Opioid Pharmacology

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Nomenclature

- ***Opium*** **is the dried powdered mixture of 20 alkaloids obtained from the unripe seed capsules of the poppy**
- ***Opiate*** **refers to any agent derived from opium**
- ***Opioid*** **refers to all substances (exogenous or endogenous) with morphine -like properties**
- ***The generic term for the class of agents is "opioid"***

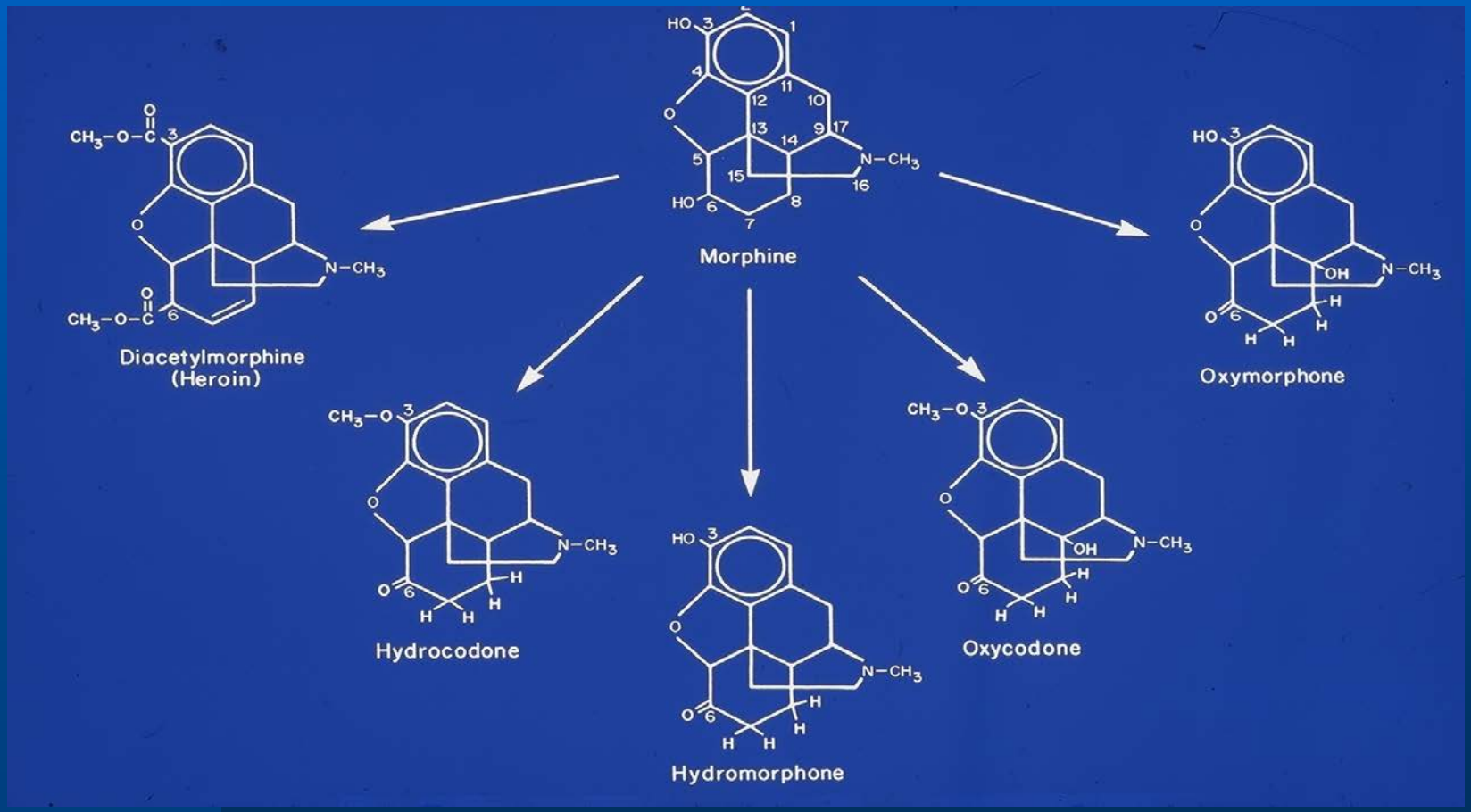
Opium Poppy

Structure-Activity

- ***Alkaloid:*** **derived from the poppy**
  - **morphine**
  - **codeine**
- ***Semisynthetic:*** **modification of morphine functional groups:**
  - **diacetylmorphine (heroin)**
  - **hydrocodone**
  - **hydromorphone**
  - **oxycodone**
  - **oxymorphone**

Morphine (Phenanthrene Ring)

Semisynthetic Opioids

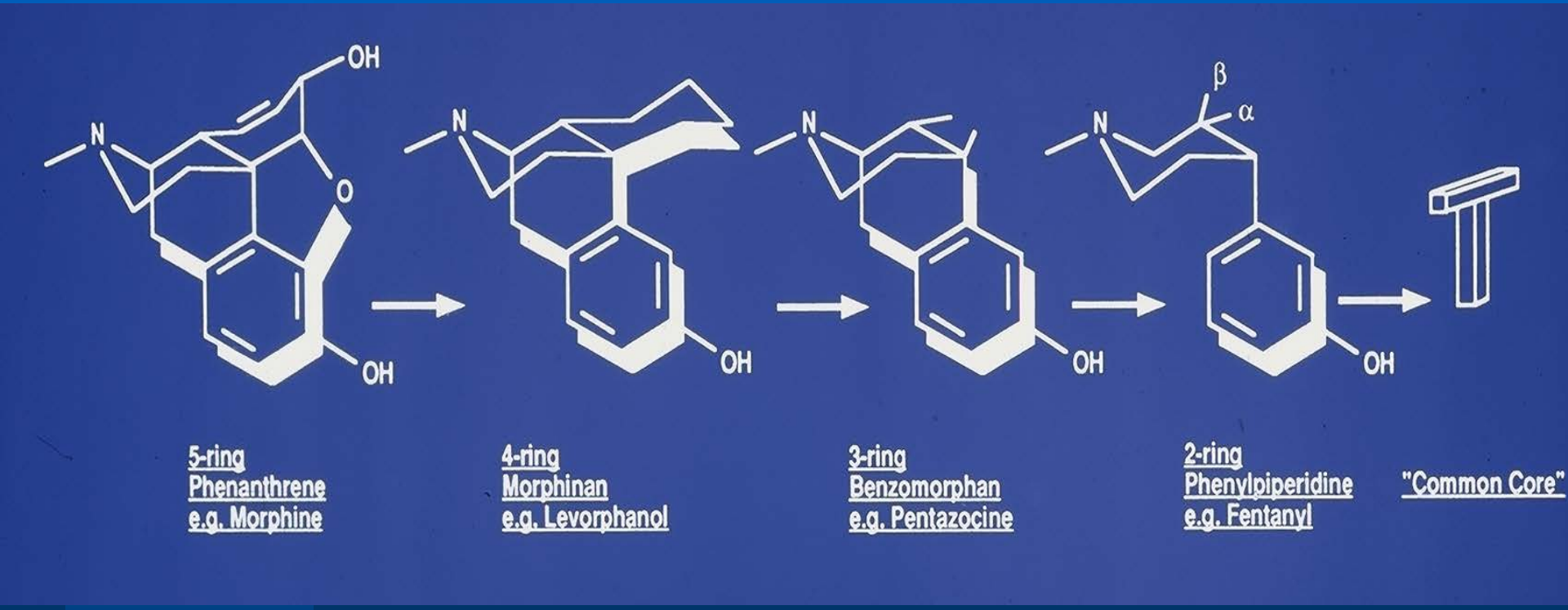


Structure-Activity

- ***Synthetic:*** ***progressive reduction in the number of*** **fused rings in phenanthrene moiety:**

Morphinan	Phenylpiperidine	Propioanilide
• levorphanol	• meperidine • fentanyl • sufentanil • alfentanil	• methadone • propoxyphene

Synthetic Opioids



Pharmacodynamics

Opioid Receptors

Opioid receptors serve two functions:

- ***Recognition***: **only L-isomers exhibit analgesic activity**
- ***Biologic action***: **The strength of attachment (binding affinity) correlates with analgesic potency**

⇓adenylate cyclase **⇑presynaptic Ca**

μ-Receptor Binding Affinities

Opioids	*Binding Affinity*
Sufentanil	**0.1**
Fentanyl	**1.6**
Morphine	**5.7**
Alfentanil	**19.0**
Meperdine	**193.0**

Binding Affinity is measured by the equilibrium inhibition constant (Ki) for [H*] sufentanil (nM). The lower the value of (Ki), the Higher the binding affinity for the μ-receptor.

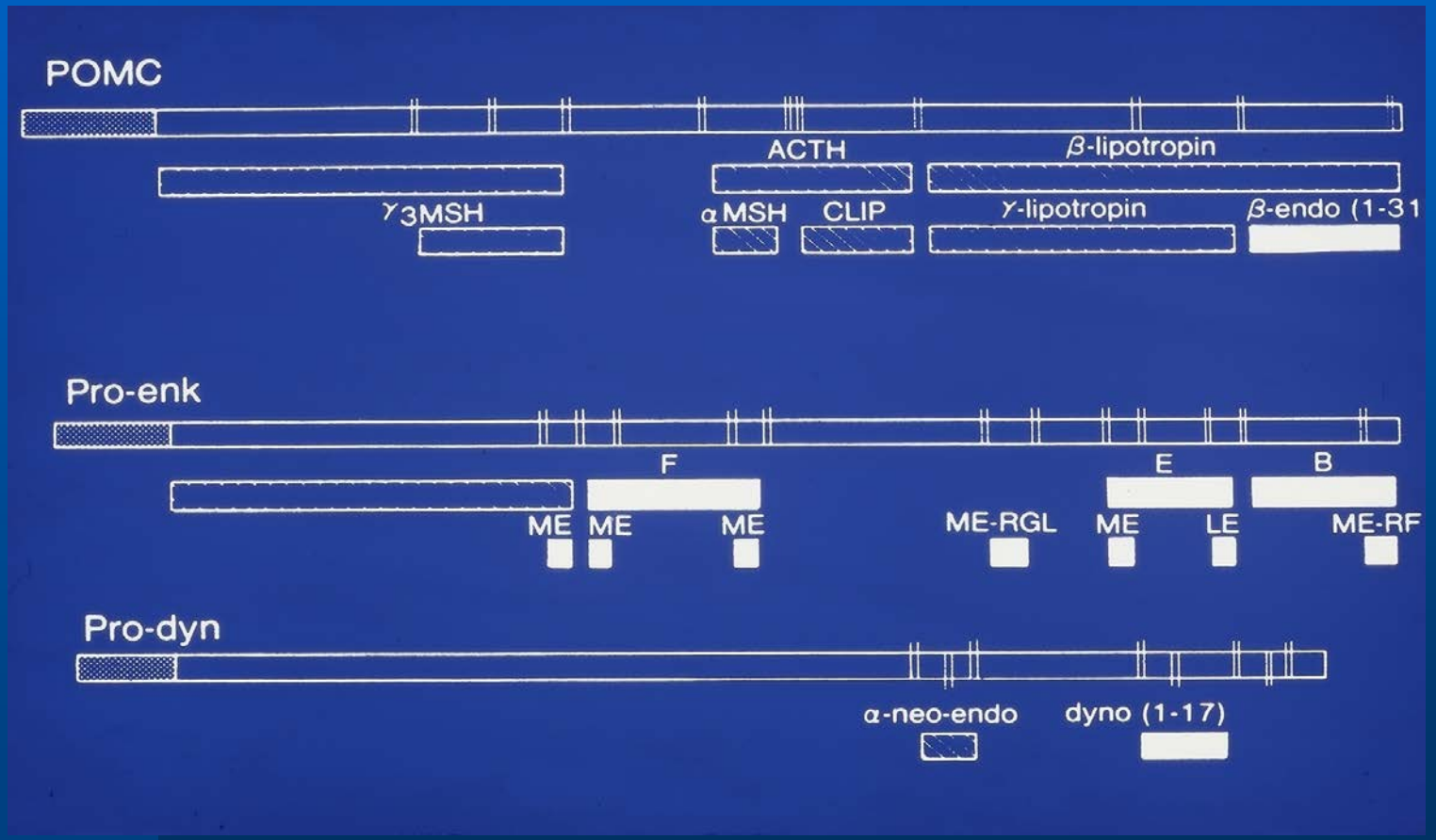
Opioid Receptor Classification

Receptor	*Prototypic drug*	*Proposed actions*
μ_1	Most endogenous , naturally-occurring or synthetic opioids	Supraspinal analgesia
μ_2	Morphine	Respiratory depression Cardiovascular effects
δ	Enkephalins	Spinal analgesia
κ	Ketocyclazocine and dynorphin	Spinal analgesia Sedation, miosis
σ	N - allylnormetazocine	Psycotomimetic effects

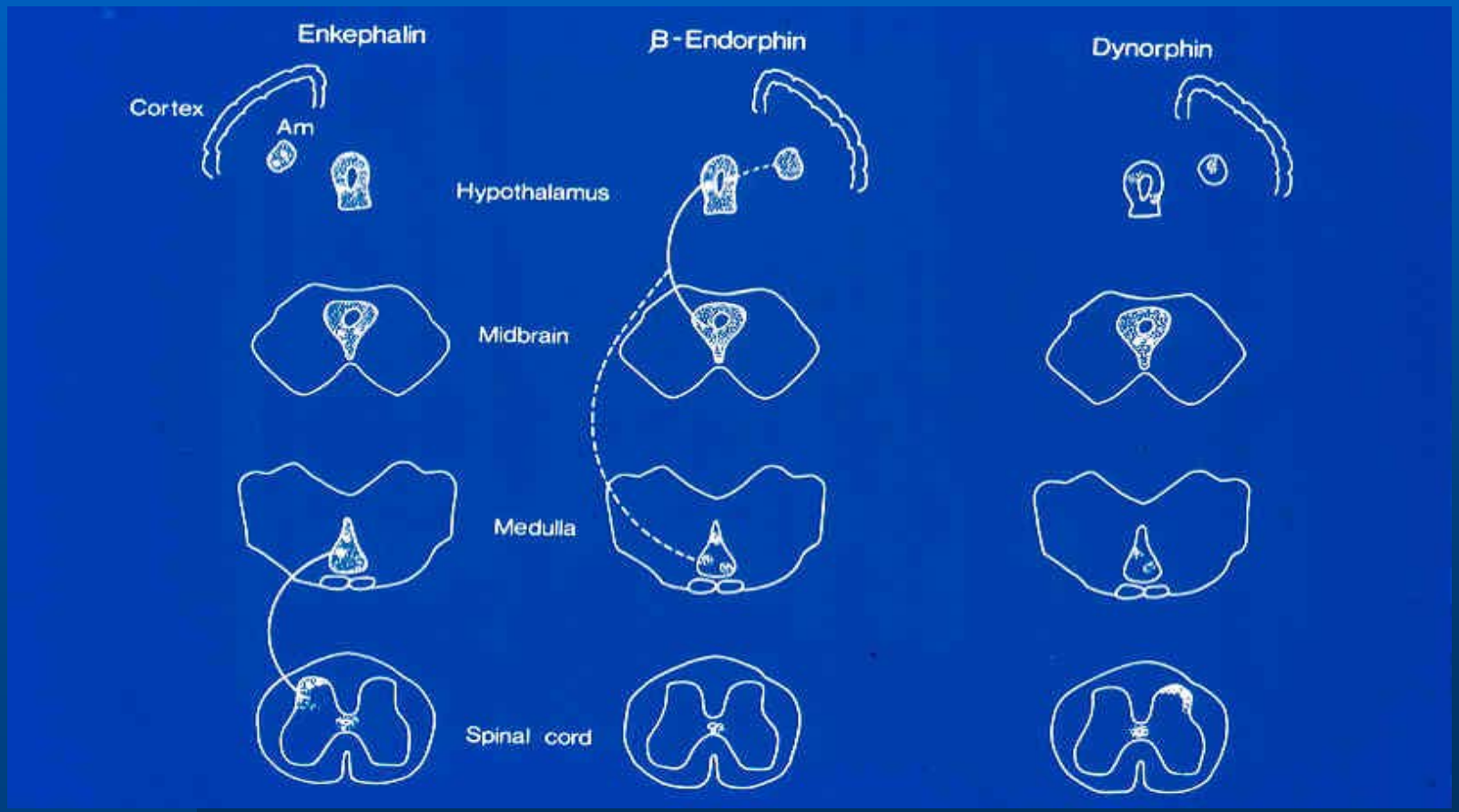
Major Groups of Endogenous Opioids

Name	Amino acid sequence
Leucine-enkephalin	Tyr-Gly-Gly-Phe-Leu-OH
Methionine-enkephalin	Tyr-Gly-Gly-Phe-Met-OH
β-Endorphin	*Tyr-Gly-Gly-Phe-Met*-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Gly-Gln-OH
Dynorphin	*Tyr-Gly-Gly-Phe-Leu*-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Try-Asp-Asn-Gln-OH
α-Neoendorphin	*Tyr-Gly-Gly-Phe-Leu*-Arg-Lys-Tyr-Pro-Lys

Secretion as Prohormones



Localization in CNS

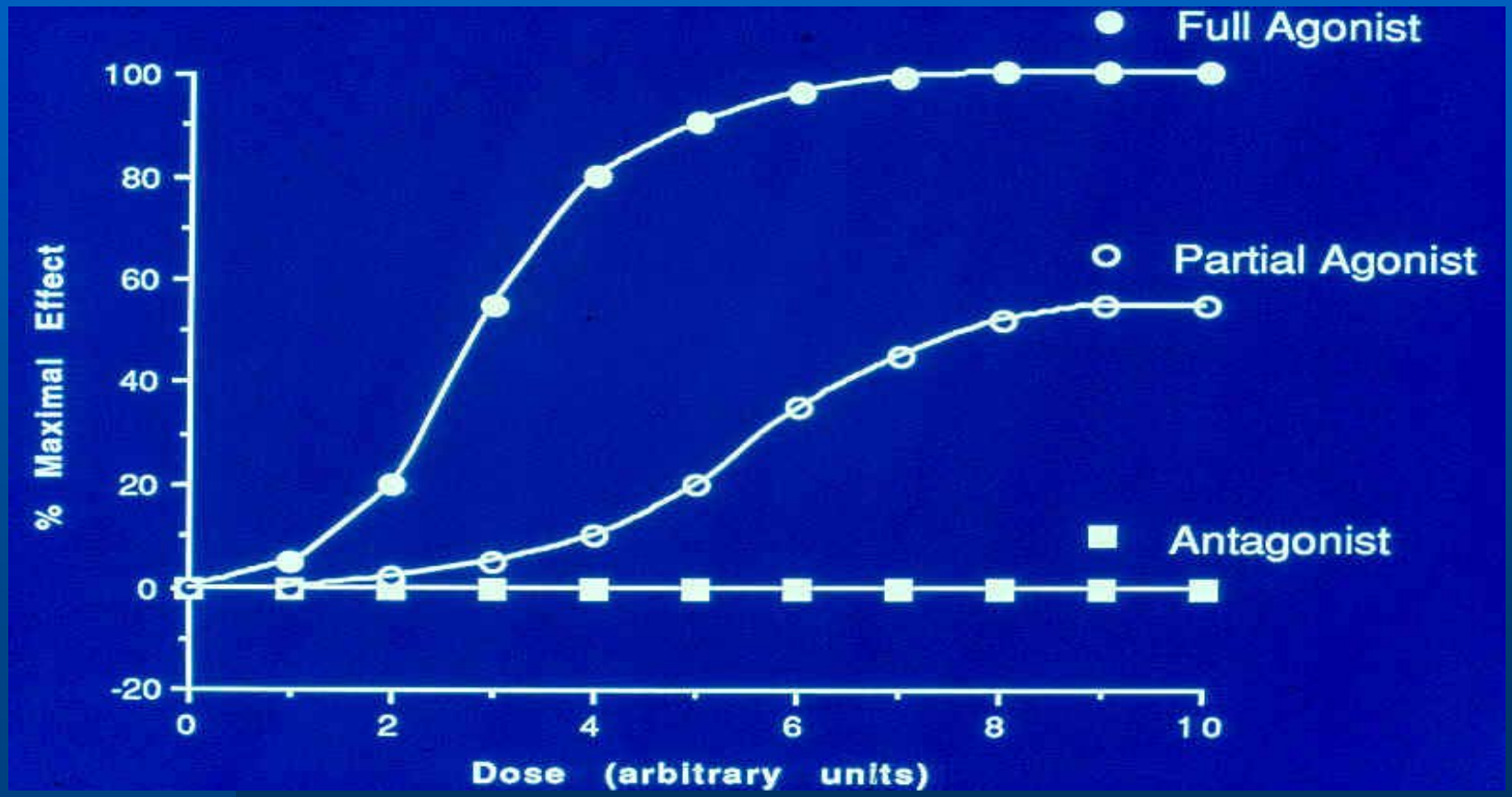


Intrinsic Activity

The relationship between receptor binding and response

- ***Agonists*** **produce a maximum biologic effect**
- ***Antagonists*** **have no intrinsic activity and prevent the access of agonists to the receptors**
- ***Partial agonists*** **have a submaximal response**

Intrinsic Activity



Partial Agonists

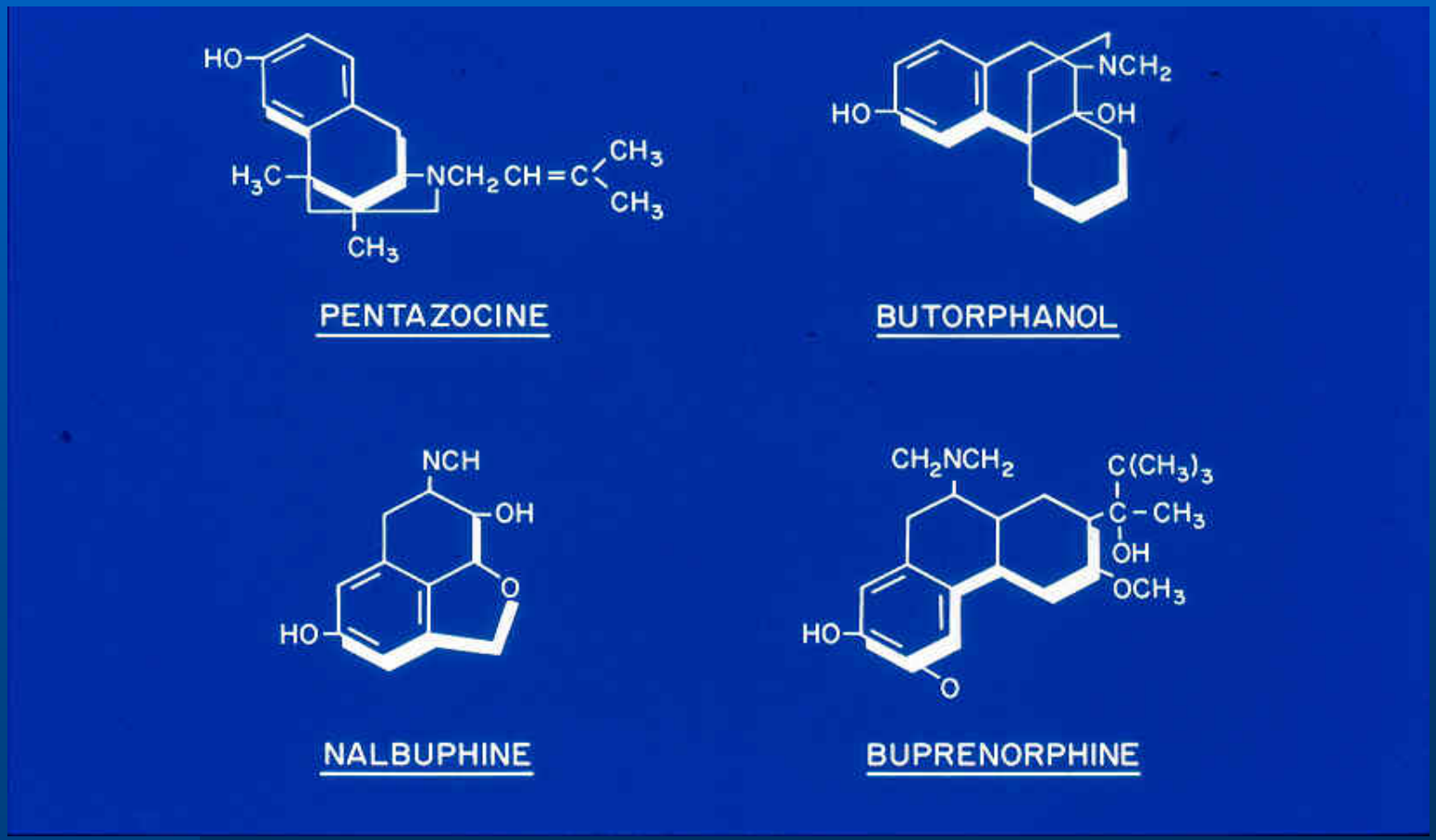
- **Less steep dose-response curve than agonists**
- **Ceiling effect**
- **Concomitant administration of a partial and full agonist reduces (antagonizes) the effect of the full agonist**

Mixed Agonist-Antagonists

- ***Partial antagonism*: interaction at a single receptor type**

- ***Agonist-antagonists*:have divergent activities at different receptors, acting simultaneously as an agonist at one and an antagonist at another**

Mixed Agonist-Antagonists



Mixed Agonist-Antagonists

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

Mixed Agonist-Antagonists

- **Less steep dose-response curve than agonists**
- **Ceiling effect**
- **Concomitant administration of a partial and full agonist reduces (antagonizes) the effect of the full agonist**
- **Addictive potential**

Mixed Agonist/Antagonists

- **Butorphanol (Stadol):**
  - **Potency: 5X Morphine (parenteral)**
  - **Nasal spray: 1mg per spray**
    - **Headache**
  - **50% less nausea/vomiting than Morphine**
  - **Sedating**
- **Nalbuphine (Nubain): equipotent to Morphine**

Buprenorphine

- Semisynthetic derivative of thebaine.
- Highly lipophilic.
- Prolonged and avid binding to μ-receptor
- 20-30X potency of MS (0.2-0.3mg = 10mg MS)
- Formerly, most common route: parenteral
- Well absorbed sublingually
  - Opioid detoxification
  - Maintenance programs

Pharmacologic Considerations: Opiates

Morphine

- **Routes: PO, IM, IV, SQ, nebulized & rectal**
- **Sustained release preparations:**
  - **MS Contin**
  - **Oramorph**
  - **Kadian**
  - **Avinza (true qd dosing)**

Morphine Metabolites

- Morphine: conjugated in the liver
- Metabolites include:
  - Morphine-3-glucuronide (M3G)
  - Morphine-6-glucuronide (M6G)
- Metabolites are cleared in kidneys
- M6G:
  - Active metabolite,
  - Accumulates in CNS
- M3G
  - May affect tolerance

Dextromethorphan

- d-isomer of morphine
- No classic analgesic effects (only L-isomer)
- NMDA antagonist (neuropathic pain)
  - Need “industrial” doses: impractical

Codeine

- Opiate (naturally occurring in poppy)
- Low affinity for opioid receptors
- 10% of dose demethylated to morphine
  - Fraction responsible for analgesia?
- Schedule II
- Most prescribed opioid in the world.
- Probably the most widely used analgesic
  - (Excluding aspirin)
- Limited by:
  - Low potency (do not use for severe pain)
  - Perceived frequency of nausea/ vomiting

Pharmacologic Considerations: Semisynthetics

Hydrocodone Combinations

- **With acetaminophen**
  - **Norco (5,7.5,10/325)**
  - **Anexia (5/500;7.5/650)**
  - **Lortab (2.5,5,7.5,10/500)**
  - **Vicoden (5/500)**
  - **Vicoden-ES (7.5/750)**
  - **Lorcet (7.5, 10/650)**
- **Vicoprofen (ibuprofen 200/7.5 mg hydrocodone)**

Oxycodone Combinations

- **Percocet/ Tylox:**
  - **oxycodone 5/acetaminophen500**
- **Percodan:**
  - **oxycodone 5/ASA 325**
- **Roxycodone/ Oxy IR**
- **OxyContin**

Oxymorphone (Opana)

- **Opana ER: 5, 10, 20, 40 mg tabs**
- **Opana (IR): 5 and 10 mg**
- **Oral: 3x potency of morphine**
- **Old N/A IV: 10X potency of morphine**
- **“Tamper-proof” gum**
- **RF: OK in mild-mod (CC > 30 mL/min)**
- **Dose 1h before or 2hr s/p eating**

Pharmacologic Considerations: Synthetics

Methadone

- Dolophine: incorrectly attributed to Hitler
- 10 mg tabs & 40 mg wafers
- Half-life:
  - Acute: 1^{o} $t_{1/2}$ = 14 h; 2^{o} $t_{1/2}$ = 55h
  - Chronic: $t_{1/2}$ = 23h
- Analgesic duration <<< $t_{1/2}$ (slow terminal elimination)
  - Sequestered & unavailable for analgesia
  - Dose q6-q8
- Beware accumulation

Methadone

- Stigma of heroin maintenance
- Must write: “for pain” in some states
  - Special license for methadone maintenance
- Inexpensive
- d-isomer = NMDA antagonist (neuropathic pain)
  - Available as racemic mixture in US
  - Available as l-enantiomer in Europe

Meperidine and Congeners

- **Meperidine (Demerol/Mepergan)**
  - **Structurally similar to atropine**
    - **Tachycardia (unlike most opioids: bradycardia)**
  - **Problems with MAO inhibitors**
  - **Normeperidine metabolite (CNS excitation)**
    - **Renally cleared**
    - **“Slow excretors”: normal creatinine clearances**
  - **Very short duration of action ≅ 3 h**
- **Diphenoxylate (Lomotil, with atropine): 20mg/ d ÷ doses**
- **Loperamide (Imodium): 4-8mg/ d, max 16mg**

Propoxyphene

- **Unique:**
  - **d-isomer has analgesic properties**
- **Darvocet/ Darvon/ Darvon Compound**
- **Potency ≅ 2x codeine**
- **More effective in combination**

Tramadol

- **Dual mechanism of action**
  - **μ-opioid activity (30%)**
  - **inhibition of serotonin/NE re-uptake (70%)**
- **Nonscheduled opioid**
  - **Less abuse potential**

Tramadol-IR and –ER Dosing

	Usual Dosing	Adverse Events
Tramadol IR	**Start at 25 mg once daily; titrate up by 25-mg increments every 3 days to 100 mg/d (25 mg qid); thereafter titrate up as necessary every 3 days to 200 mg/d (50 mg qid); do not exceed 400 mg/d**	**Dizziness/vertigo, nausea, constipation, headache, somnolence**
Tramadol ER	**Start at 100 mg qd, titrate up as necessary by 100-mg increments every 5 d–not to exceed 300 mg daily**	**Dizziness, nausea, and constipation**

ACR Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum*. 2000;43:1905-1915; Ballantyne JC, Mao J. *N Engl J Med*. 2003;349:1943-1953.

Concept: Equianalgesic Dosing

- ***“ All opioids can be made equipotent or equianalgesic by adjusting for physicochemical and pharmacokinetic differences among individual opioids by correcting for dose and route of administration.”***

Opioid Analgesic Equivalents

Opioid	*Route*	*Equianalgesic dose*
Morphine	Parenteral	10 mg
	oral	30 mg
Hydromorphone	Parenteral	2 mg
	oral	4 mg
Meperidine	Parenteral	75 mg
	oral	300 mg
Methadone	Parenteral	10 mg
	oral	20 mg

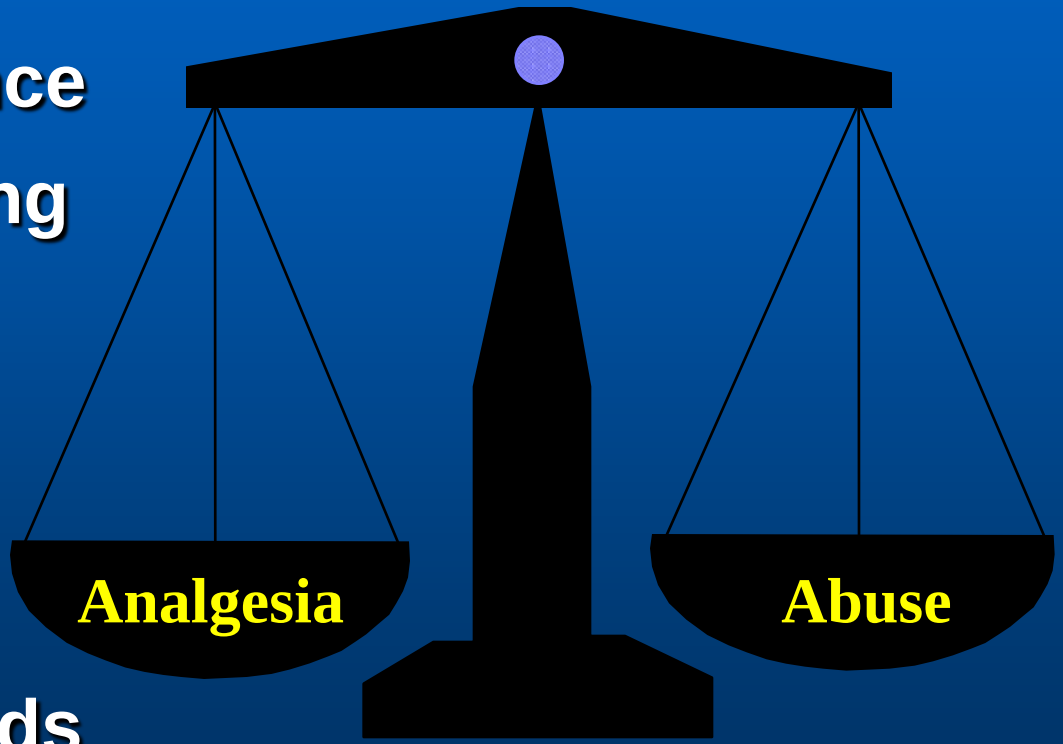
Equianalgesia: Route of Administration

ORAL	PARENTERAL	EPIDURAL	SUBARACHNOID	ICV
ACUTE 600: / CHRONIC 300:	100	10	1	0.1

Scheduling

Controlled Substances Act 1970

- Concept of balance
- Intro of scheduling
- "Narcotic drugs" defined, not by pharmacology
- Defined by law enforcement needs



Schedule I

- **No accepted medical use in the US**
  - **Heroin**
  - **LSD**
  - **Peyote**
  - **Mescaline**
  - **Marihuana (except for refractory nausea)**

Schedule II

- **High abuse potential:**
  - **Morphine**
  - **Codeine**
    - **Add ASA or acetaminophen = Schedule III**
    - **Add expectorant = Schedule V**
  - **Hydromorphone**
  - **Methadone**
  - **Oxycodone**

Schedule III

- **Hydrocodone + acetaminophen**
  - **Norco (5/325, 10/325)**
  - **Anexia (10/660)**
  - **Lortab (2.5, 5, 7.5, 10/500)**
  - **Lorcet (7.5, 10/660)**
  - **Vicoden (5/500, 7.5/750, 10/660)**
  - **Vicoprofen (ibuprofen 200/7.5 hydrocodone**
- **Tylenol #x (codeine)**

Abuse Potential

- **Actual abuse not directly tied to schedule**
- **Schedule II abuse < Schedule III or IV**
- **In past, Schedule II monitored closely:**
  - **Couldn't be refilled**
  - **Couldn't be prescribed by telephone**
  - **Why Vicodin (III) ⇧ popularity c/w Percocet (II)**

Schedule IV and V

- **Schedule IV: Benzodiazepines**
- **Schedule V:**
  - **Antitussive**
  - **Antidiarrheal**
  - **Analgesic**
    - **e.g., Buprenorphine**

Scheduling: No Relation Pharmacology

- **Codeine:**
  - **Schedule II**
  - **+ Acetaminophen or ASA = Schedule III**
  - **+ Cough syrup = Schedule V**

Tolerance, Physical Dependance, Addiction

Definitions
&
Concepts

Tolerance

- **With continued use, progressively more and more opioid is necessary to produce the same effect**
- ***Pharmacologic property* of a class of agents**
- **Incomplete cross tolerance**

Physical Dependence

- **A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.**

- ***Not synonymous with tolerance or addiction***

“Cold Turkey”: Opioid Withdrawal

- **Symptoms of opioid withdrawal:**
  - **Diaphoresis**
  - **Lacrimation**
  - **Coryza**
  - **Tachycardia**
  - **Abdominal cramps**
  - **Nausea**
  - **Vomiting**

Other Withdrawal Syndromes

- **Rebound hypertension**
- **Exacerbations of asthma after stopping steroids in steroid-dependent patients**
- **Rebound insomnia**
- **Discontinuation syndrome with SSRIs**
- **Rebound anxiety**
- **Seizures after D/C benzodiazepines**

Addiction

- ***A psychic and physical state characterized by compulsive behavior to obtain a drug in order to experience its psychic effects, despite full knowledge of its harmful effects***

- **Not a pharmacologic property**
- **Not synonymous with tolerance or physical dependence**

Physical Dependence & Addiction

Addiction

- **Compulsive desire to obtain drugs for their euphoric effect despite full knowledge of the action**
- **Behavioral**

Addiction: 5“Cs”

- **Chronic**
- **Compulsive *use***
- **Control *impaired***
- **Craving**
- **Continued *use despite harm***