OST
Pharmacology & Therapeutics

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Disclaimer

In the past two years I have received no payment for services from any agency other than government or academic.

Objectives

- To provide an understanding of the pharmacokinetics and pharmacodynamics of methadone and buprenorphine
- And the therapeutic implications thereof

Definitions & Concepts

- Opiate – descended from the opium poppy: Morphine, Codeine, Thebaine
- Opioid – anything that behaves like an opiate

- Pharmacokinetics - what the body does to the drug
- Pharmacodynamics – what the drug does the body

Pharmacodynamics of opioids

- Act on opioid receptors:
- μ **Mu -** Analgesia, euphoria, most important in terms of OST
  - Seven known subtypes, probably a lot more
- κ **Kappa –** Analgesia, dysphoria
- δ **Delta -** Analgesia, antidepressant
- **ORL1 –** Anxiety, appetite, tolerance to mu agonist

Opioids

- Agonists – Morphine, hydromorphone, oxycodone, methadone, fentanyl
- Partial agonist – Buprenorphine
- Antagonist – naloxone, naltrexone
- Agonist/antagonist – pentazocine (Talwin®) Kappa agonist/mu antagonist, also a delta agonist

Cross tolerance

- **Tolerance** – Need increasing dose of drug to get desired effect or toxicity

- **Cross tolerance –** tolerance to one drug in a class will confer **some** tolerance to other drugs of the same class

- Cross tolerance is **rarely** if ever complete

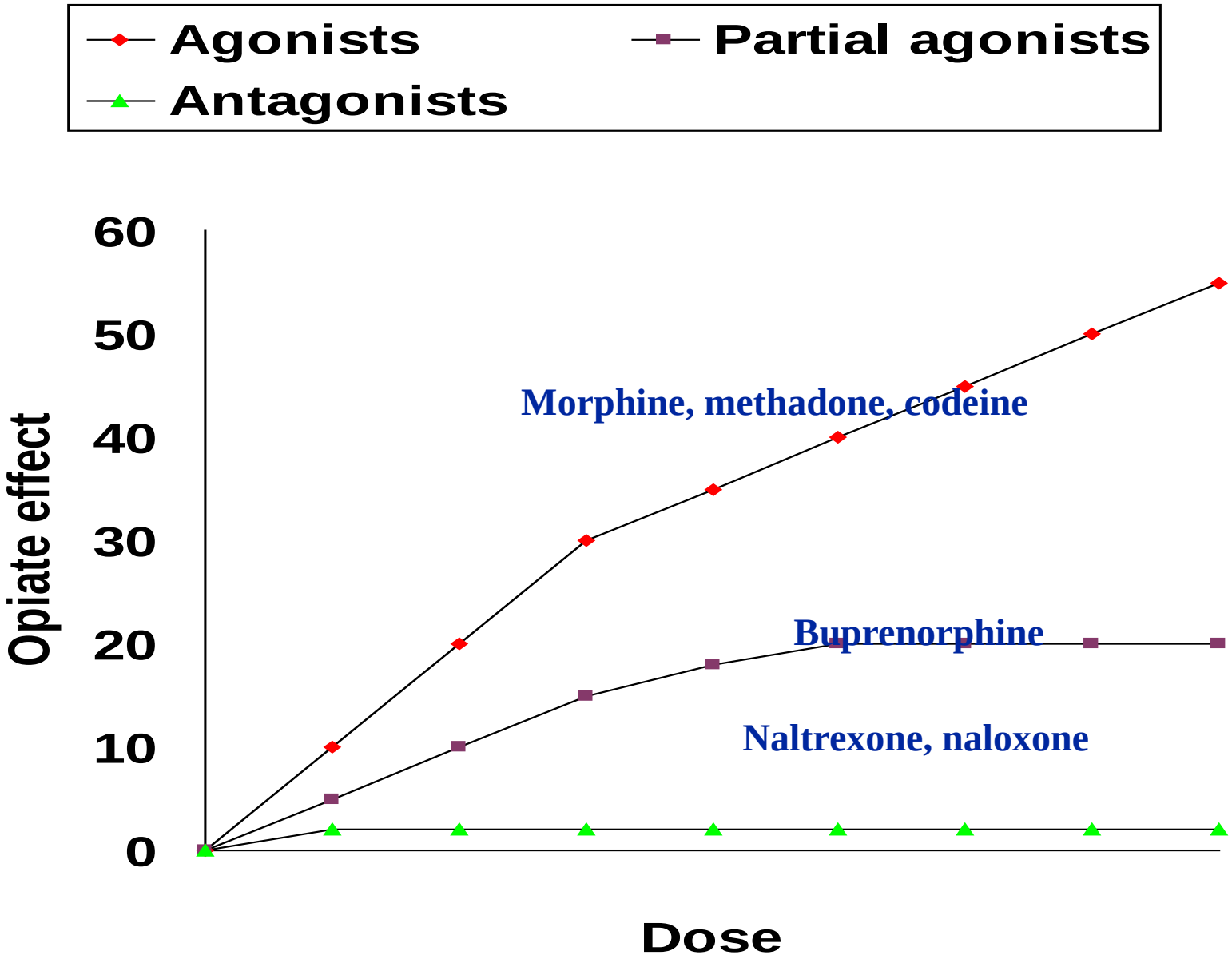
Affinity to Mu Receptor

- A drug with higher affinity will dislodge an drug with lower affinity from the receptor.
- Drugs with high affinity are protective form overdose by drugs of lower affinity
- Morphine < Methadone < Buprenorphine < Fentanyl < Naloxone
- Note fentanyl – high dose buprenorphine does confer some protection from fentanyl overdose

OST MEDICATION

- Naltrexone – long acting antagonist used in the highly motivated
- Methadone – Full agonist
- Buprenorphine – Partial agonist
- Naloxone – Short acting antagonist combined with Buprenorphine and marketed as SUBOXONE®

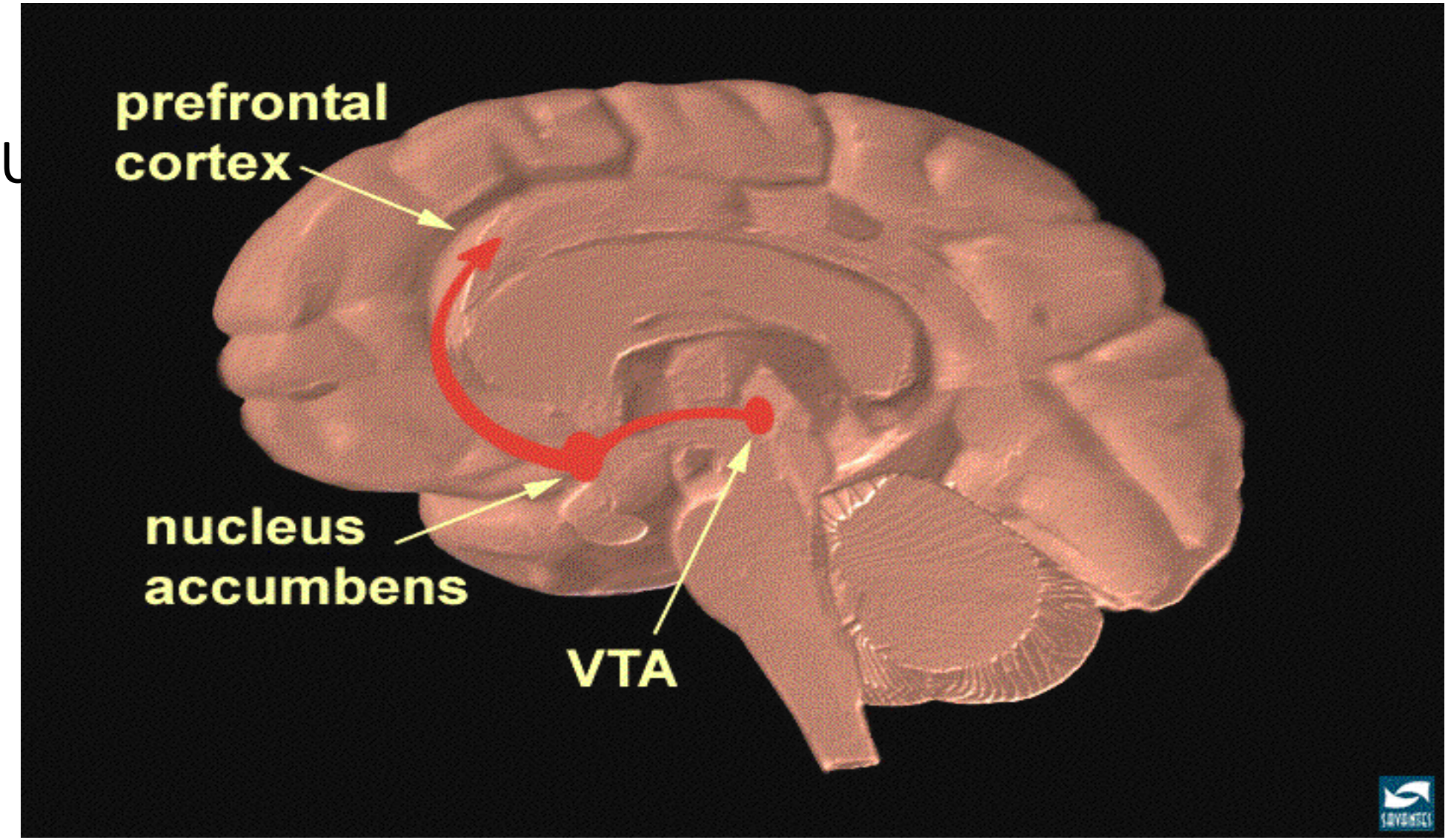
Classification of Opioids



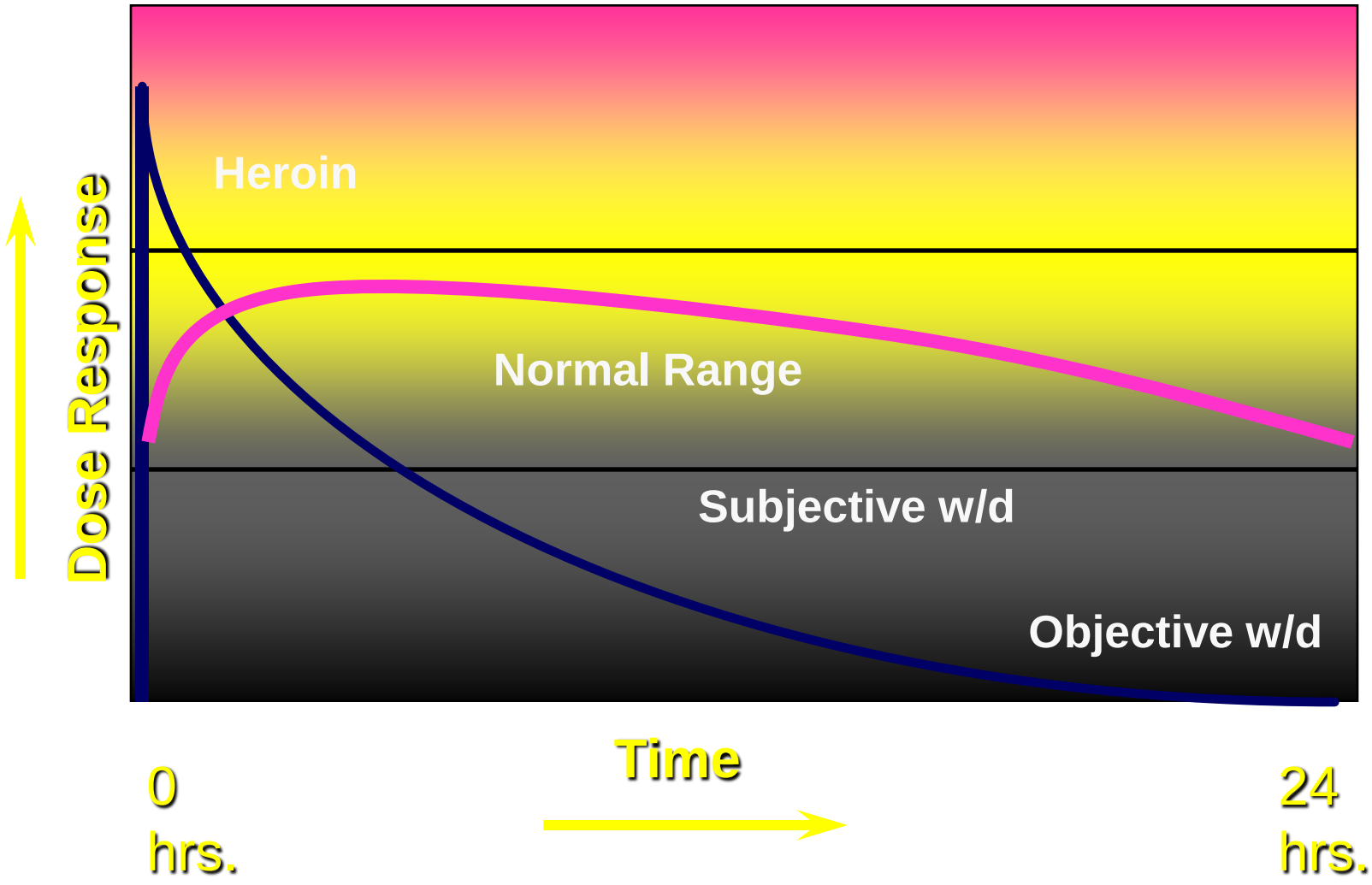
Mu Receptor effect

- Found throughout body
- Inhibit neural activity
- In brain cause analgesia, lethargy, respiratory depression and death
- Exception is in Ventral Tegmental Area where neurons release **dopamine** in Nucleus Accumbens via the Mesolimbic Forebrain Bundle causing euphoria
- Somewhat mitigated by narcosis effect of opioid (in SA –heroin is called “mother”).

Pleasu



Methadone 24 Hour Dose Response



Slide courtesy of Dr. J. Thomas Payte

Mu Receptor effect

- In GI tract slows peristalsis – nausea, constipation.
- Blocks hypothalamic pituitary axis
  - Secondary hypogonadism
  - Adrenocortical dysfunction
- Anticholinergic effect
  - Sweating
  - Decreased saliva production – teeth
- Immunological – Killer cell suppression; tolerance develops

OST MEDICATION

- Mostly PHARMACOKENETICS

Pharmacology of Methadone

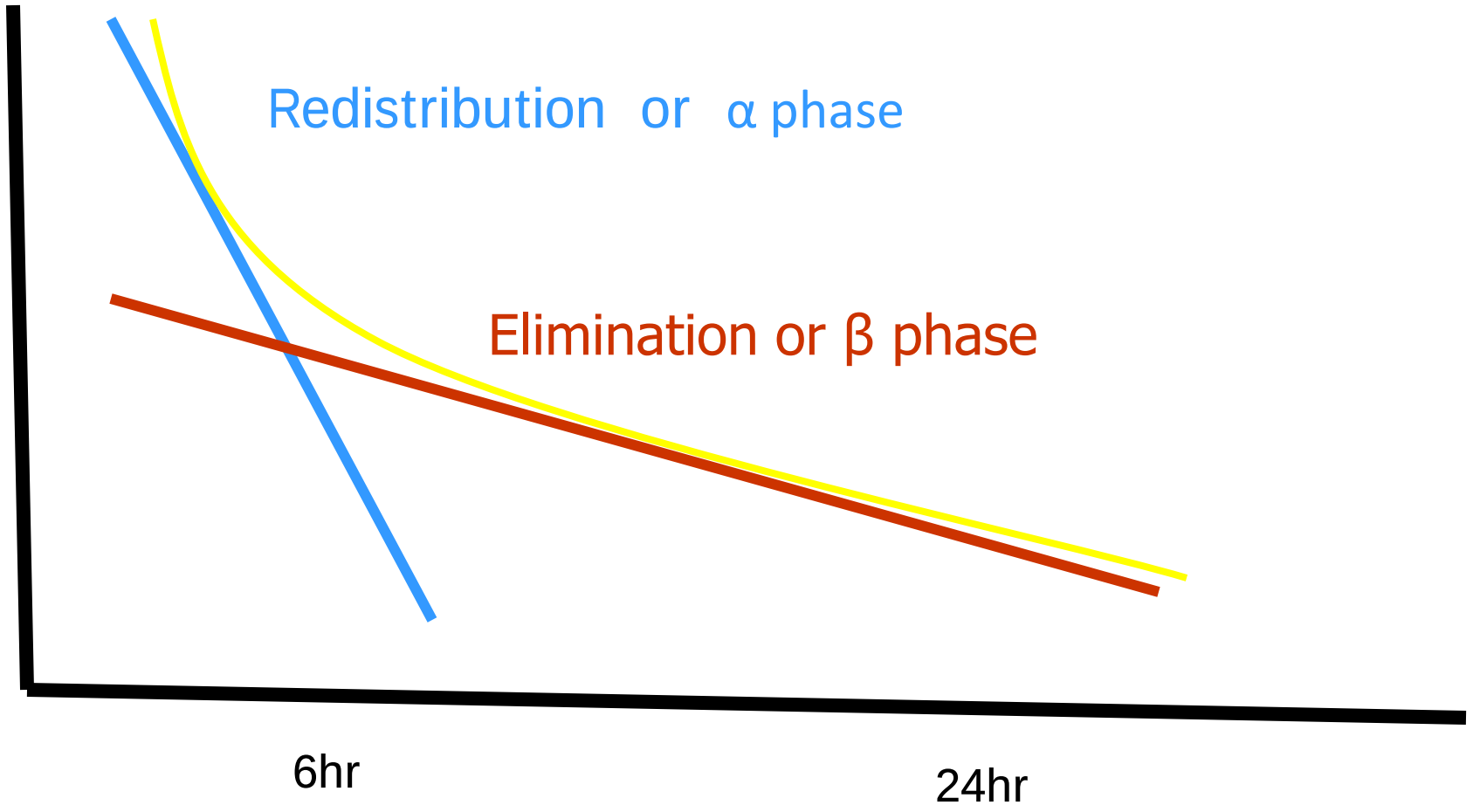
Isomers

- l-methadone (R enantiomer) is a potent mu receptor agonist
- d-methadone (S enantiomer) little mu receptor effect but moderate NMDA receptor antagonist
  - Especially useful in treatment of neuropathic pain (PCP and Ketamine)
  - Interferes with hERG potassium channel – prolonged QTc

Pharmacokinetics

- Rapid absorption throughout GI Tract. Complete in less than a hour
- Rule of thumb for vomiting methadone dose
  - < 15 minutes replace complete does
  - 15-30 minutes -replace half dose
  - > 30 minutes – do not replace
- Peak blood level at 3-4 hours
- Biphasic metabolism

Methadone Elimination



Pharmacokenetics

- Analgesic effect only during α phase
- Methadone has to be administer q6-8h for analgesia
- Volume of distribution – 4.0-7.0 liter/kg
- VD greater than 1.0 liter/kg means extensive concentration in tissues
- Isolated blood levels have no therapeutic meaning.
- Post mortem blood levels in patients on methadone are not useful (post mortem redistribution)

Pharmacokinetics

- **Excretion** of methadone and its metabolites (EDDP) is 60% renal.
- In renal failure 95% methadone is excreted by the gut – safe to give in renal failure.
- Metabolism not affected by mild to moderate hepatic failure. In severe failure methadone bypasses the liver and dosage has to be modified upwards or downwards as clinically indicated

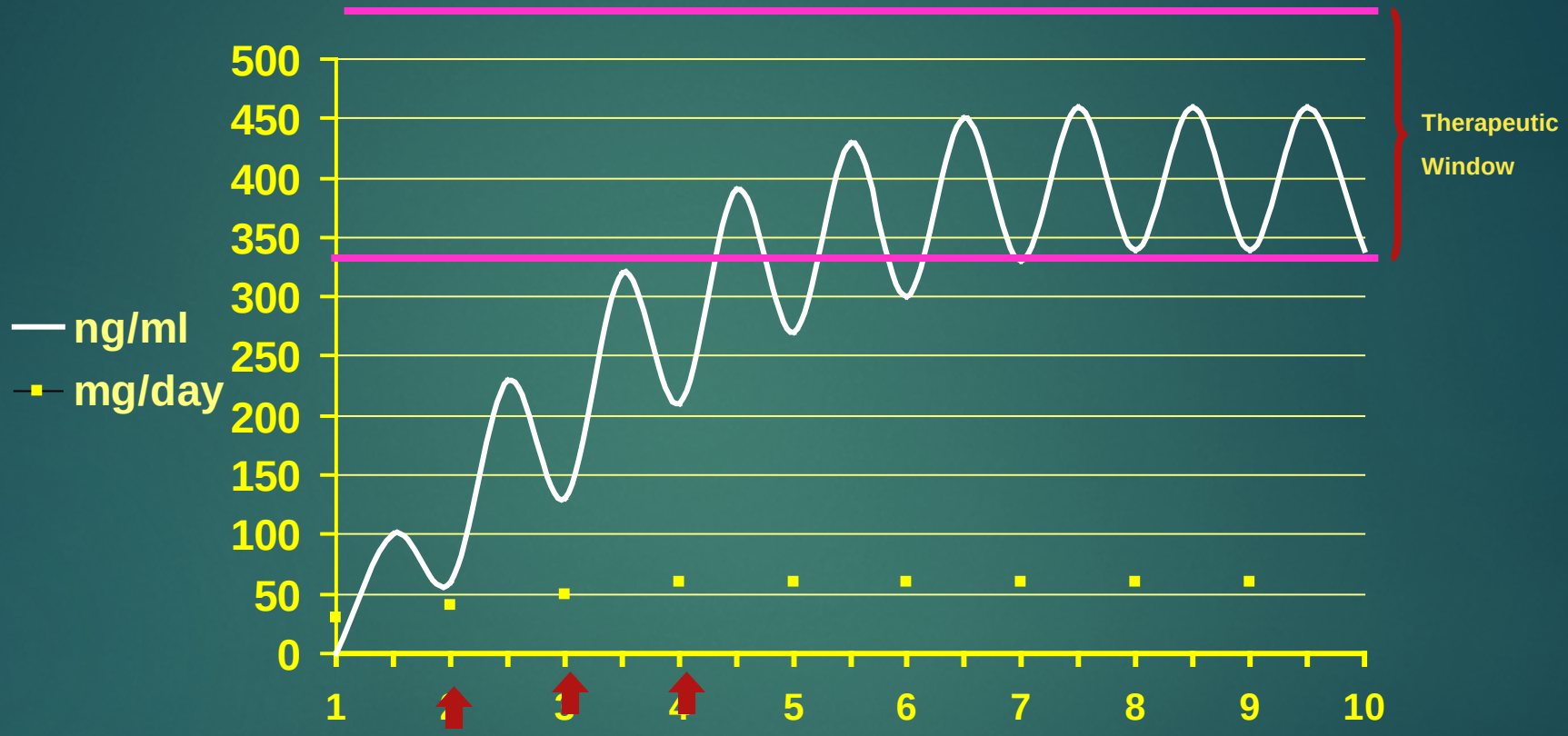
Half Life

- Means the time it takes for the concentration of a drug to drop to half its peak concentration in the blood.
- On average 24 hours, but can vary as per bell curve

Steady State

- Steady state is when taking the same dose no longer results in an increase in serum concentration of the drug
- Steady state is achieved after ± five half lives.

Methadone Induction Simulation



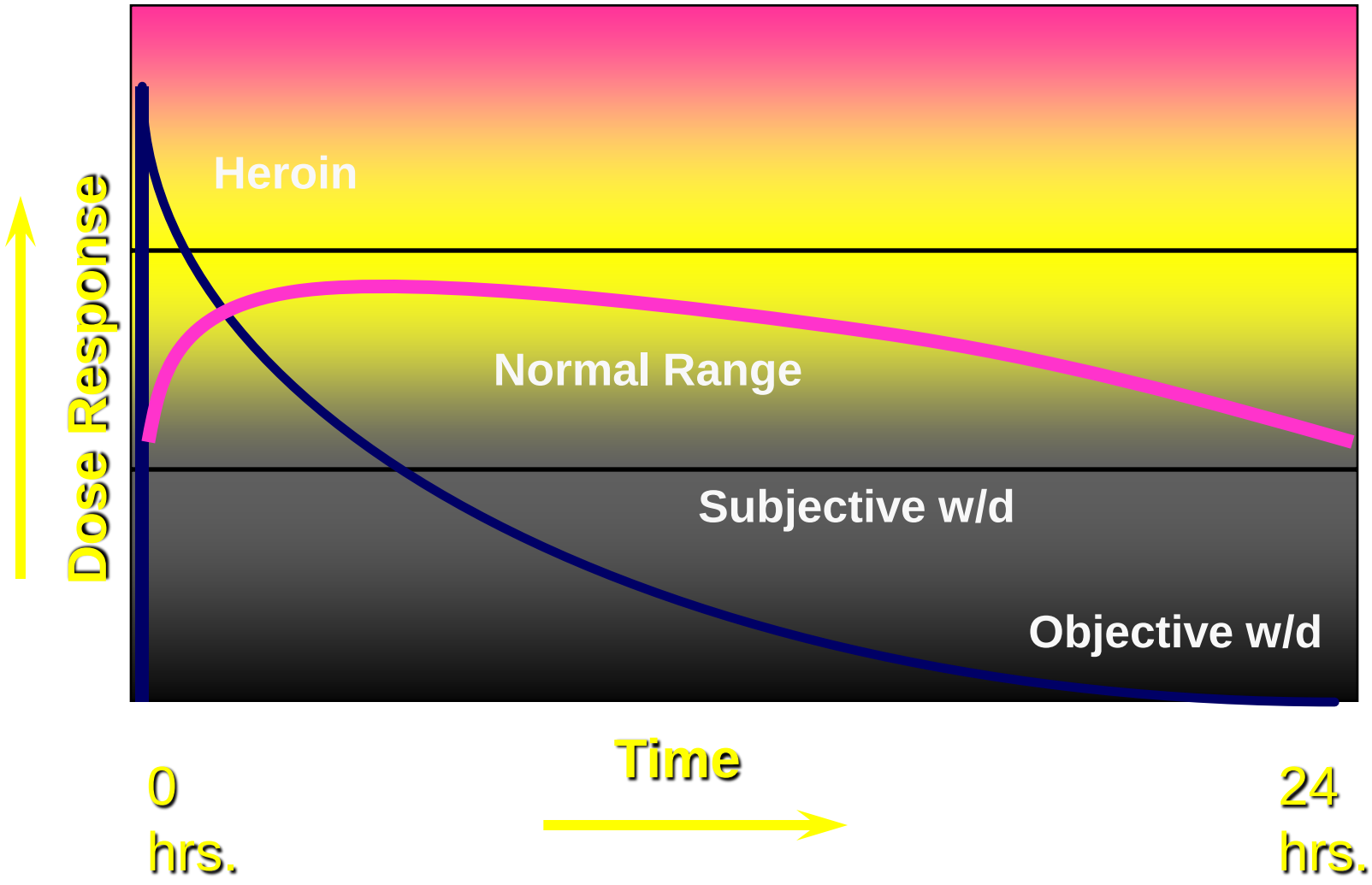
Slide courtesy Dr. J. Thomas Payte: Opioid Maintenance Pharmacotherapy

INDUCTION
Saskatchewan Protocol

- Methadone 30 mg daily x 3 days then
- Methadone 40 mg daily x 3 days then
- Methadone 50 mg daily x 3 days then
- Methadone 60 mg daily x 7 days then
- Titrate to effect at a rate of no more than 10 mg/day/week

- Why can we get away with the rapid increase up to 60 mg?
- By day 4 you are at 85% of steady state

Methadone 24 Hour Dose Response



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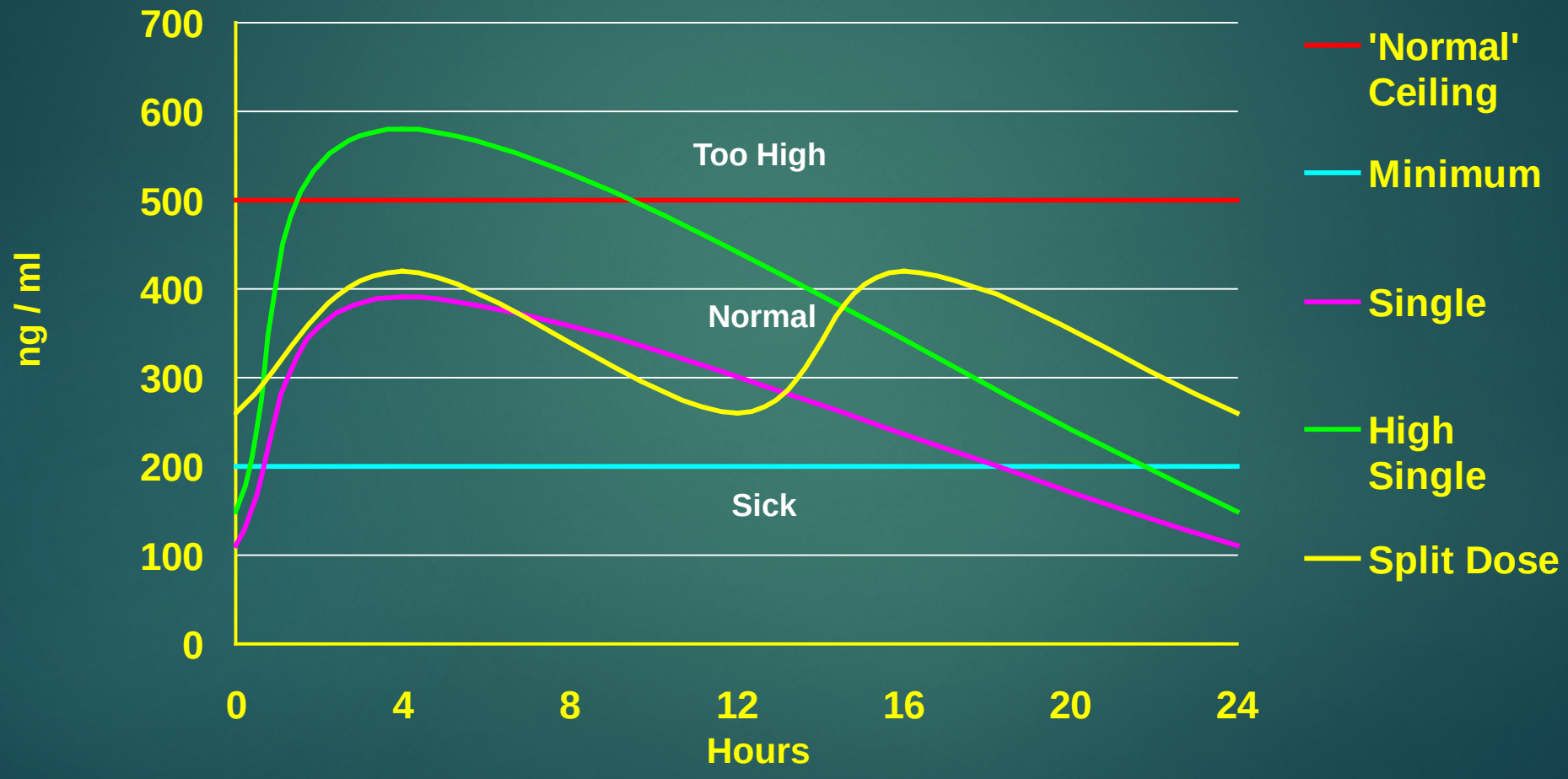
Rapid Metabolizers

- Metabolized by Cyp 3A4 (also 2B6 & 2C19) to EDDP
- Inducible enzyme – many drug-drug interactions shorten half life
- Terminal pregnancy shortens half life
- Natural fast metabolizers

Rapid Metabolizer - High Single and Split Dose Simulation



Courtesy: Payte, Opioid Agonist Treatment of Addiction, 2001

Rapid Metabolizers

- Peak/Trough Ratio > 2.0
- Peak = 4 hours after drink; trough = immediately before drink
- Diagnosis can made clinically
- Split dose = total daily dose needs to be a bit higher
- First day of split give full dose in AM and half dose in PM, then 2 half doses.
- Split doesn’t have to be 50/50, can be two thirds/ one third

Buprenorphine

- A synthetic opioid

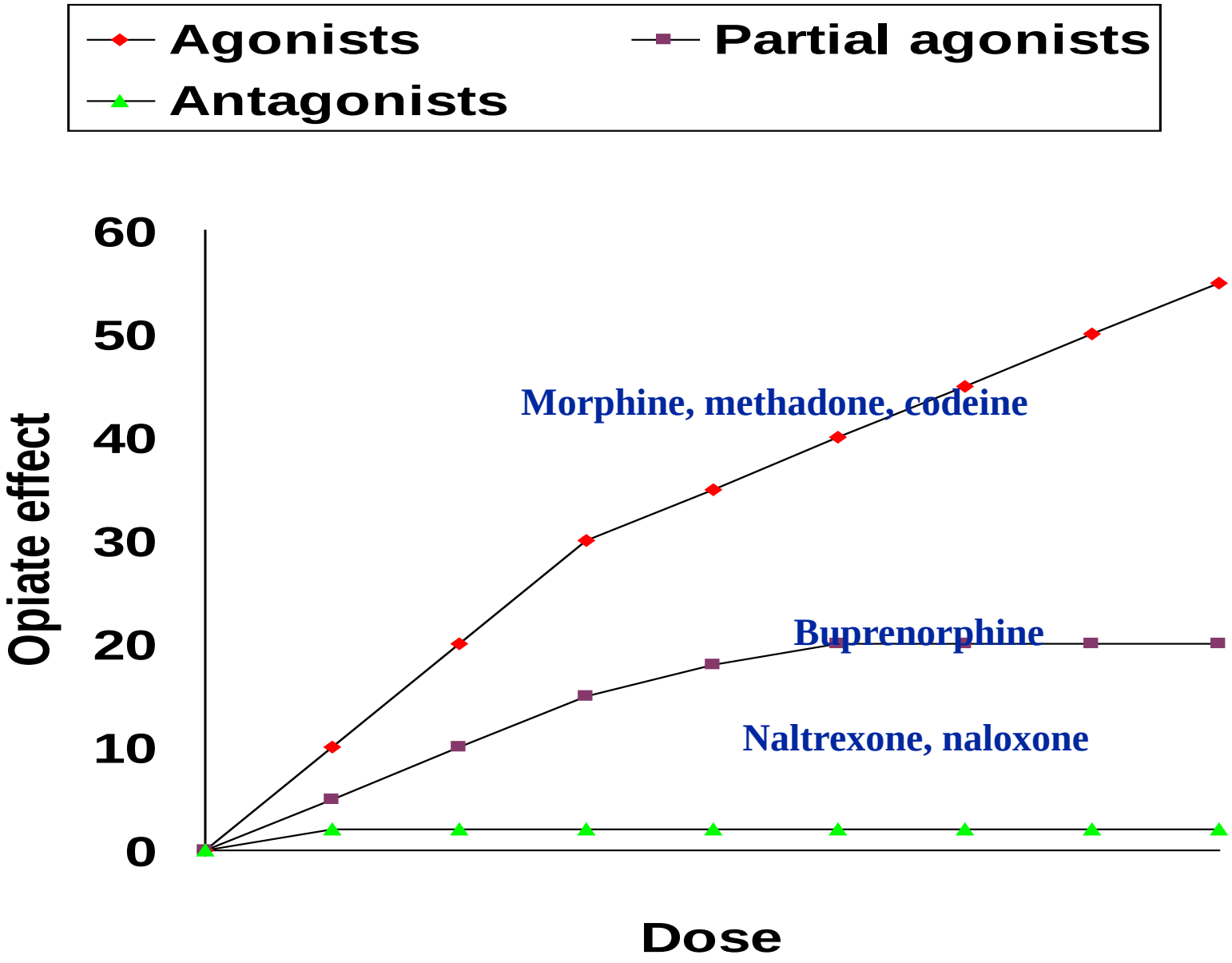
- Partial agonist at the μ receptor
  - Low intrinsic activity only partially activating opiate receptors
  - Dose - response curve exhibits ‘ceiling’ effects

- High affinity for the μ receptor
  - Binds more tightly to opiate receptors than other opiates or opiate agonists

Precipitated Withdrawal

- Administering buprenorphine to a fully agonised opioid dependent person will cut the mu receptor effect dramatically and precipitate with withdrawal.
- Hence the difficulty in switching from methadone to Suboxone.

Classification of Opioids



Pharmacokenetics

- Well absorbed orally
- Almost completely metabolized first pass through liver
- Given sublingually
- Half life is ± 37 hours when given SL.
- Metabolized by Cyp 3A4 to norbuprenorphine, which is active.
- Lots of Drug/Drug interactions.

Adverse effect

- Typical opioid but tend to be milder
- Unlike methadone, no immunological or endocrine effects

Methadone to Suboxone

- Doesn’t work if patient required high dose methadone
- Try to taper methadone dose down to 30 or 40 mg per day
- Stop methadone and prescribe daily observed Kadian®100 mg per day for four or five days.
- Stop Kadian for 24 hours
- Suboxone SL 4/1mg, repeat in 4 hours if needed.
- Titrate to effect – most patients comfortable on 16/4 mg
- Maximum dose is 36/8 or 24/6 depending on nationality