LONG TERM PHARMACOTHERAPY OF OPIOID DEPENDENCE

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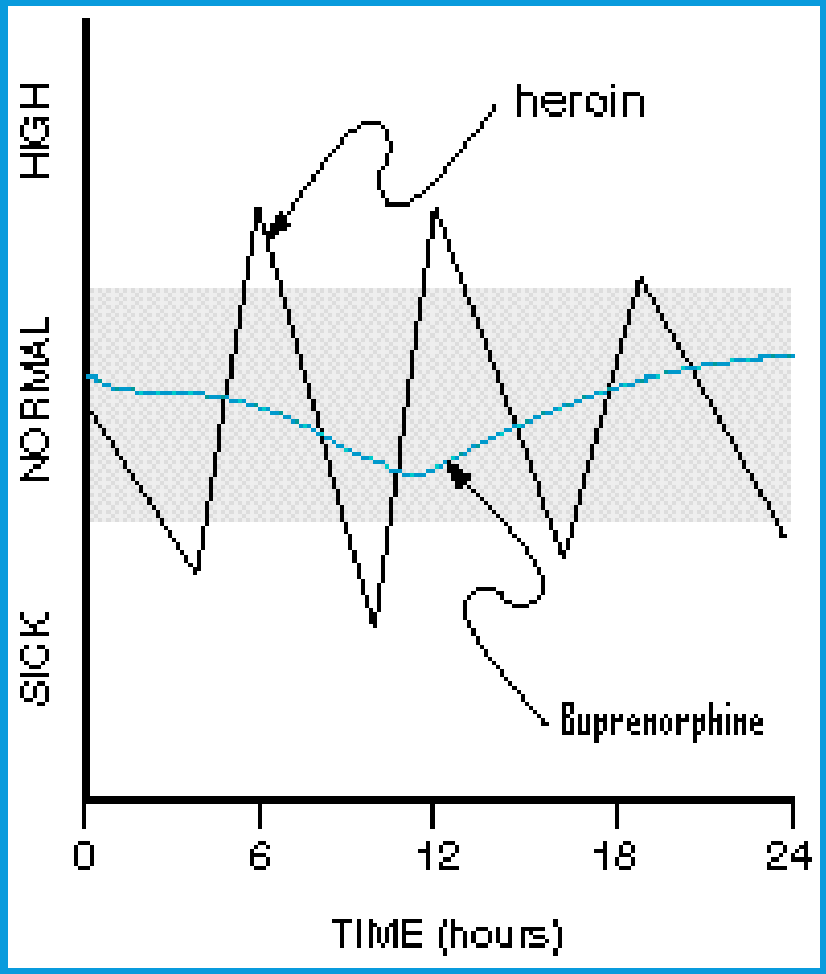
LONG TERM OPTIONS

- FULL AGONIST
- PARTIAL AGONIST
- ANTAGONIST
- PARTIAL AGONIST+ ANTAGONIST

RATIONALE FOR AGONIST MAINTENANCE OR SUBSTITUTION TREATMENT



FULL AGONIST

- Activates the mu receptor
- Increasing full agonist dose produces increasing mu opioid receptor specific activity
- METHADONE

METHADONE

EFFICACY

- The patient can carry on a normal life. Daily drug-seeking ceases.
- Once daily by mouth without the use of injection needles, so limits exposure to diseases like hepatitis and HIV.
- Methadone’s gradual, long lasting effects eliminate drug hunger or craving.

- Relieves withdrawal symptoms

- No change in tolerance to methadone over time, so it does not take more of the drug to achieve the same results.

- Euphoria-blocking effects of methadone make taking illicit opioids undesirable.

- Used properly, methadone is generally safe and nontoxic, with minimal side effects.

SYRUP METHADONE

- Rusan Pharmaceuticals
- Orange Colour
- One litre Bottles
- Dispensor
- 5mg/ml

SYRUP ADVANTAGES

- Best known product
- Well accepted by clients, colour is easy to identify, which helps prevent accidental overdose
- Unlikely to be injected because Mixed chloroform is painful
- The volume and viscosity makes injection inefficient
- Looks like large dose
- Long shelf life: 36 months

DISADVANTAGES

- Sugar may cause tooth decay in long-term users
- Storage difficult due to volume
- Causes vein damage if injected
- May attract children
- May interfere with control of diabetes
- Large volume to take – especially for people on high doses

INDICATIONS

- Voluntary consent
- Established Opioid dependence
- Evidence of failed attempts
- Above 18 years

CONTRAINDICATIONS

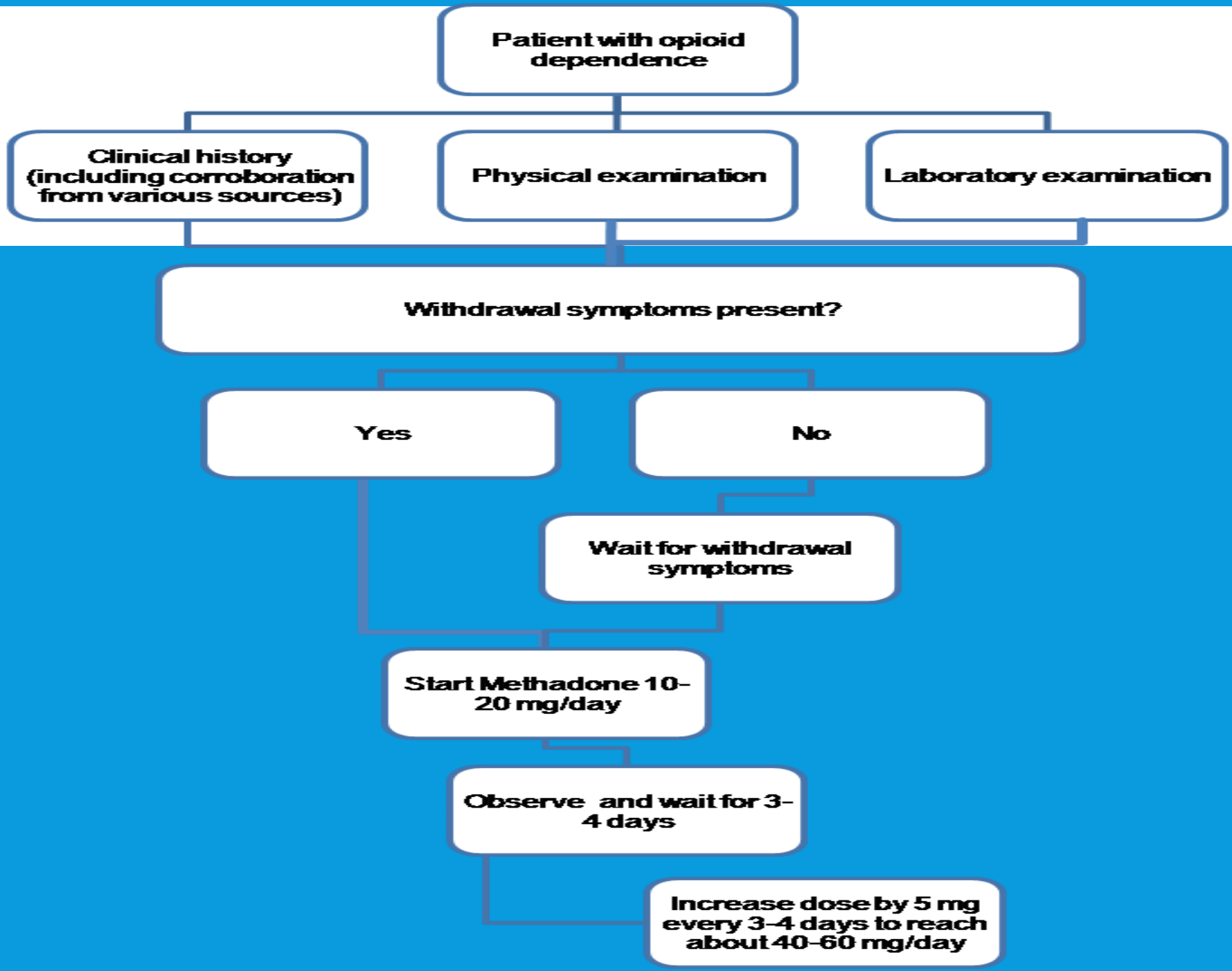
- RELATIVE

Severe Hepatic /Respiratory Insufficiency

- GENERAL

Inability to give consent

Lack of evidence of Opioid Dependence


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

TYPICAL PRESCRIPTION PATTERN

- 20 mg daily for one week, then
- 30 mg daily for one week, then
- 40 mg daily for one week, then
- 50 mg daily for one week, then
- 60 mg daily thereafter

COMMON SIDE EFFECTS

- Sleep disturbance
- Teeth problems
- Reduced libido and sexual dysfunction
- Lethargy
- Excessive sweating
- Constipation

PARTIAL AGONIST

- Activates the receptor at lower levels
- At higher doses, even when partial agonist binds all mu receptors, maximal agonist effect is never achieved
- BUPRENORPHINE

BUPRENORPHINE

PHARMACODYNAMICS

- Partial agonist at the mu opiate receptor
  - Low intrinsic activity partially activates receptors

- High affinity for the mu receptor
  - Affinity comparable to naloxone / naltrexone
  - Competes with other opioids and blocks their effects

- **Slow dissociation from mu opioid receptor** – prolonged therapeutic effect for opioid dependence treatment.

PHARMACODYNAMICS

- At low doses it produces morphine like subjective, physiological and behavioral effects.
- These include analgesia, sedation , pupillary constriction and euphoria.
- When the dose is increased- ceiling effects at 8-16mg BPN, S/L.(30-60mg morphine).
- Respiration was maximally suppressed after 16 mg of BPN.

PHARMACODYNAMICS

- The ceiling effect on euphoria limits abuse liability.
- The ceiling effect on respiration increases safety in clinical practice.
- The potential for lethal overdose is remote even at 10 times the therapeutic dose.
- Following repeated administration, it blocks the subjective effects of parenterally administered morphine or heroin.
- It can substitute for morphine or heroin and suppress symptoms of mu-opiate withdrawal.

PHARMACOKINETICS

- Extensive first-pass metabolism in the liver, therefore unsatisfactory for oral use.
- Available as a sublingual preparation that takes about 5–15 minutes to dissolve.
- Most of the drug is excreted in the feces (70%) and urine (30%).

PHARMACOKINETICS

Buprenorphine (sublingual dose)

- Onset of effects : 30–60 minutes
- Elimination half-life :24–37 hours
- Peak clinical effects :1–4 hours
- Duration of effects 8–12 hours at low doses (e.g. <4 mg)
- 24–72 hours at high doses (e.g. >16 mg)

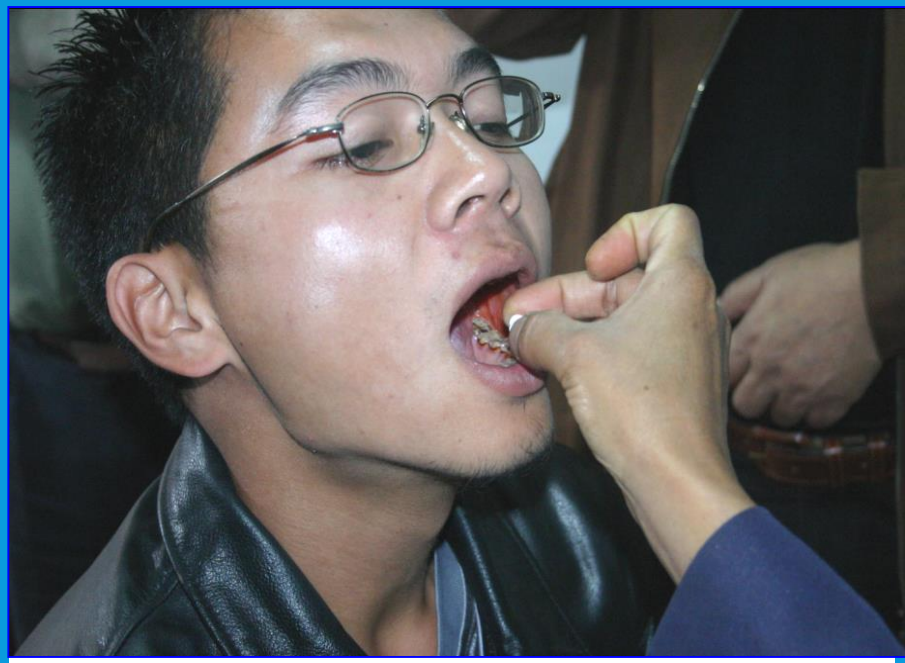
AVAILABILITY

- Available as
  - Sublingual tablets (0.2, 0.4, 2 mg and recently 8mg)
  - Injections
- Lower strength (0.2 mg & as Injections) since late 1980s
- Higher strength (0.4 and 2 mg) introduced in early 2000
- *Trade name*
- Addnok , Bupin and Norphin.

BUPRENORPHINE INDUCTION ('START LOW & GO FAST')

- Start with low doses of buprenorphine according to recent opiate use.
- At least 6 hours and preferable 12 hours after last heroin use *to avoid precipitated withdrawal*
- Review the patient frequently and titrate the dose carefully and quickly to 4-8 mg per day

Precipitated withdrawal: Starting buprenorphine treatment in opioid dependent people may precipitate symptoms of withdrawal because buprenorphine displaces residual illicit opioid agonists from receptors and because its partial agonist activity reduces the stimulation of receptors.



DRUG INTERACTIONS

Opioid Agonists

- Patients suffering with chronic pain –if full mu agonist for pain relief is required in a patient maintained on buprenorphine, then discontinue buprenorphine

DRUG INTERACTIONS

Opioid Antagonists

- Buprenorphine treatment should not be combined with opioid antagonists (e.g., Naltrexone,since the naltrexone can precipitate an opioid withdrawal syndrome in buprenorphine-maintained patients.
- Thus, physicians should not prescribe naltrexone for patients being treated with buprenorphine for opioid addiction.

ANTAGONIST

- Occupies without activating
- Opioid antagonists bind and occupy mu opioid receptors but result in no specific intrinsic activity regardless of dose
- Not reinforcing
- Blocks abused agonist opioid types
- NALOXONE AND NALTREXONE

ANTAGONISTS

- Naltrexone
  - Pure antagonist
  - Orally active
  - Long duration
- Naloxone
  - Pure antagonist
  - Parentally administered
  - Short duration

NALTREXONE

EFFICACY

- Selectively competes with exogenously administered opiates for CNS and non-CNS opiate receptors
- Does not experience the effect of agonist
- Drug seeking behaviour becomes extinct
- Eventually reduces craving
- Physical dependence not re-established
- No tolerance develops

PHARMACODYNAMICS

- Non-specific opiate antagonist and binds to all three receptors-mu, kappa, sigma
- Plasma half-life is 4 hours but duration of opiate receptor blockade is higher
- 50 mg blocks for 24 hours and 100 mg for 48 hours and 150 mg for 72 hours

PHARMACOKINETICS

- Absorbed following oral administration
- Peak plasma levels in an hour
- High first pass metabolism
- Oral bioavailability is 60%
- 20% bound to plasma proteins
- Half-life 4 hours and of active metabolite is 10-12 hours
- First pass metabolism in the liver via glucoronic acid conjugation with transformation to the active metabolite 6-beta naltrexol

INDICATIONS

- Maintenance treatment
  - Opiate Dependence
  - Alcohol Dependence
- Opiate Detoxification when combined with clonidine

BEST RESULTS

- Younger patients
- Short duration of use
- High Motivation
- Stable occupation
- Good Social Support
- No co-morbid psychopathology
- Currently abstinent and concerned about possible relapse
- Recent history of prolonged abstinence/Recent relapse

ADMINISTRATION

- Educate about mechanism of Action
- Emphasize compliance
- Discuss supervision
- Adequate washout- 3days for short acting and 7 days for long acting
- Self-report, report from family, urine screening, Naloxone Challenge Test, gradual induction

NCT

- IV
  - 0.2 mg-observe for 30 secs
  - 0.6 mg -observe for 20 minutes
- SC
  - 0.8 mg-observe for 20 minutes

INDUCTION

- 25 mg and after 1 hour 25 mg
- 50 mg daily
- After 1-2 weeks-thrice/week
- 6 to 12 months/stable recovery

SIDE EFFECTS

- GI symptoms -nausea, vomiting, diarrhea, abdominal pain
- Anxiety, restlessness
- Dysphoria
- Headache
- Insomnia
- Mild hypertension
- Hepatotoxicity-Baseline LFT, every month for 3 months and then every 3-6 months

Caution in liver or renal impairment

Risk of opioid overdose after discontinuation

Cessation 72 hours prior to surgery

SPECIAL POPULATIONS

- Safety not established in pregnant women and adolescents

Drug Interactions

- Safety of combined use with Disulfiram not established

- Depot preparation…Naltrexone Implants(6 to 8 months)…not yet approved by DCGI

SUMMARY

- Blocks the euphoric effect of opioids
- Safe, non-toxic, no abuse liability, no dependence potential, long duration of action, does not produce withdrawals on cessation
- Less craving
- Requires motivation
- 30-40% abstinent at 6 months after termination

BUPRENORPHINE-NALOXONE

BUPRENORPHINE- NALOXONE COMBINATION

RATIONALE

- Reports of buprenorphine tablets being misused through injectable route are available.

- To tide over this misuse, a buprenorphine-naloxone combination tablet has been evaluated.

RATIONALE

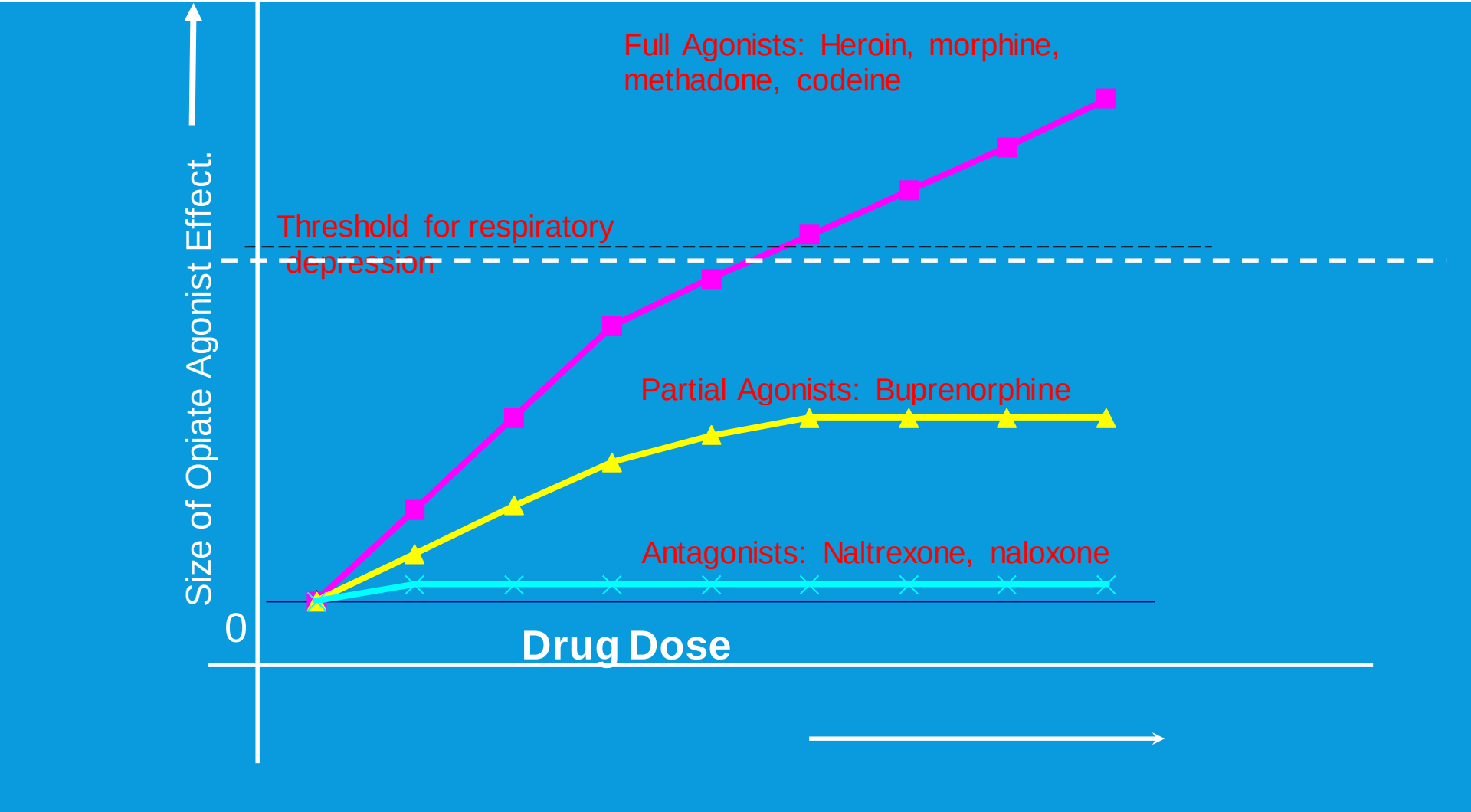
- Intended route (sublingual)- the patient will experience a predominant buprenorphine effect.
- However, if dissolved and injected -the antagonist effect of naloxone predominates because of it's high parenteral bioavailability(Stoller,2001).
- These antagonist effects would produce/precipitate opiate withdrawal symptoms, which are distressful to the patient and hence would discourage its abuse.

(Mendelson et al, 1997; Fudala et al, 1998; Johnson and McCagh, 2000; Stoller et al, 2001).

EFFICACY

- The innovative combination (2mg+0.5mg) sublingual tablet effectively treats opioid dependence or blocks the effects of illicit opioids, without noticeable negative effects of naloxone.
- Provides greater patient autonomy in the form of biweekly or weekly (as opposed to daily or alternate-daily) visits to the treatment center.
- Makes a provision for `take-home' medications, thus providing patients with more time for vocational/ rehabilitative activities.

OPIOID DOSE-RESPONSE EFFECTS



SUMMARY

- Important to provide long term pharmacotherapy
- Range of Options
- Different patients suitable for different medications
- Antagonist has no abuse liability but poor retention in treatment
- Most patients suitable for agonist but medication to be given by accredited professionals in the framework of recognized medical practice

THANK YOU…