

# General Opioid Pharmacology and The Pharmacology of Buprenorphine and Buprenorphine/Naloxone

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CA Area IHS Conference and the  
American Osteopathic Academy of  
Addiction Medicine

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[WWW.AOAAM.ORG](http://WWW.AOAAM.ORG)

IHS AOAAM Buprenorphine Waiver Course

## Outline for this talk

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- I. General opioid pharmacology
- II. The pharmacology of buprenorphine
- III. The pharmacology of buprenorphine/naloxone
- IV. Summary: buprenorphine pharmacology

# Opiates & Opioids

*Opiates* = naturally present in opium

- e.g. morphine, codeine, thebaine

*Opioids* = manufactured

- Semisynthetics are derived from an opiate
  - heroin from morphine
  - buprenorphine from thebaine
- Synthetics are completely man-made to work like opiates
  - methadone



**The sap is extracted  
by slitting the pod**

*Highly refined Southwest Asian heroin or  
Southeast Asian heroin*



# Opioid Receptor Types

## Mu Receptor

Associated with opioid addiction

Mu is for morphine

Morphine for Morpheus Greek God of Dreams

Activation produces analgesia, euphoria,  
Respiratory depression, and pupil constriction

## Kappa Receptor

Activation also produces analgesia

Hope for analgesia with less abuse potential  
not realized because produces psychosis

## Delta Receptor

Activation in humans not well characterized

# Opioid Receptors

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## Drugs and medications that activate mu receptors:

morphine

methadone

codeine

fentanyl

heroin

hydromorphone

buprenorphine

oxycodone

hydrocodone

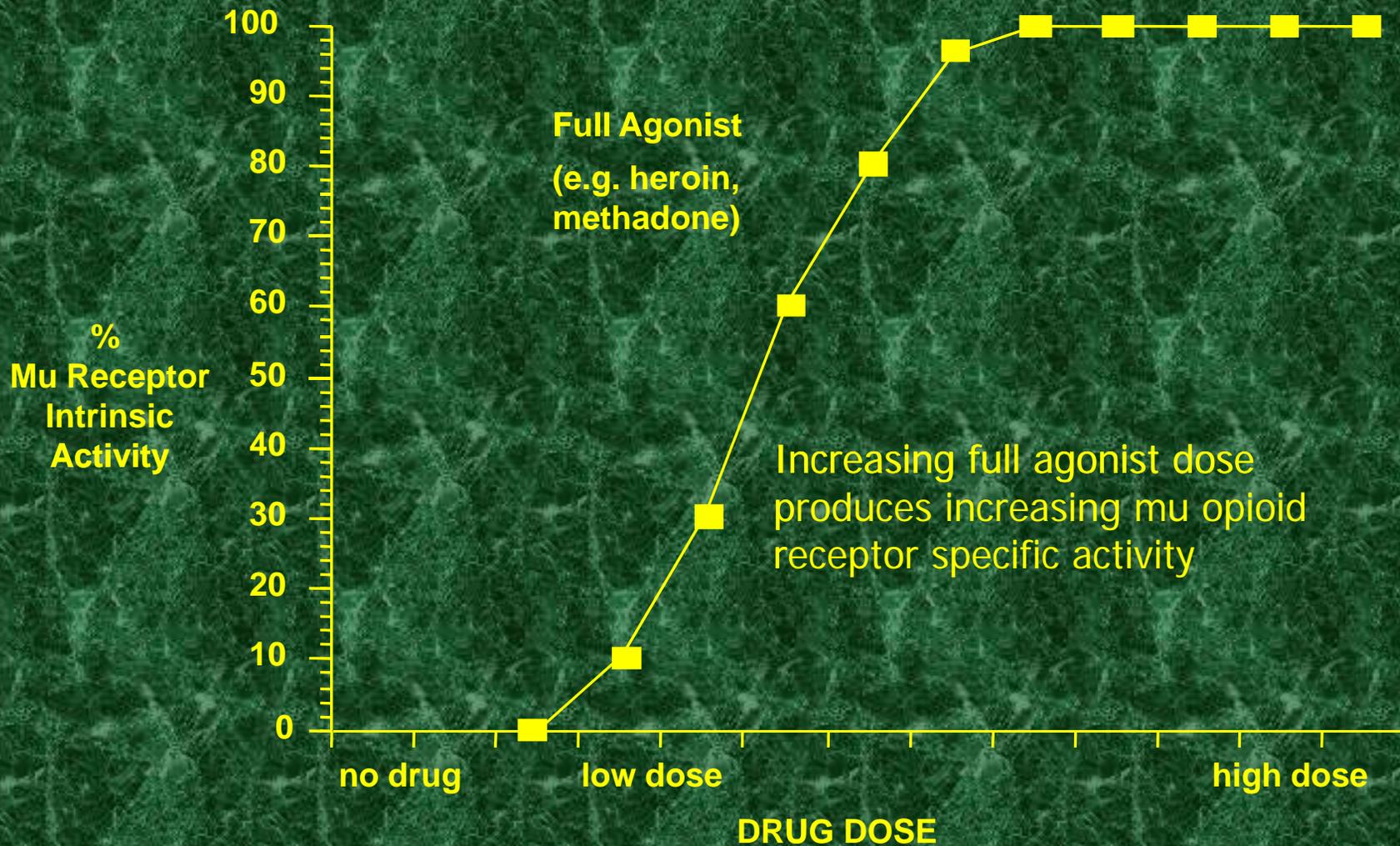
# Function at Receptors: Full Agonists

**Mu  
receptor**

**Full agonist binding ...**

- ① activates the mu receptor
- ② is highly reinforcing
- ③ is the most abused opioid type
- ④ includes heroin, methadone, & others

# Full Agonist Activity Levels



# Function at Receptors: Antagonists

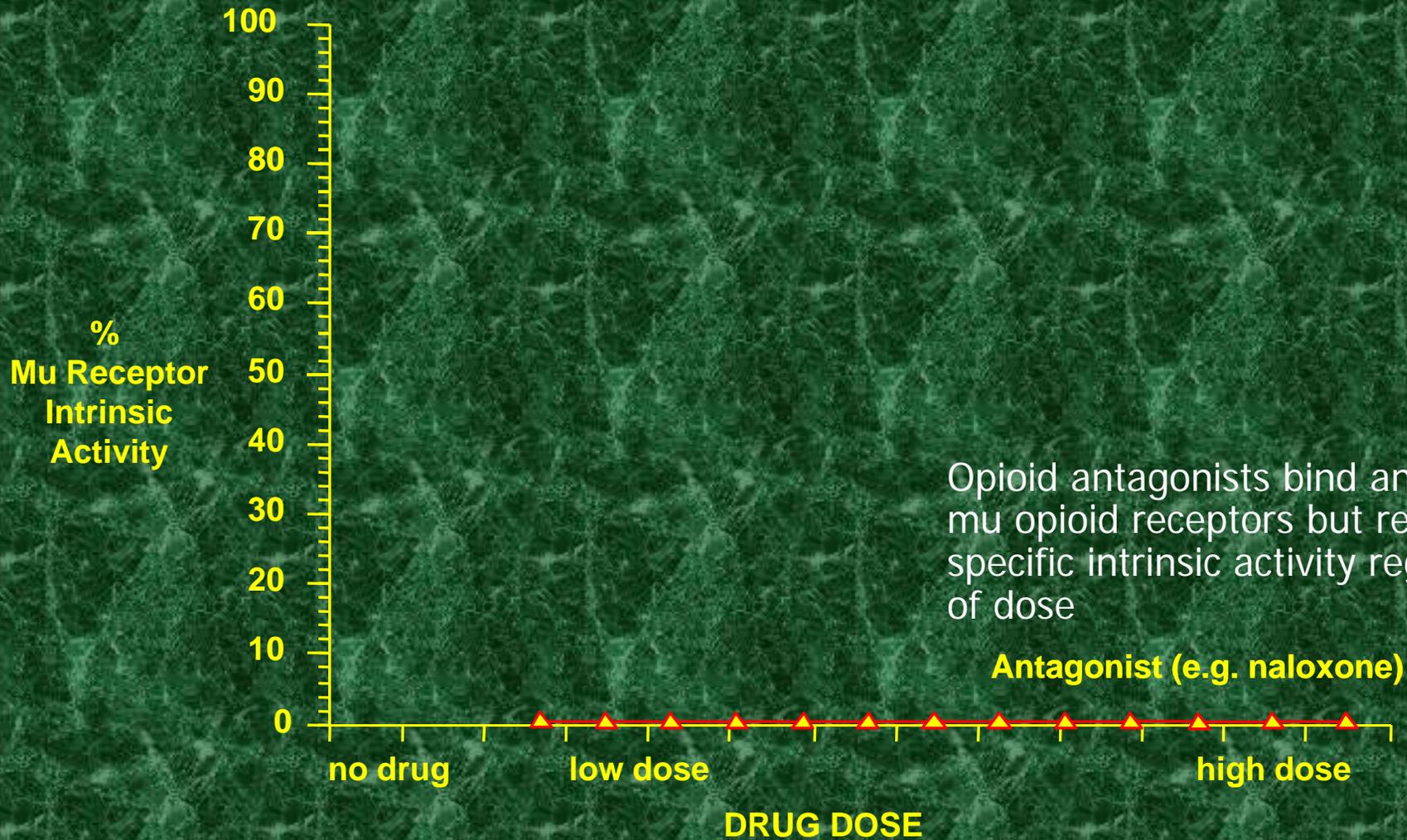
**Mu  
receptor**



**Antagonist binding ...**

- ① occupies without activating
- ② is not reinforcing
- ③ blocks abused agonist opioid types
- ④ includes naloxone and naltrexone

# Antagonist Activity Levels



Opioid antagonists bind and occupy mu opioid receptors but result in no specific intrinsic activity regardless of dose

**Antagonist (e.g. naloxone)**

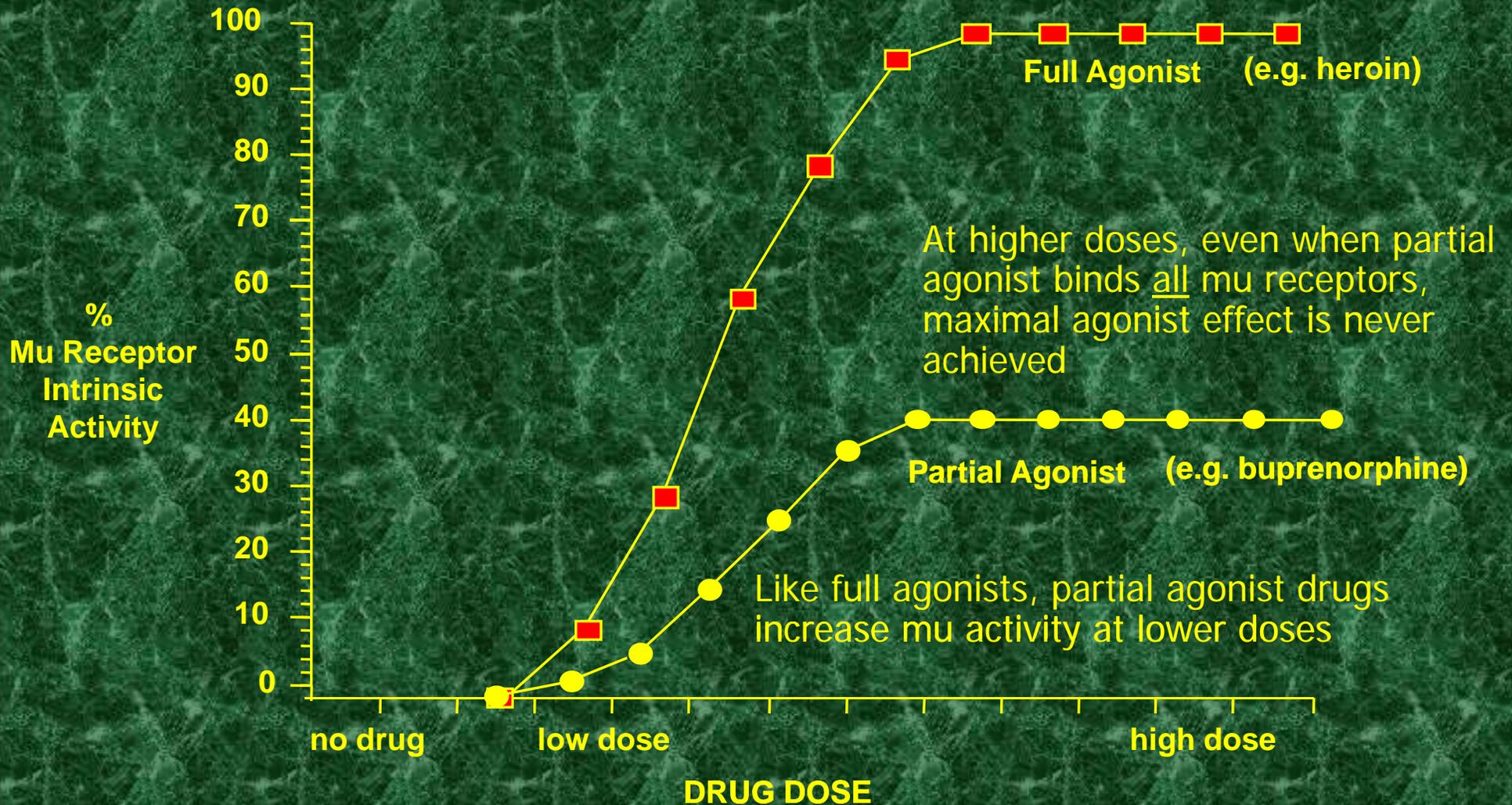
# Function at Receptors: Partial Agonists

**Mu  
receptor**

**Partial agonist binding ...**

- ① activates the receptor at lower levels
- ② is relatively less reinforcing
- ③ is a less abused opioid type
- ④ includes buprenorphine

# Partial Agonist Activity Levels



# Receptor Affinity

- AFFINITY is the strength with which a drug physically binds to a receptor
  - Buprenorphine's affinity is very strong and it will displace full agonists like heroin and methadone
  - Note receptor binding strength (strong or weak), is NOT the same as receptor activation (agonist or antagonist)

**Mu  
Receptor**



**Buprenorphine's affinity is higher  
Full Agonist  
Bound to Receptor**

**Therefore  
Full Agonist is displaced**

# Receptor Dissociation

- DISSOCIATION is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine's dissociation is slow
  - Therefore Buprenorphine stays on the receptor a long time and blocks heroin or methadone from binding

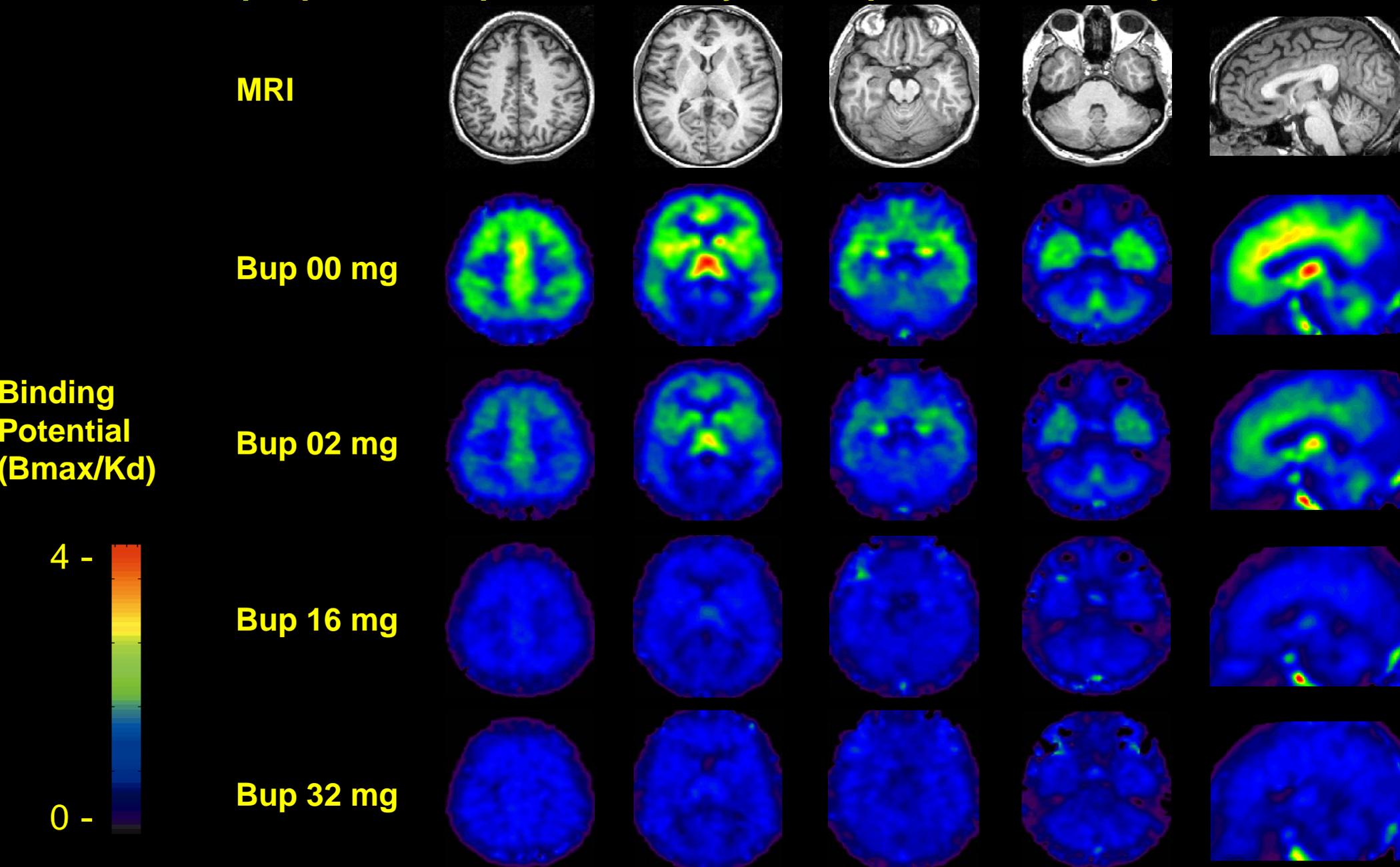
**Mu  
Receptor**

**Bup dissociation is slow**



**Therefore  
Full Agonists can't bind**

# Effects of Buprenorphine Dose on $\mu$ -Opioid Receptor Availability in a Representative Subject



# Opioid Agonist Drug Effects

## Acute Use Effects

Euphoria	Vomiting	Constricted Pupils	Depressed Respiration
Drowsiness	Decreased Pain Sensation	Decreased Awareness	Decreased Consciousness

## Large Dose Acute Effects

Non-Responsive	Pinpoint Pupils	If Severe Anoxia Pupils May Dilate	Bradycardia & Hypotension
Skin Cyanotic	Skeletal Muscle Flaccid	Pulmonary edema in ~50%	Slow or Absent Respiration

## Chronic Use Effects

Physical dependence	Psychological dependence	Lethargy and indifference	Reduction in bowel movement
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# Chronic Use

- Repeated administration of opioids and activation of the mu receptors results in neuronal adaptation:
  - Physiological manifestations
    - Physical Tolerance
      - Diminishing effect from the same dose
      - Need for larger doses to produce the same effect
    - Physical Dependence
      - If dose is reduced or stopped withdrawal syndrome develops
      - Not the same as DSM-IV “Substance Dependence”
  - Behavioral manifestations “Psychological Dependence”
    - Loss of control
- Chronic, relapsing nature of opioid dependence
- Basis for pharmacotherapies to stabilize circuits

# Opioid Withdrawal Syndrome

Characteristic Signs & Symptoms	
Dysphoric mood	Piloerection
Nausea-Vomiting	Diarrhea
Body Aches	Yawning
Lacrimation	Mild fever
Rhinorrhea	Insomnia
Pupillary dilation	Irritability
Sweating	Opioid Craving

## Repeated Administration and Withdrawal

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Two types of opioid withdrawal associated with mu opioid agonists:

Spontaneous withdrawal

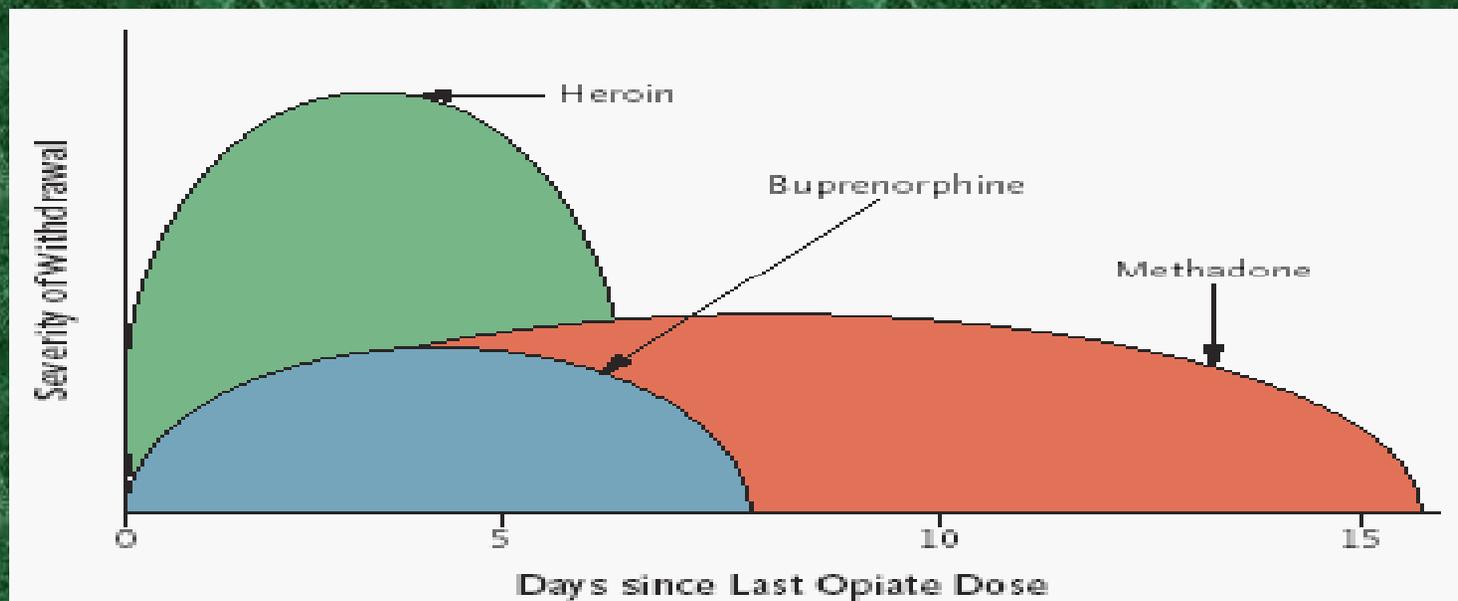
Precipitated withdrawal

# Spontaneous Withdrawal Syndrome

- Develops if a physically dependent person suddenly stops, or decreases, opioid use
- Severity usually less with longer half-life drugs
- Duration depends on half-life of opioid

	Onset	Peak	Duration
Heroin	4 - 6 hours	~3 days	4 - 7 days
Methadone	1 - 2 days	~7 days	12 - 14 days

# Comparison of Spontaneous Withdrawals



- **Blind abrupt discontinuation of buprenorphine 8mg/day**
  - Only minor elevation of withdrawal scale scores
  - Less intense than heroin withdrawal
  - Less intense and briefer than methadone withdrawal

Kosten, O'Connor NEJM 2003

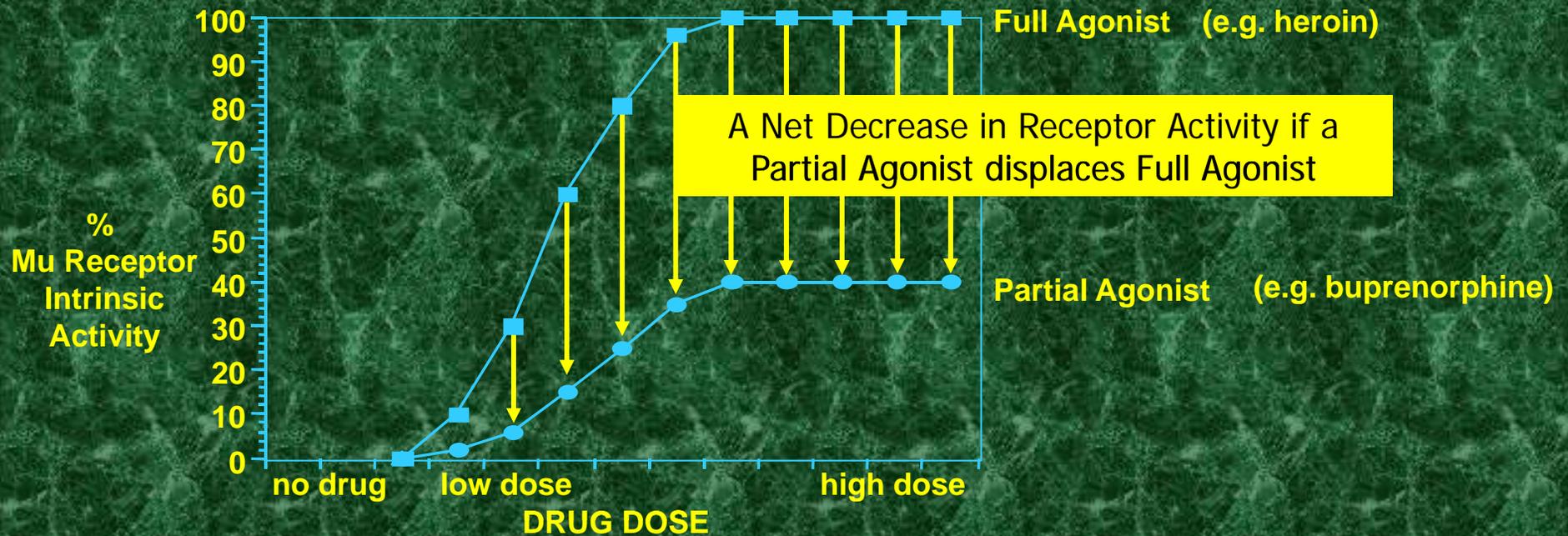
# Precipitated Withdrawal Syndrome

- Precipitated in a physically dependent person, by administration of either:
  - an opioid antagonist drug (e.g. naloxone, naltrexone) or
  - an opioid partial agonist drug (e.g. buprenorphine)
- Qualitatively similar to spontaneous withdrawal but faster onset
- Duration depends upon half-life of drug

	Onset	Peak	Duration
Naloxone	minutes	minutes	~20 minutes
Naltrexone	minutes	minutes	1 - 2 days
Buprenorphine	minutes	minutes	1 - 2 days

# Buprenorphine Precipitated Withdrawal

Displaces full agonist off mu receptors



## Repeated Administration and Withdrawal

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### Precipitated Withdrawal (*continued*)

Withdrawal precipitated by a partial agonist is more likely if there is:

High level of physical dependence

Short time interval between administration of full agonist and partial agonist

High dose of partial agonist

# Characteristics of Abuse Potential

- Route of administration
  - Faster route has a greater abuse potential
    - Injecting IV ➤ Injecting SQ ➤ Oral, Snorting
- Drug Half life
  - Shorter half-life has a greater abuse potential
    - Heroin ➤ Methadone
- Lipophilicity (faster across blood brain barrier)
  - Higher lipophilicity has a greater abuse potential
    - Heroin ➤ Morphine ➤ Methadone
- Degree of mu agonist activity

## Basic Opioid Pharmacology – Summary

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1. Opioids and opioid receptors [ $\mu$ ,  $\kappa$ ,  $\delta$ ]
2. The functions of drugs at receptors [full agonists, antagonists, partial agonists]
3. Repeated administration and withdrawal of opioid drugs [dependence, withdrawal]
4. Affinity and dissociation [strength, speed]
5. Characteristics of drugs with abuse potential [route, half-life, lipophilicity]

## Affinity and Dissociation

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Buprenorphine has:

- high affinity for mu opioid receptor –
  - competes with other opioids and blocks their effects. Kappa receptor antagonist
- slow dissociation from mu opioid receptor –
  - prolonged therapeutic effect for opioid dependence treatment (contrasts to its relatively short analgesic effects)

# Metabolism, Elimination & Half-life

- Liver Metabolism

- Cytochrome P450 3A4 dealkylates into norbuprenorphine
  - Active metabolite
  - Norbuprenorphine undergoes further glucuronidation, very polar
  - Therapeutic levels are from 1-9 ng/ml. Deaths in France had 1-27 ng/ml with alprazolam (both injected)

- Elimination

- Excreted in feces (70%) and urine (30%)
  - Mean elimination half-life = 37 hours in sera
- commercial screening urine drug test is now available
  - Will NOT show as morphine positive on screen
  - Can identify by GC/MS but expensive

## Abuse Potential

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Buprenorphine is abusable (epidemiological, human laboratory studies show)

Diversion and illicit use of analgesic form (by injection)

Relatively low abuse potential compared to other opioids

Obadia Y, et al. Injecting misuse of buprenorphine among French drug users. *Addiction* 90(2):267-272, 2001

# Abuse Potential

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## Non-dependent opioid user

Single doses of buprenorphine produce typical mu agonist effects

shown when given by injection and sublingual route

Onset of effects slower for sublingual route, suggesting lower abuse potential – but sublingual route still has abuse potential (as shown on next slide, where experienced opioid abusers identified sublingual buprenorphine as an opioid agonist)

# Abuse Potential

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## Physically dependent opioid user

Abuse potential of buprenorphine varies as function of three factors:

level of physical dependence

time interval between last dose of agonist  
and first dose of buprenorphine

dose of buprenorphine

# Abuse Potential

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## Level of physical dependence

The higher the level of physical dependence, the greater chance of precipitated withdrawal

For example, with maintenance on 60 mg/day of methadone – precipitated withdrawal seen with single doses of sublingual buprenorphine.

With maintenance on 30 mg/day methadone – no precipitated withdrawal with buprenorphine.

# Abuse Potential

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## Time interval

At short time intervals (e.g., 2 hours after a dose of methadone), increased likelihood of buprenorphine precipitated withdrawal

At longer time intervals, more likely buprenorphine is either placebo-like or opioid agonist-like

# Abuse Potential

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## Dose of buprenorphine

Low single doses of buprenorphine given acutely produce minimal effects (e.g., placebo-like or opioid agonist-like)

Higher doses can precipitate withdrawal

## Potential for Physical Dependence

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Repeated administration of buprenorphine produces or maintains physical dependence

However, the degree of physical dependence is less than that produced by full agonist opioids

This means withdrawal syndrome, while occurs with buprenorphine, may be less severe

Eissenberg T. et al. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. *J Pharmacol Exp Ther* 276:449-459, 1996.

## Sublingual Naloxone

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Sublingual naloxone has relatively poor bioavailability

Doses of up to 1-2 mg sublingual naloxone do not precipitate withdrawal in opioid dependent volunteers

Sublingual naloxone does have a bitter taste

Preston KL, et al. Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend* 25:27-34, 1990.

## Combination of Buprenorphine plus Naloxone

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Sublingual buprenorphine has good bioavailability

Addition of naloxone to buprenorphine to decrease abuse potential of tablets

Combination ratio is 4 to 1 (buprenorphine to naloxone)

Buprenorphine tablet with naloxone marketed as Suboxone (2/0.5 and 8/2 mg tablets)

Buprenorphine tablet without naloxone marketed as Subutex (2 and 8 mg tablets)

## Combination of Buprenorphine plus Naloxone

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Combination tablet containing buprenorphine with naloxone – if taken under tongue, predominant buprenorphine effect

## Combination of Buprenorphine plus Naloxone

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If opioid dependent person dissolves and injects buprenorphine/naloxone tablet – predominant naloxone effect (and precipitated withdrawal)

Strain EC et al. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacol*, 148:374-383, 2000.

Mendelson J et al. Buprenorphine and naloxone combinations; the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacol* 141:37-46, 1999.

## Diversion and Misuse

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The sublingual form of buprenorphine/naloxone combination might be diverted and misused sublingually as well (although the slower onset and lower peak effects may make this route of misuse less attractive for persons seeking a quick and intense opioid high effect) Most diversion is for treatment of opioid withdrawal.

## Summary

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Buprenorphine is a partial mu agonist opioid with a profile of effects similar to other mu agonists, but less risk of respiratory depression and a lower level of physical dependence

Addition of naloxone to buprenorphine should decrease its abuse potential in persons dependent on mu agonists (e.g., heroin) but this form could be abused and diverted by non-dependent individuals

Buprenorphine/naloxone combination is the preferred form for unsupervised dosing to diminish the likelihood of diversion to injected abuse