Long Term Pharmacological Treatment of Opioid Dependence – Agonist maintenance

Opioid Agonists

Natural derivatives of opium poppy

- **Opium**
- Morphine
- **Codeine**

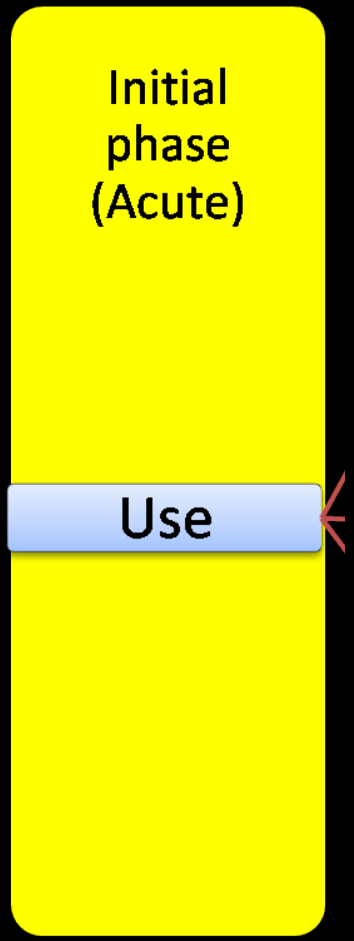
Semi synthetics: Derived from chemicals in opium

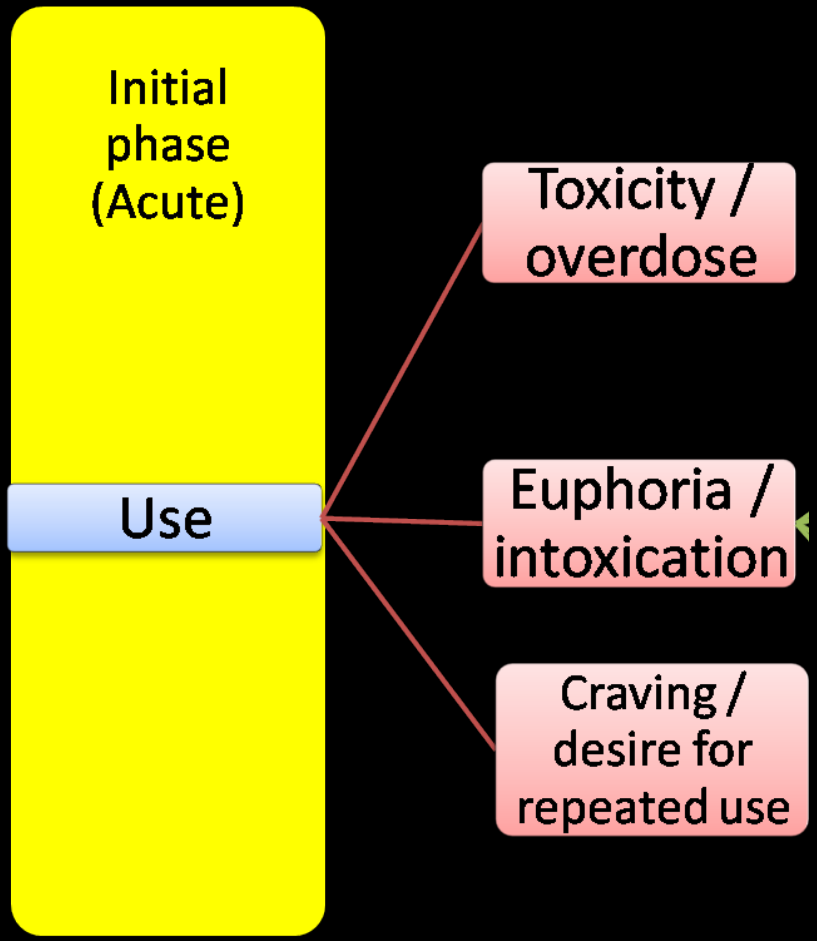
-Diacetylmorphine – Heroin

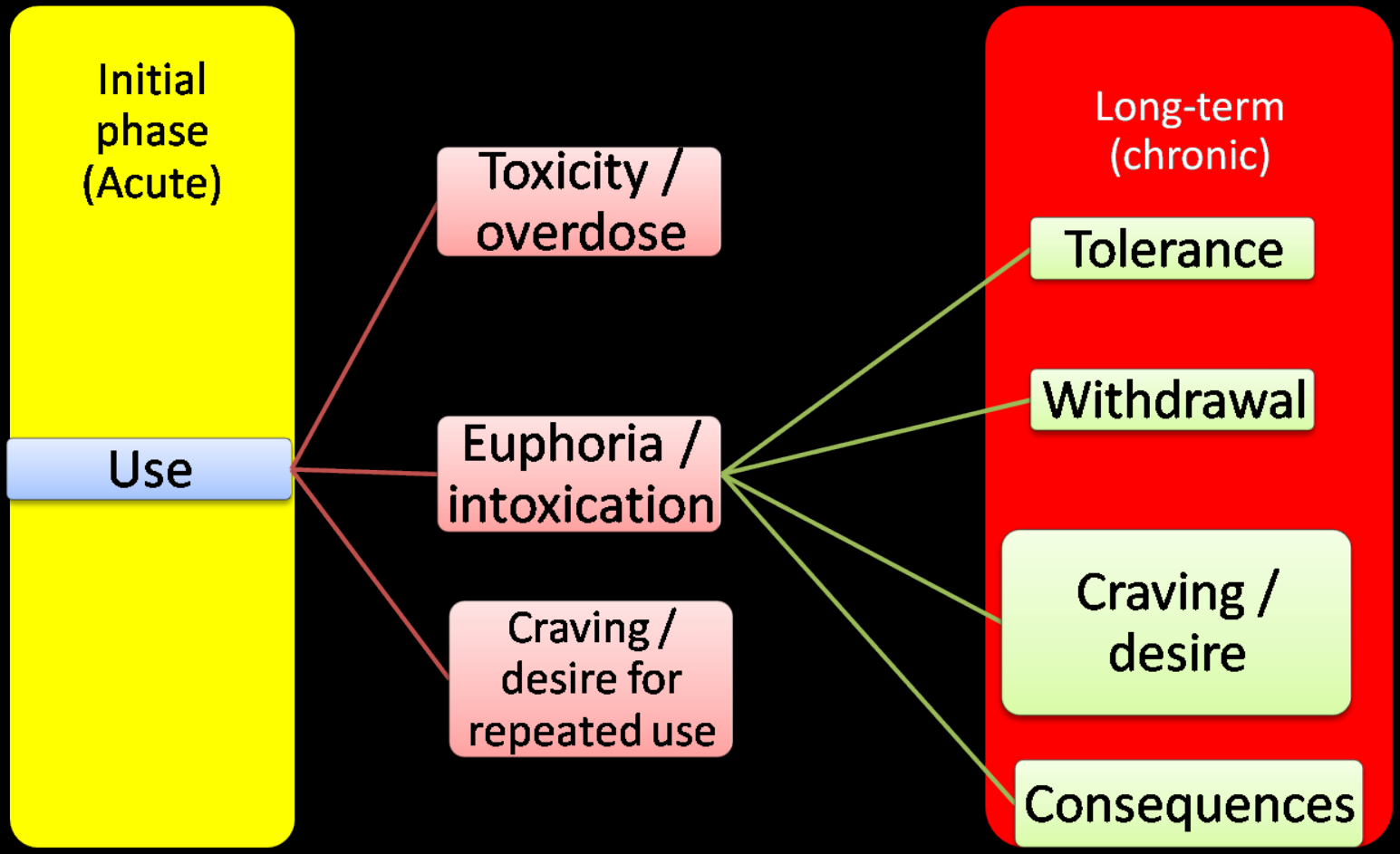
- Hydromorphone
- Oxycodone

Synthetics

- **Propoxyphene**
- **Methadone**
- **Levo-alpha-acetylmethadol**
- **Buprenorphine**
- **Pentazocine**


Initial
phase
(Acute)
Use

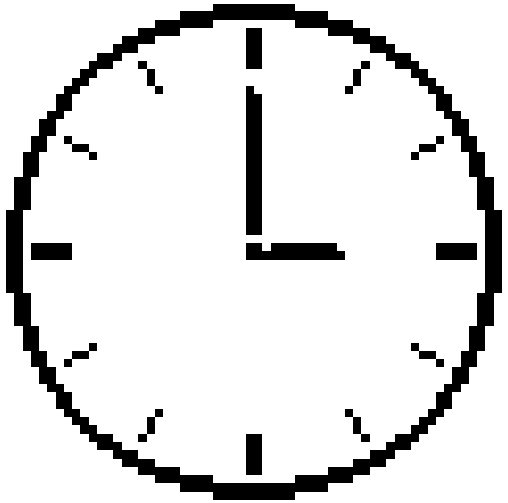

Initial phase (Acute)
Use
Toxicity / overdose
Euphoria / intoxication
Craving / desire for repeated use


Initial phase (Acute)
Use
Toxicity / overdose
Euphoria / intoxication
Craving / desire for repeated use
Long-term (chronic)
Tolerance
Withdrawal
Craving / desire
Consequences

Opioid Withdrawal Syndrome

Acute Symptoms

HOURS to DAYS

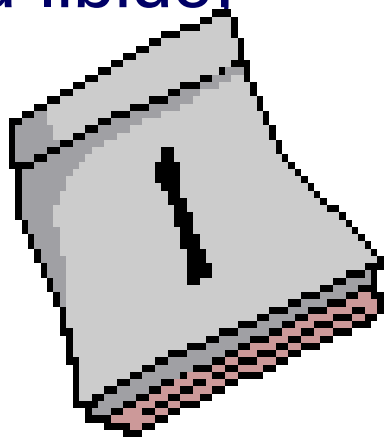


- **Opening of all holes !**
  - ✓ Pupillary dilation
  - ✓ Lacrimation (watery eyes)
  - ✓ Rhinorrhea (runny nose)
  - ✓ Yawning, sweating, chills, gooseflesh
  - ✓ Stomach cramps, diarrhea, vomiting
- Aches and Pains, Muscle spasms (“kicking”)
- Restlessness, anxiety, irritability

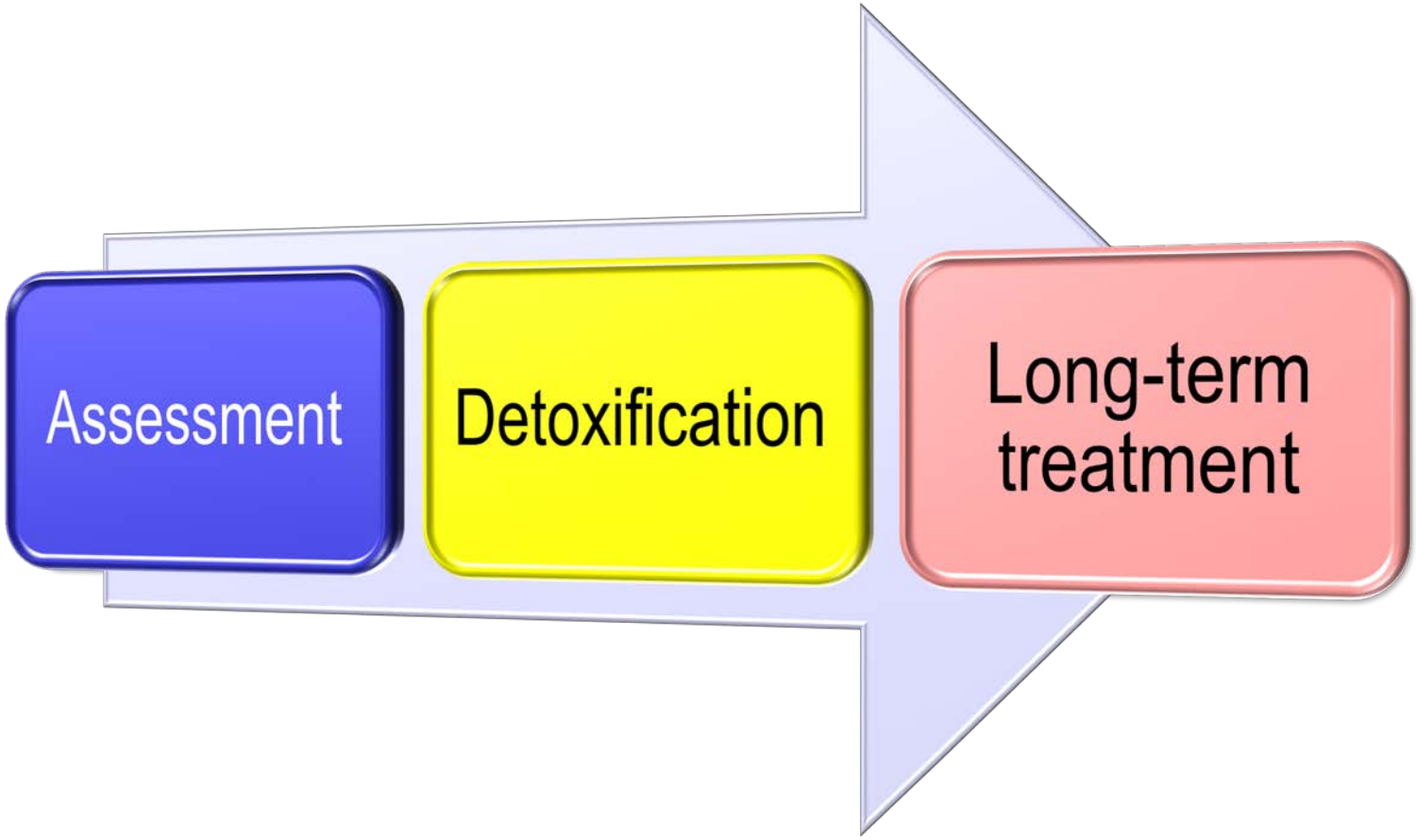
Opioid Withdrawal Syndrome
Protracted withdrawals

WEEKS to MONTHS

- Deep muscle aches and pains
- Insomnia, disturbed sleep
- Poor appetite
- Premature ejaculation, Reduced libido, impotence, anorgasmia
- Depressed mood, anhedonia
- Drug craving



Treatment of opioid dependence



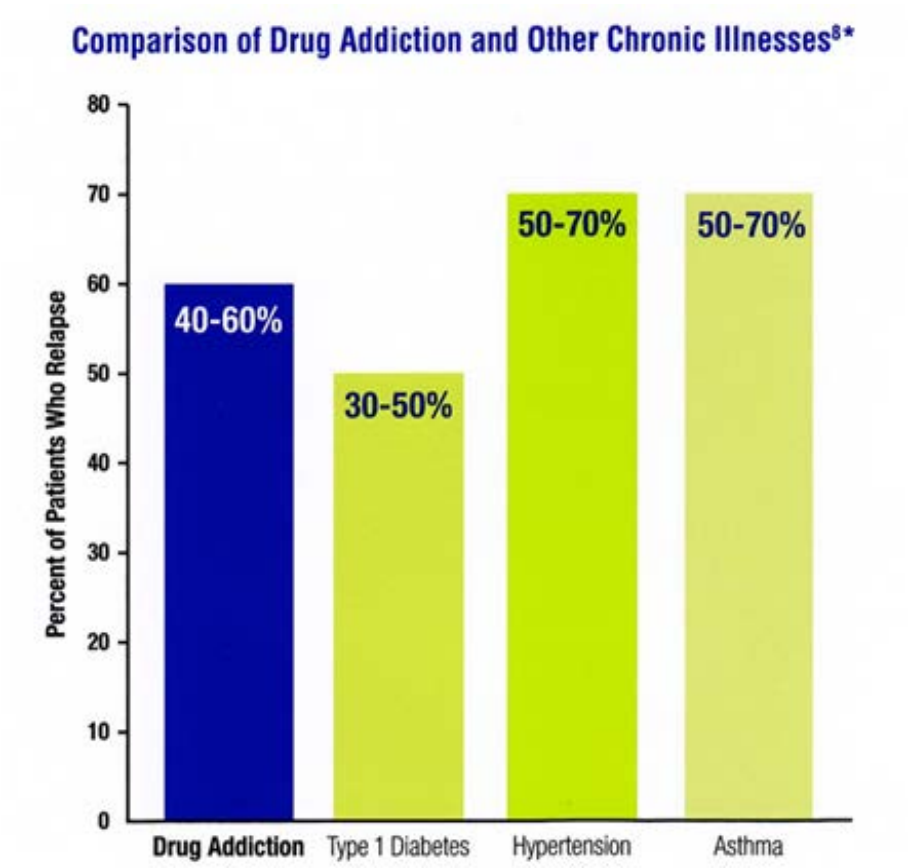
Detoxification alone...

- Treatment of withdrawal symptoms
- Short-term
- Associated with very high rates of relapse

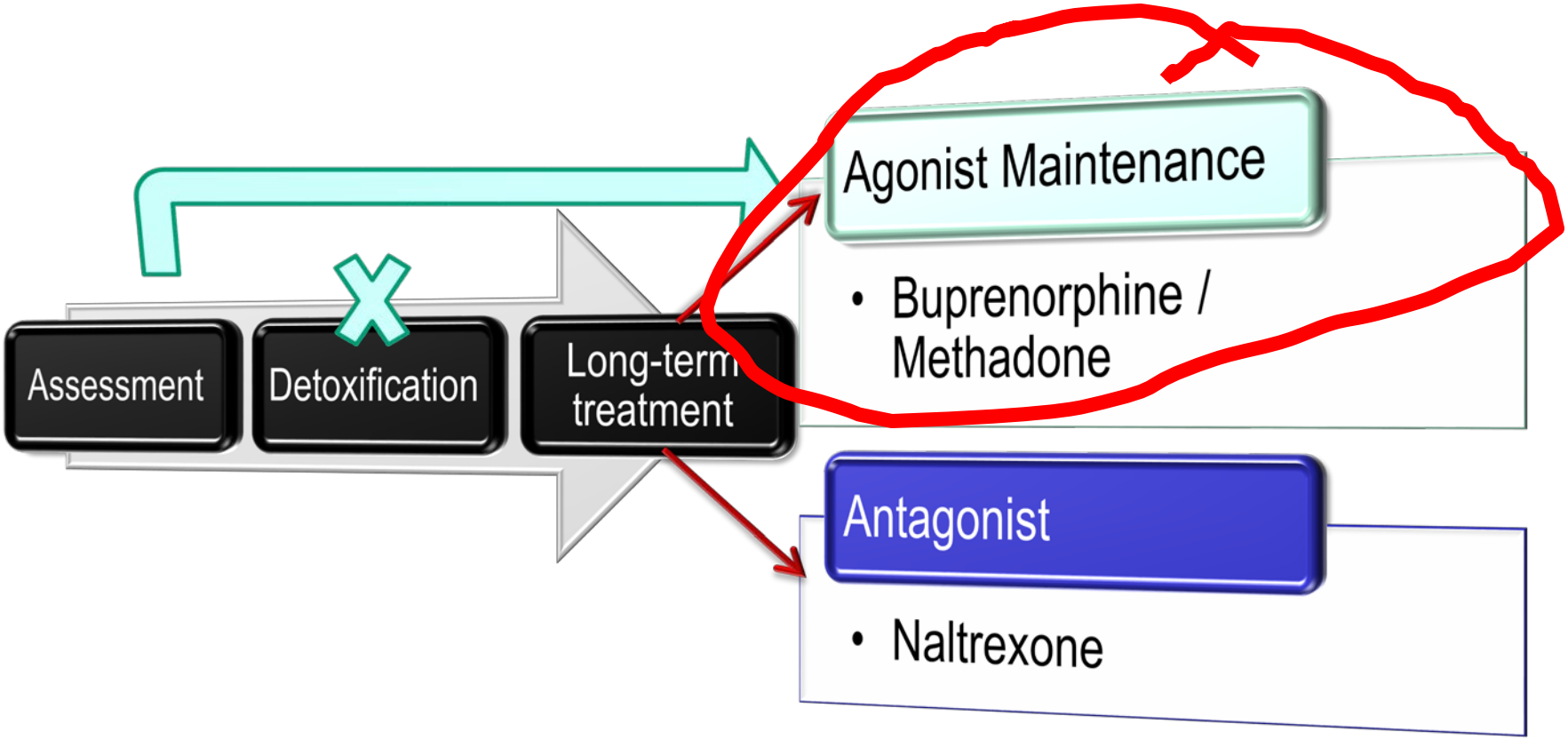
...hence the need of long-term treatment...

Treatment of opioid dependence

- Opioid Dependence is a chronic, relapsing disorder
- Should be seen as a ‘chronic non-communicable disease’

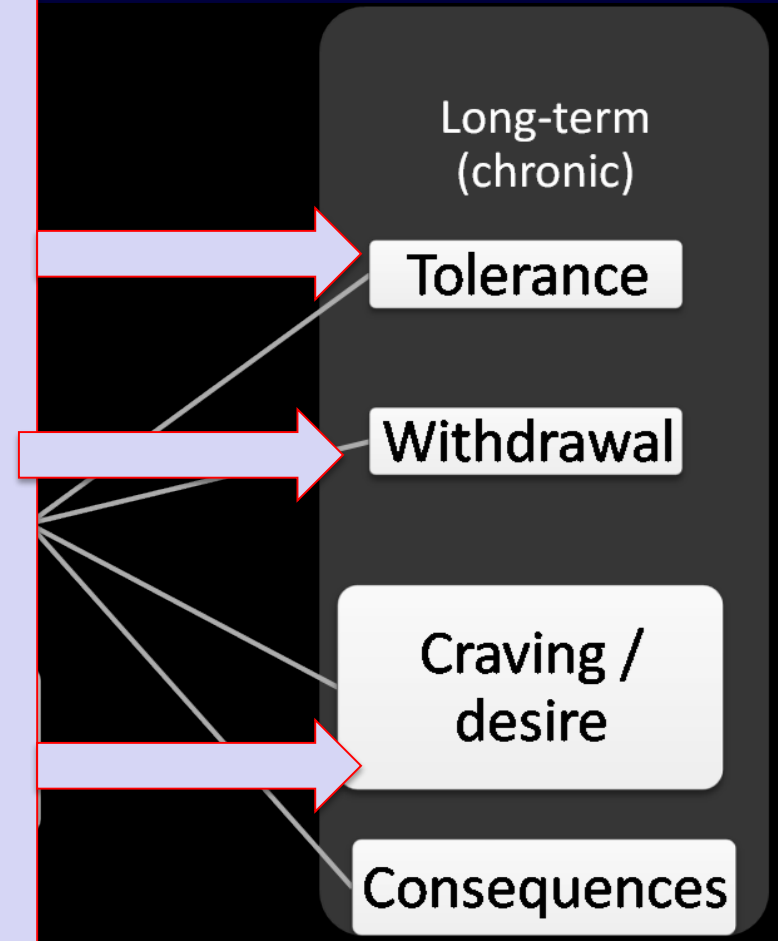


Treatment of Opioid Dependence



Pharmacological approaches

Medications acting in multiple ways



Philosophy of Agonist Substitution

Drugs of abuse: (e.g. Heroin)

- **An illicit,**
- **medically unsafe, short-acting, more addictive Opioid,**
- **Taken by injecting route…**

Is substituted with…

Agonist medications: (e.g. Buprenorphine)

- **…legal, safer, long-acting agonist medication of known purity and potency along with psychosocial rehabilitation**

What kind of PATIENTS are suitable for agonist maintenance?

- Opioid Dependence
  - ✓With a long history
- Priority to Injecting Drug Users
- Failed attempts at achieving abstinence through other means (detoxification)
- Age > 18 years
- Informed consent
- Feasibility to comply with requirements

What kind of medications are suitable for agonist maintenance?

- Ability to control withdrawal symptoms
- Should reduce desire to take illicit drugs
- Minimum side-effects
- Long acting (so that frequent dosing is not required)
- Easy to administer
- Low euphoria – low dependence potential
- Economical
- Easily available

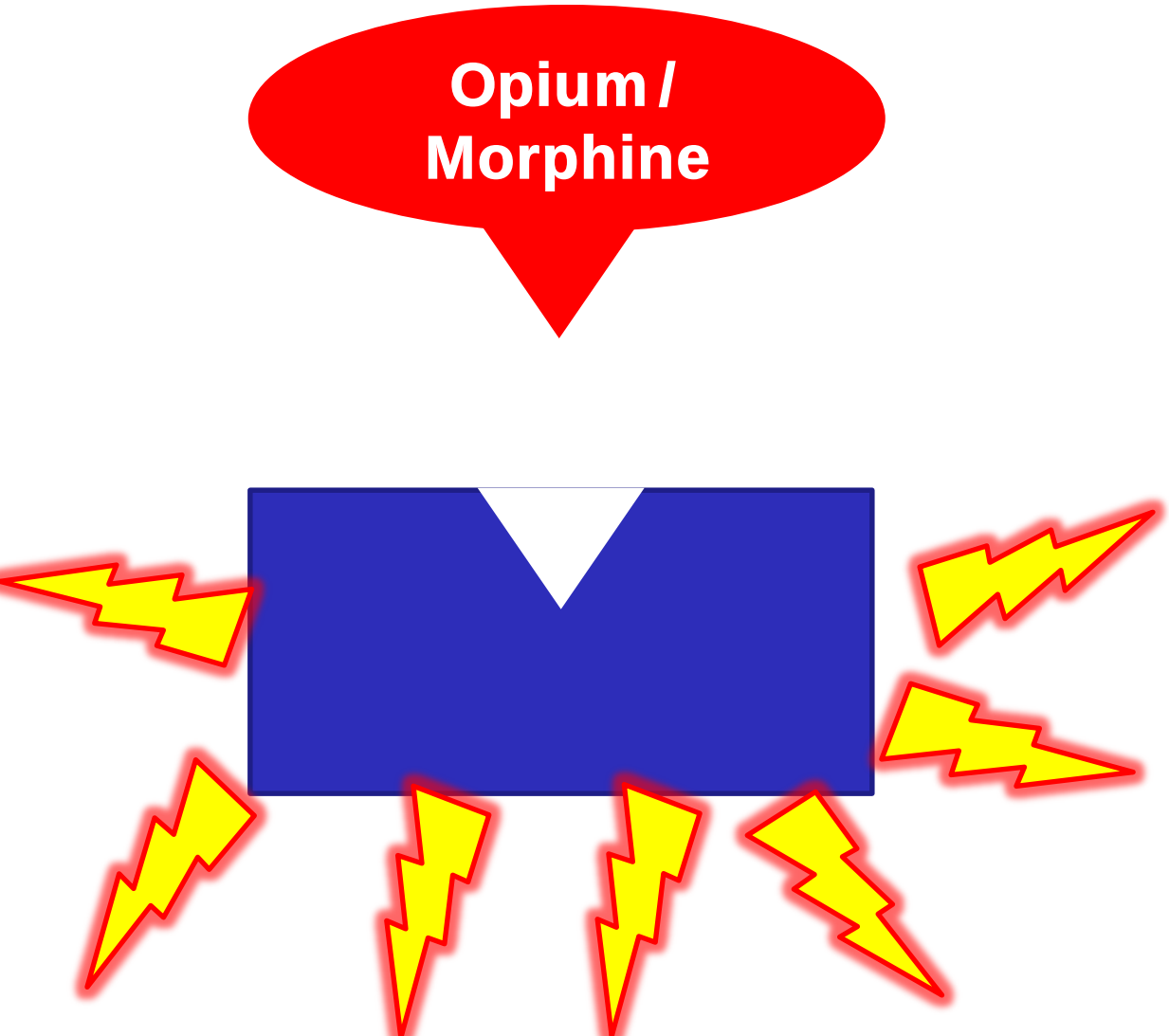
Medications suitable for agonist maintenance

- Methadone — Available in India
- Buprenorphine — Available in India
- LAAM — Not in India
- Slow-Release Oral Morphine — Available in India
- ? opium — ???

Opioid Agonists

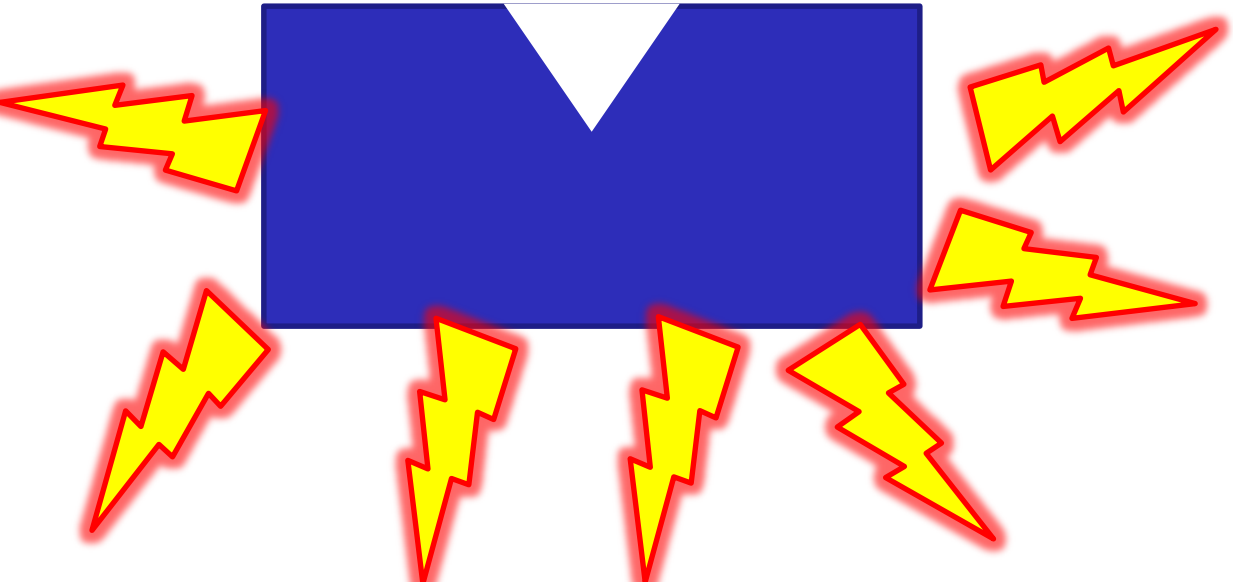
Site of action of Opioids

Opioid Agonists

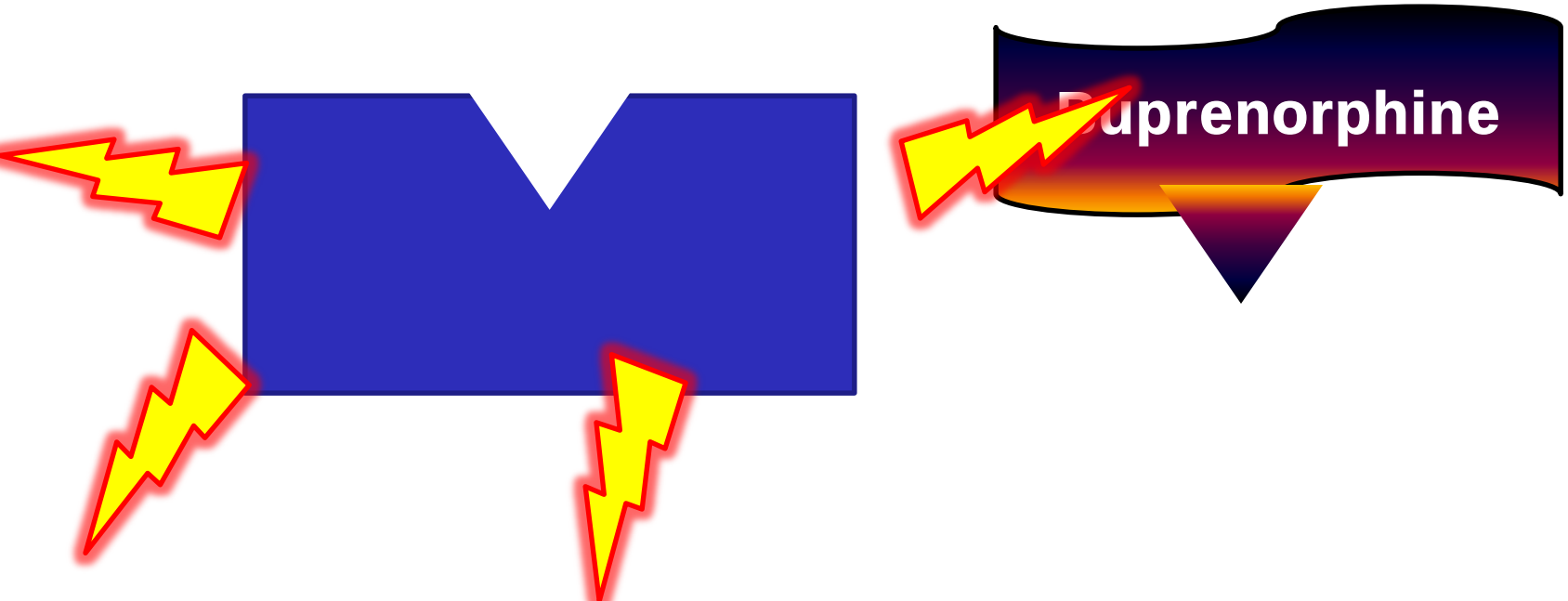


Opioid Agonists

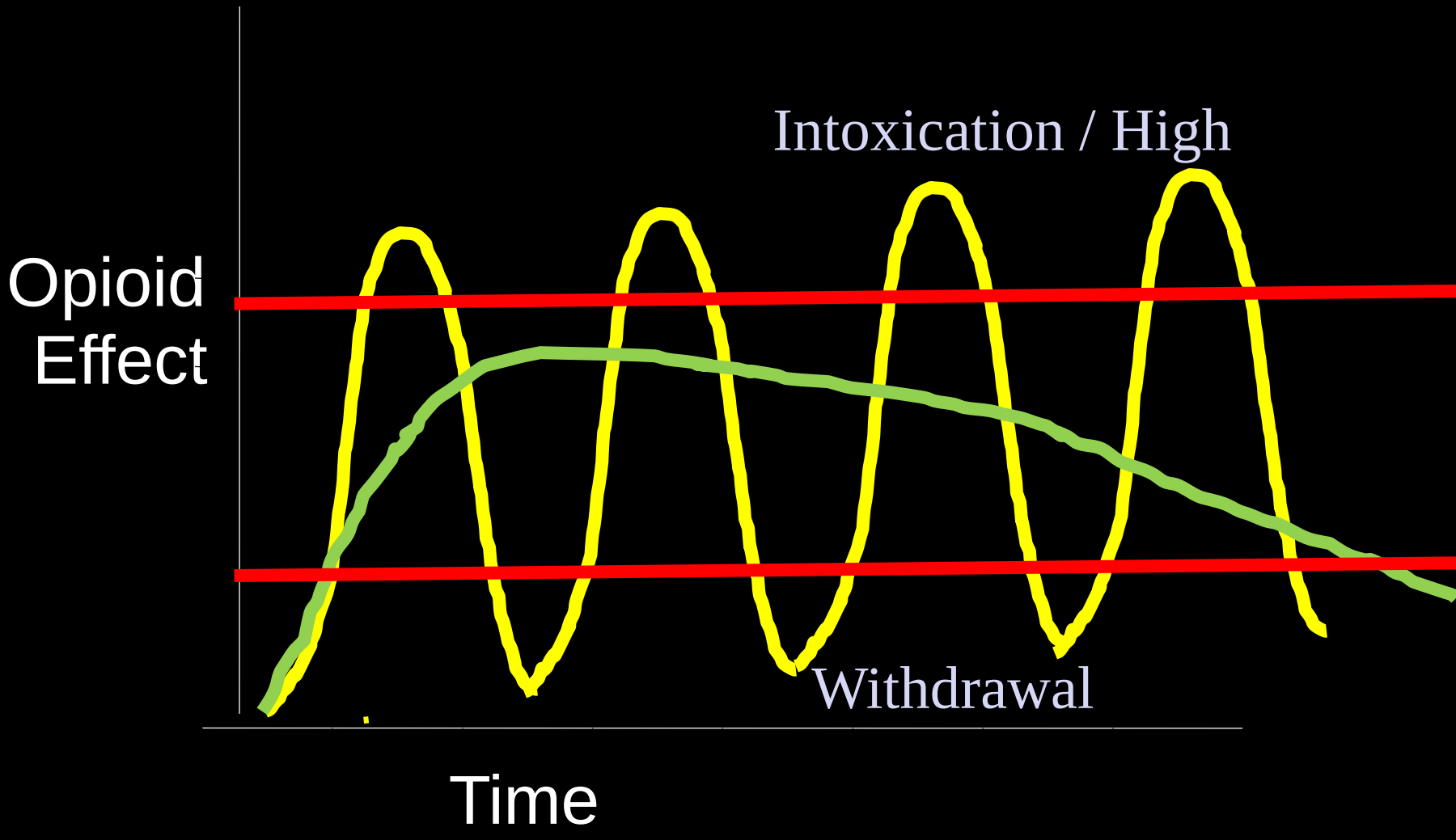
Heroin



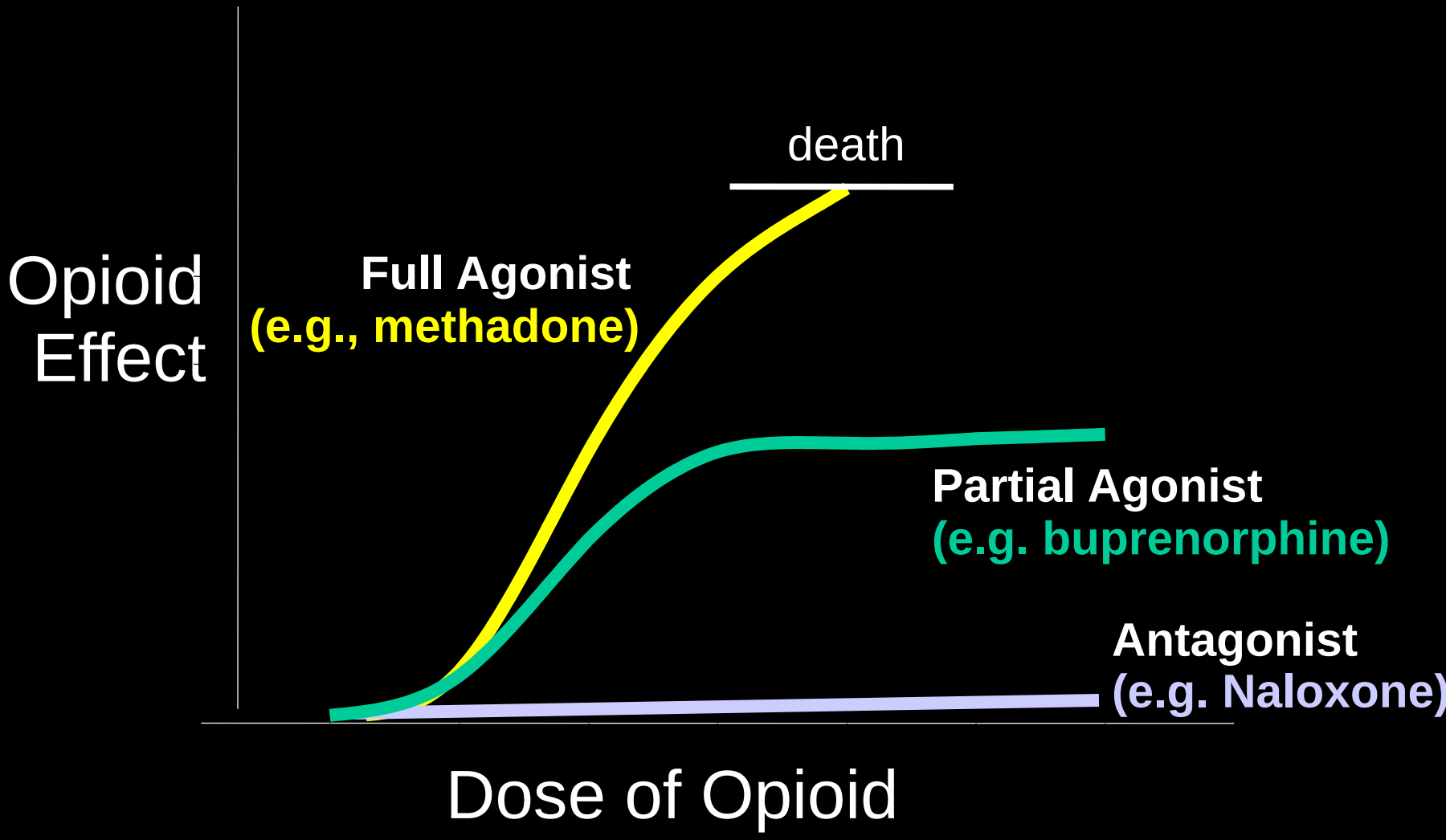
Opioid Agonists



Heroin vs. Long-Acting Agonists



Partial vs. **Full** Opioid Agonist



Buprenorphine: Advantages

- **Safe:** Partial agonist, a ceiling effect above which higher doses do not increase activity - respiratory depression unlikely
- **Safe:** Sublingual medication - low activity if swallowed, therefore safer around children
- Less euphoria
- Lower Street Value:
  - If used when "high" on heroin → severe withdrawal
  - If used when in withdrawal → relief

Buprenorphine treatment in India: Guidelines

- **Many guidelines available (WHO SEARO; NACO; UNODC; NDDTC, AIIMS):**

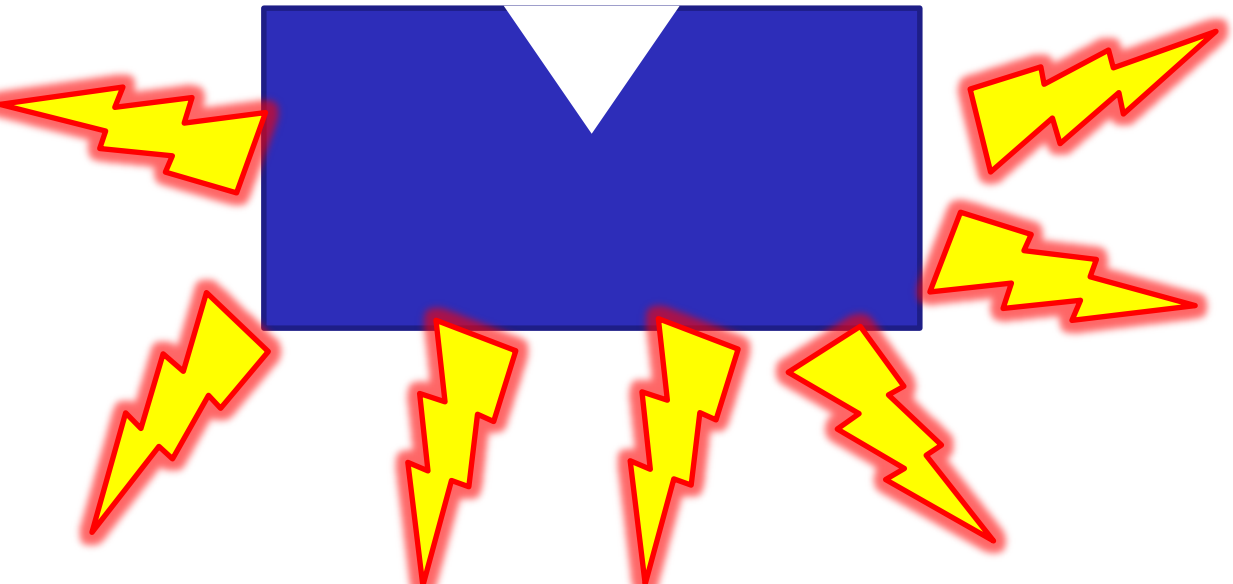
Buprenorphine Maintenance: Guidelines

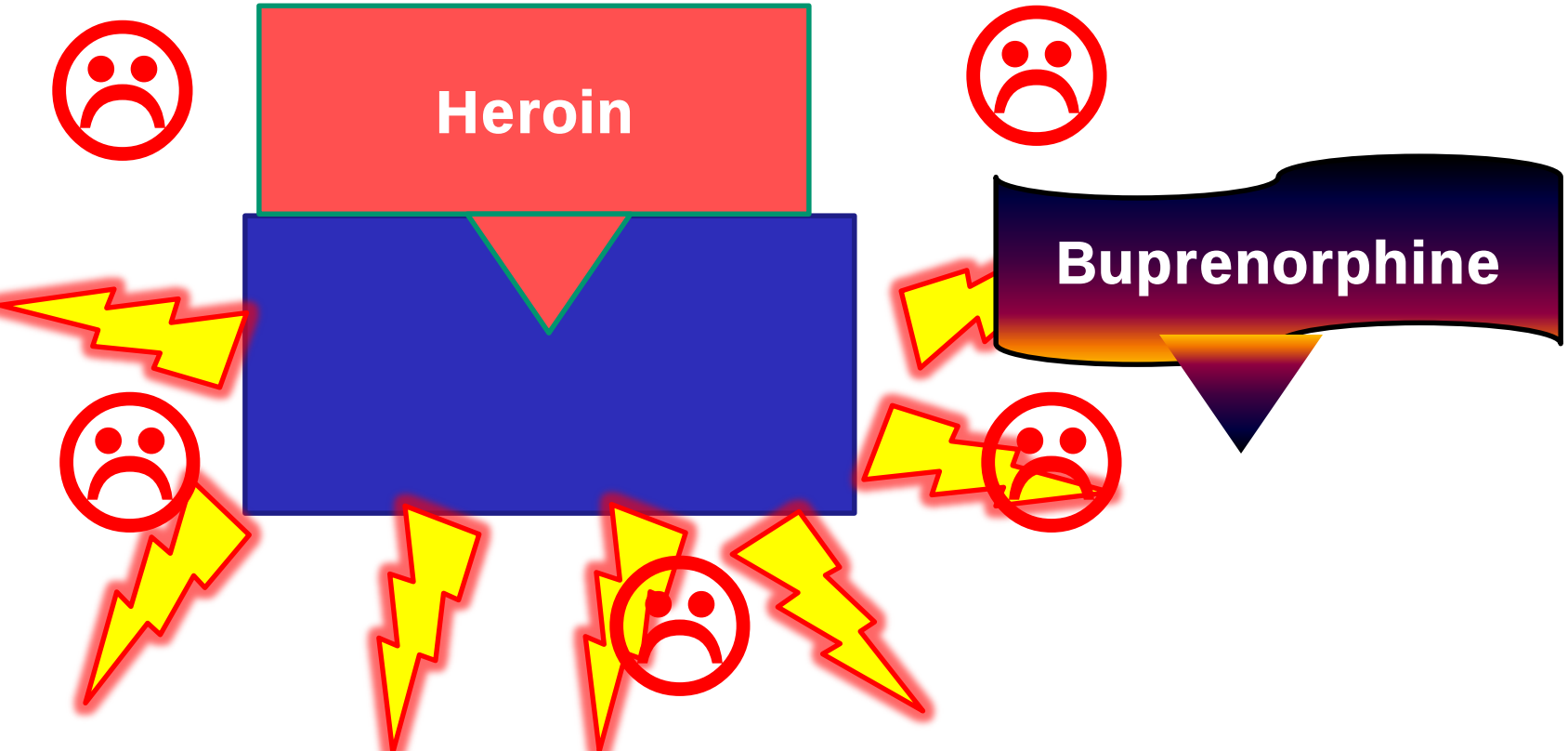
Phase
Pre-induction
Induction
Maintenance
Discontinuation

Buprenorphine Maintenance: Guidelines

Phase	Characteristics
Pre-induction	Wait for withdrawals to appear
	If the patient is under intoxication, buprenorphine can precipitate withdrawals !

Heroin




Heroin
Buprenorphine

Buprenorphine Maintenance: Guidelines

Phase	Characteristics
Pre-induction	Wait for withdrawals to appear
	If the patient is under intoxication, buprenorphine can precipitate withdrawals !

Buprenorphine Maintenance: Guidelines

Phase	Characteristics
Pre-induction	Wait for withdrawals to appear
Induction	Initiate with 2 mg → observe → reach to optimum dose within 3-7 days
	1st dose – 2 mg Observe for ~ 2 hours Additional dose if necessary

Buprenorphine Maintenance: Guidelines

Phase	Characteristics
Pre-induction	Wait for withdrawals to appear
Induction	Initiate with 2 mg → observe → reach to optimum dose within 3-7 days

☹ **Under-medicated patients:**	• craving or withdrawal between doses
😐 **Over-medicated patients:**	• buprenorphine side effects
☺ **Properly medicated patients:**	• neither of these experiences

Buprenorphine Maintenance: Guidelines

Phase	Characteristics
Pre-induction	Wait for withdrawals to appear
Induction	Initiate with 2 mg → observe → reach to optimum dose within 3-7 days
Maintenance	Continue Optimum dose Ensure compliance Monitor for drug use Rehabilitate / reintegrate

Duration?

- Not fixed; months to years
- Decided by whether the treatment goals have been met.

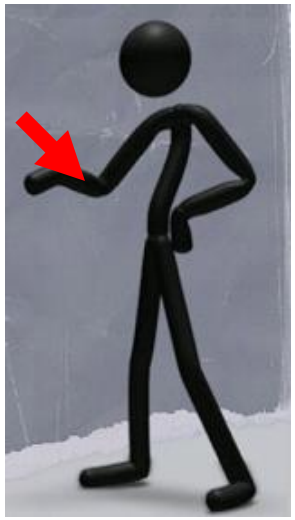
Buprenorphine Maintenance: Guidelines

Phase	Characteristics
Pre-induction	Wait for withdrawals to appear
Induction	Initiate with 2 mg → observe → reach to optimum dose within 3-7 days
Maintenance	Continue Optimum dose Ensure compliance Monitor for drug use Rehabilitate / reintegrate
Discontinuation	Only when treatment goals have been met! May be followed by antagonists

Diversion potential: Buprenorphine

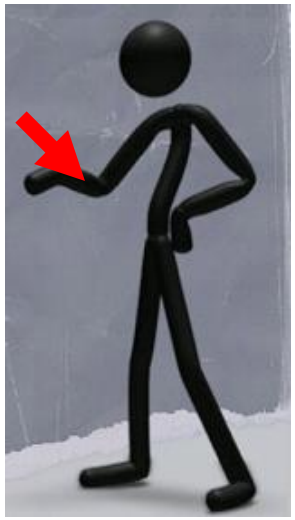
	Incorrect
Route	**Oral**
Buprenorphine Absorbed?	**NO**
Outcome	😐 **(No Action)**

Diversion potential: Buprenorphine



	Incorrect	Incorrect
Route	**Oral**	**IV**
Buprenorphine Absorbed?	**NO**	**Yes**
Outcome	😐 **(No Action)**	**Pt:** ☺ **Doc:** ☹

Diversion potential: Buprenorphine



	Incorrect	Incorrect	Correct
Route	**Oral**	**IV**	**Sublingual**
Buprenorphine Absorbed?	**NO**	**Yes**	**YES**
Outcome	😐 **(No Action)**	**Pt:** ☺ **Doc:** ☹	☺**!**

Buprenorphine-Naloxone combination

Buprenorphine + Naloxone sublingual

60% bioavailability of buprenorphine + 0% bioavailability of naloxone

Effect of buprenorphine

Buprenorphine + Naloxone sublingual (injected)

100% bioavailability of buprenorphine + **100% bioavailability of naloxone**

No agonist effect / precipitation of withdrawals

Methadone: Guidelines

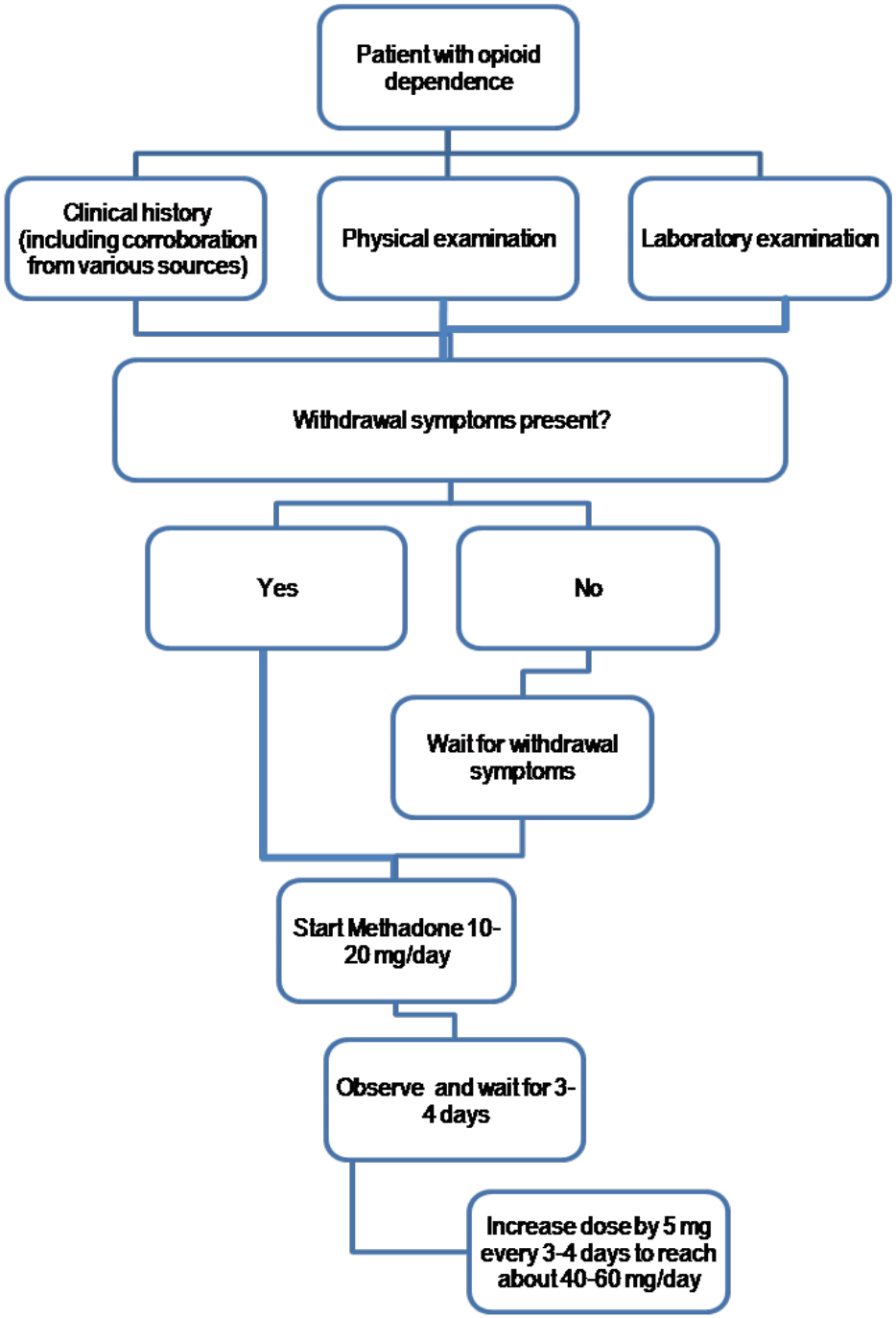
Induction

Stabilisation

Induction

The aim of induction

- To start treatment safely and minimise the discomfort of the patient


Patient with opioid dependence
Clinical history (including corroboration from various sources)
Physical examination
Laboratory examination
Withdrawal symptoms present?
Yes
No
Wait for withdrawal symptoms
Start Methadone 10-20 mg/day
Observe and wait for 3-4 days
Increase dose by 5 mg every 3-4 days to reach about 40-60 mg/day

Induction Dose

The calculation of the right starting dose should take the following factors into account:

- The right dose varies from person to person and from time to time
- Illicit heroin varies in purity from area to area and from time to time
- The characteristics of the various medications vary: e.g. methadone is a long acting opiate
- Too much medication can be fatal and too little is unlikely to be effective.

Induction

- General guideline

START LOW AND GO SLOW

First week

- Methadone 10 to 20 mg/day X day 1 to day 3
- Methadone 25 mg/day X day 4 to day 6
- Methadone 30 mg/day X day 7 to day 9

- Maximum dose at the end of 1st week < 40 mg/day

- Why dose increase only after 3 days?

✓ The patient will experience increasing effects from the methadone each day (accumulation)

Typical reasons for dose increase

1) Signs and symptoms of withdrawal
2) Amount and/or frequency of opioid use not decreasing
3) Persistent cravings for opioids
4) Failure to achieve a dose that blocks the euphoria of short acting opioids

Induction

Stabilisation

Stablisation

- The time needed to properly stabilise someone on methadone treatment can take up to six weeks or more.
- Target dose for stabilisation ?
  - ✓About 60 mg/day
- Most patients likely to be comfortable around this dose

Stablisation Dose

- Western studies:
  - ✓ Minimum stabilisation dose: 60 mg/day
  - ✓ Maximum stabilisation dose: 120 mg/day

- South Asian patients?
  - ✓ Dose requirement likely to be lower
    - Racial / genetic difference
    - Difference in ‘habit size’
  - ✓ Most South Asian patients should do well on 60 – 80 mg/day

Stablisation

- The stabilization phase can be considered to have reached
  - ✓ When the patient feels comfortable throughout 24 hours
  - ✓ With no subjective or objective withdrawal before doses
  - ✓ Experiences no sedation or euphoria after doses.

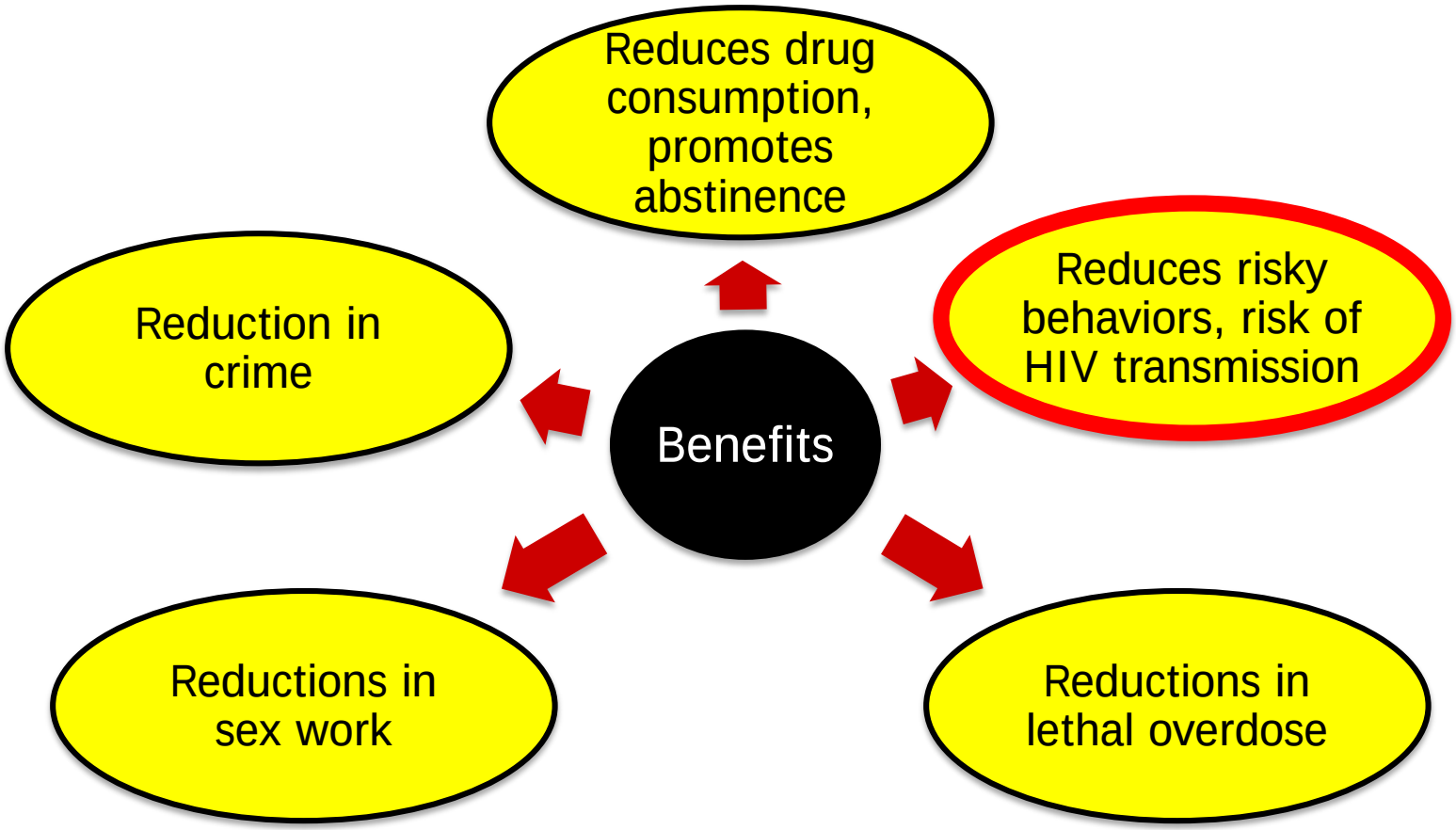
Should there be a need to increase or decrease the dose after stablisation?

☹ **Under-medicated patients:**	• craving or withdrawal between doses
😐 **Over-medicated patients:**	• Methadone side effects
☺ **Properly medicated patients:**	• neither of these experiences

Need to increase or decrease the dose after stablisation

Criteria for dose increases (once stable) can include:	Criteria for dose decreases (once stable) can include:
Signs and symptoms of withdrawal (objective and subjective)	Persistent nodding
Amount and/or frequency of opioid drug use not decreasing	Somnolence
Persistent cravings for opiates	Patients wish to reduce to minimum effective dose

Effectiveness of OST

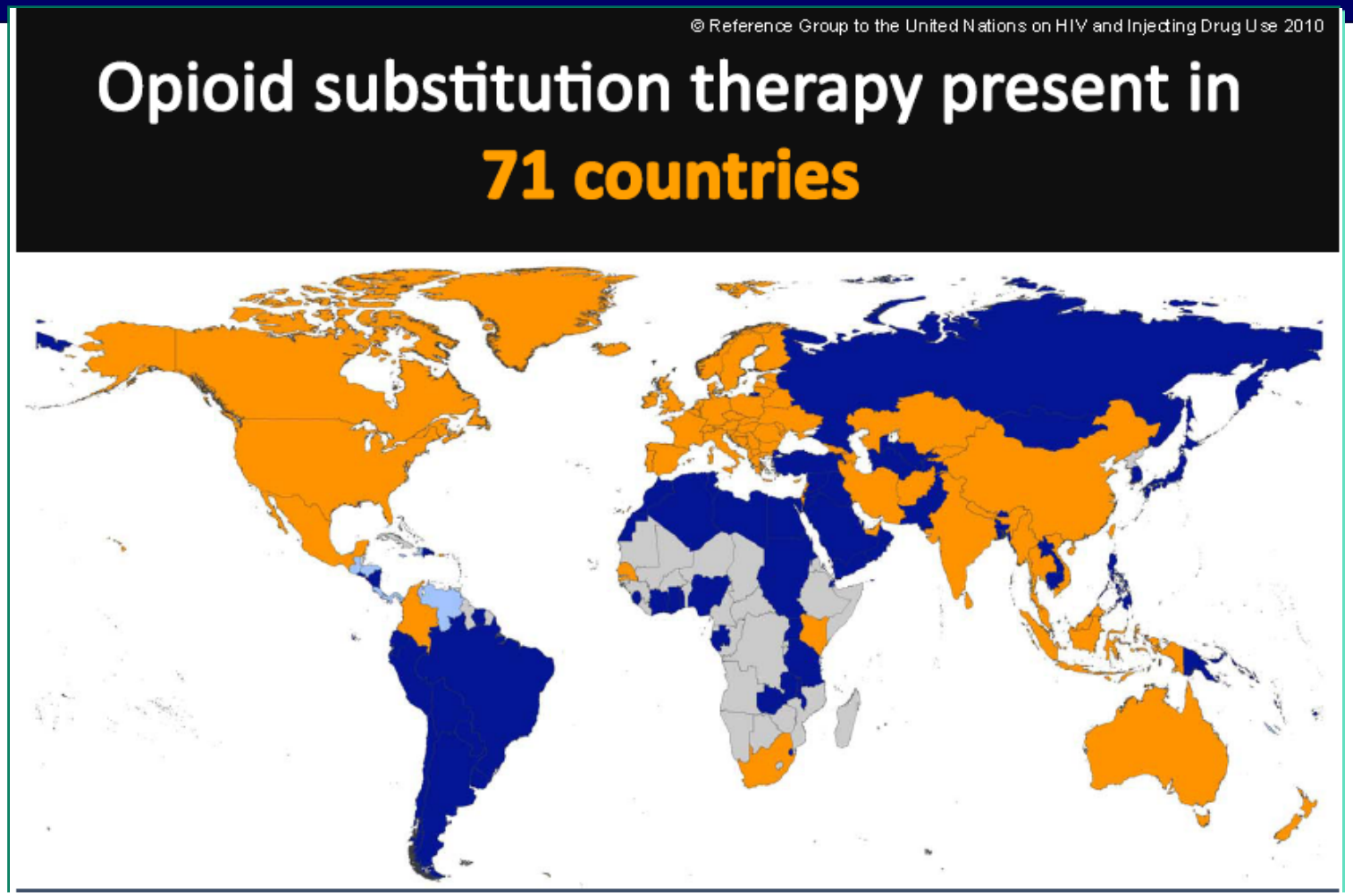



THE ADVENTURES OF
METHADONE MAN
AND
BUPRENORPHINE BABE
25¢
STOPPING HIV
IN ITS
TRACKS!!

OST: current global status

- Both Buprenorphine and Methadone
  - ✓Endorsed by the UN system
  - ✓Listed as ‘essential medications’ by WHO
  - ✓Are being used in a number of countries

OST: current global status



OST: current global status

Buprenorphine treatment in India: current status

- Available as DOTS at:
  - ✓Some government institutes
  - ✓51 NGO centres (with NACO support)
  - ✓5 NGO + government hospitals in Punjab

Myths about substitution treatment

MYTH #1: Patients are still addicted

FACT: It is true that a person on OST upon missing a dose will experience Withdrawl symptoms. However concept of Addiction or Dependence Syndrom is much broader and ***may*** or ***may not*** include physical dependence.

- ✓ **Physical dependence on a medication for treatment of a medical problem *does not* mean the person is engaging in pathologic use and other behaviors.**

MYTH #2: Buprenorphine is simply a substitute for illegal drugs

FACT: Buprenorphine ***is*** a replacement medication; it is ***not simply*** a substitute

- ✓ **Buprenorphine is a legally prescribed medication, not illegally obtained.**
- ✓ **Buprenorphine is a medication taken sublingually, a very safe route of administration.**
- ✓ **Buprenorphine allows the person to function normally.**

MYTH #3: Providing medication alone is sufficient treatment for opioid addiction

FACT: Buprenorphine is an important treatment option. However, the ***complete*** treatment package must include other elements, as well.

- ✓ Combining pharmacotherapy with counseling and other ancillary services increases the likelihood of success.

Myth # 4: Buprenorphine is a cure for addiction

FACT

- ✓It is not a cure
- ✓It is a treatment modality that helps in repairing the damage caused by opioid dependence

To conclude...

- Opioid dependence is a chronic, relapsing disorder
- No single approach is likely to work for ALL patients
  - ✓Patients must have access to a MENU OF OPTIONS to choose from
- Those with higher public-health risk (i.e. IDUs) must receive priority