
Noroxycodone	**LC-MS/MS**	**POS**	**31,765**	**38,225**	**50.00**
Oxymorphone	**LC-MS/MS**	**POS**	**207**	**249**	**50.00**

Patient notes poor relief with oxycodone

Opioid Side Effects

Opioid Side Effects

- Opioids are well known to cause a variety of side effects, most commonly constipation, nausea and vomiting, sedation, and respiratory depression
- These side effects can be significant, and some patients avoid opioids even in the face of significant pain, in an effect to limit such side effects, which may act as a significant barrier to adequate pain relief

Constipation

- Constipation is the most common adverse effect from opioids, occurring in 40% to 95% of patients treated with opioids
  - Swegle JM, Logemann C. Opioid-induced adverse effects. *American Family Physician*. 2006;74(8):1347-52.
- It is essential that prophylactic treatment be instituted on the initiation of opioid treatment, since this, of all the side effects of opioids, does not resolve over time.

Constipation

- Treatment consists of “pushing the mush” [Hans Hansen, MD]
  - Bulk laxatives (psyllium)
  - Hyperosmotics (lactulose, polyethylene glycol, milk of magnesia)
  - Promotility agents (metoclopramide, misoprostol, or tegaserod)
  - Lubricants (mineral oil)
  - Stool softeners (ducusate) and/or cathartics (senna).
  - Opioid antagonists

Nausea and Vomiting

- Nausea has been reported to occur in up to 25% of patients treated with opioids

  Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain Medicine*. 2001;93:247-257.

  – Promethazine (oral, rectal, or parenteral)
  – Scopolamine transdermal
  – metoclopramide (which can also help treat constipation)
  – 5HT3 antagonists such as ondansetron

Pruritis

- 2-10% of patients on opioids will develop pruritis

  McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain*. 2003;231-256.

- Results from a direct release of histamine, and not usually an antigen/antibody reaction
  - It is therefore better considered an adverse reaction than an allergic reaction
  - Usually treated symptomatically with antihistamines such as diphenhydramine and cyproheptadine.

Sedation

- The incidence of sedation can vary from 20 to 60%, is usually associated with an initiation or increase in opioids, and is usually transient

Cherny N, Ripamonti C, Pereira J, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol*. 2001;19:2542-2554

  - Can be compounded by the presence of infection, dehydration, metabolic abnormalities, or coadministered drugs such as benzodiazepines
    - Methylphenidate 10mg, used daily, reduced drowsiness scores by 35%

Bruera E, J. Miller M, Macmillan K, Kuehn N. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. *Pain*. 1992;48(2):163-6.

Respiratory Depression

- A significant proportion of patients taking long-term opioids develop central apnea during sleep
  - 10 patients in a methadone maintenance program were evaluated with overnight polysomnography.
    - All 10 patients had evidence of central sleep apnea

Teichtahl H, Prodromidis A, Miller B, et al. Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction* 2001;96(3):395–403.

Endocrine Effects

- Amenorrhea developed in the 52% female patients on opioids for chronic pain

  Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained action opioids for control of nonmalignant pain. J Pain. 2008;9:28-36.

- Testosterone levels were subnormal in 74% of males on sustained release oral opioids

  Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002;3:377-84.

- Osteoporosis seen in chronic opioid use may be due to the endocrine effects
- Bioequivalent hormone replacement therapy has been advocated

Opioid Induced Hyperalgia (OIH)

Focused Review

Pain Physician 2009; 12:679-684

Opioid Induced Hyperalgesia: Clinical Implications for the Pain Practitioner

Sanford M. Silverman, MD

Opioid Induced Hyperalgia (OIH)

- Defined as pain sensitization from chronic opioid administration
  - OIH is often overlooked as a potential complication of opioid therapy
- Observed by Albutt in 1870:

  "At such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia, which may be an evil. Here experience is needed. Does morphia tend to encourage the very pain it pretends to relieve?"

Albutt C. On the abuse of hypodermic injections of morphia. *Practitioner* 1870; 5:327-331.

Tolerance vs Hyperalgia

- **Tolerance** is a pharmacologic concept, occuring when there is a progressive lack of response to a drug, thus requiring increased dosing.
  - Common effect of many drugs
- It can be overcome by increasing the dose of the drug.

Tolerance vs Hyperalgia

- **Hyperalgia** is an increased pain sensitivity resulting in increased pain despite increasing doses of opioids
  - May be related to opioid metabolites such as M3G
  - May be related to NMDA receptor agonism
- Tolerance is a necessary condition for OIH, but the converse is not true.

Clinical Suspicion

- Clinicians should suspect OIH when:
  - Opioid treatment effectiveness seems to wane in the absence of disease progression
    - Particularly if found in the context of unexplained pain
  - Patient reports diffuse allodynia unassociated with the original pain
  - There are increased levels of pain with increasing dosages of opioids.

Treatment Options

- Increase the dose of opioid and evaluate for increased efficacy (tolerance).
- Reduce or eliminate the opioid and evaluate efficacy (OIH).
- Utilize opioids with unique properties that may mitigate OIH (such as methadone and buprenorphine).
- Utilize specific agents that are NMDA receptor antagonists (such as methadone and dexamethorphan).

Opioid withdrawal - abstinence syndrome

Severity depends on dose used and rate of elimination.

- Rhinorrhea
- Lacrimation
- Chills
- Goose flesh - 'cold turkey'
- Muscle aches
- Diarrhea
- Yawning
- Anxiety
- Hostility
- Hyperalgesia

Precipitated withdrawal by a partial agonist or antagonist administration

Clonidine, an α2-adrenergic receptor agonist, is effective at reducing the sympathetic nervous system hyperactivity associated with acute opiate withdrawal.

So How Do You Address the Patient That Says, “The Pain Medicine is Not Working”?

- Drug seeking?
  - Check PDMP
- Poor absorption?
  - Check urine toxicology
- Poor metabolism?
  - Check urine toxicology
- Poor receptor sensitivity?
  - Check genetics
- Opioid hyperalgia
  - Increase/decrease/change opioid
- Non-opioid sensitive pain
  - Re-evaluate for interventions

Opioid Pharmacology

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Background: Mu agonists have been an important component of pain treatment for thousands of years. The usual pharmacokinetic parameters (half-life, clearance, volume of distribution) of opioids have been known for some time. However, the metabolism has, until recently, been poorly understood, and there has been recent interest in the role of metabolites in modifying the pharmacodynamic response in patients, in both analgesia and adverse effects. A number of opioids are available for clinical use, including morphine, hydromorphone, levorphanol, oxycodone, and fentanyl. Advantages and disadvantages of various opioids in the management of chronic pain are discussed.

Objective: This review looks at the structure, chemistry, and metabolism of opioids in an effort to better understand the side effects, drug interactions, and the individual responses of patients receiving opioids for the treatment of intractable pain.

Conclusion: Mu receptor agonists and agonist-antagonists have been used throughout recent medical history for the control of pain and for the treatment of opiate induced side effects and even opiate withdrawal syndromes.

Key words: Opioid metabolism, opioid interactions, morphine, codeine, hydrocodone, oxycodone, hydromorphone, methadone, intractable pain, endorphins, enkephalins, dynorphins, narcotics, pharmacology, propoxyphene, fentanyl, oxymorphone, tramadol

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Comprehensive Review

A Review of the Role of Genetic Testing in Pain Medicine

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Background: Pain clinicians have always been challenged by the variability of response to pain treatment. Differences in the degree of pain stimulation and pain sensitivity, weight and age differences, prior opioid use and tolerance, as well as the differences in bioavailability of various opioid formulations have been cited as causes for the wide variability in analgesia seen with opioids. Genetics may explain the variability of responses and help to predict more effective (or less dangerous) medication choices and doses. Genetics may also help to predict the response to specific opioids and antidepressants.

Objectives: In this review article, we discuss the genetic influence of nociception, analgesia, and hyoanalgesia. The CYP450 enzymes involved in the metabolism and activity of opioids and adjuvant analgesics are genetically controlled, as are the opioid receptors and a variety of brain chemistries.

Methods: This article discusses the specific pain implications of genetic variations in CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A7, OPRM1, OPRK1, OPRD1, COMT, GABA, UGT, MC1R, GCH1, ABCB1, P-glycoprotein, 5HTR1A, 5HTR2A, MTHFR, CACNA2D2, and 5-HTTLPR.

Results: Recent research findings suggest the relationship between genetic predisposition and clinical behavior, including the risk of opioid misuse and addiction. While urine drug testing may hint at genetic issues regarding opioid metabolism, cheek swab DNA testing has become economically viable, and we review the current and future genetic pain issues that may influence the decisions that pain clinicians make every day.

Conclusion: Genetic testing may explain and predict many of the clinical responses seen with opioids and adjuvant medications, and may help the clinician identify those patients at genetic risk of opioid misuse and addiction.

Key words: Genetics, genetic testing, opioid metabolism, drug interactions, urine drug testing,

Thank You

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