# Long Term Pharmacotherapy Opioids including Choice of Agent

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# Opioid Classification

# Full Agonist

- Activates the mu receptor
- Highly reinforcing
- Most abused opioid type
- Includes morphine, heroin, methadone, & others
- Increasing full agonist dose produces increasing mu opioid receptor specific activity

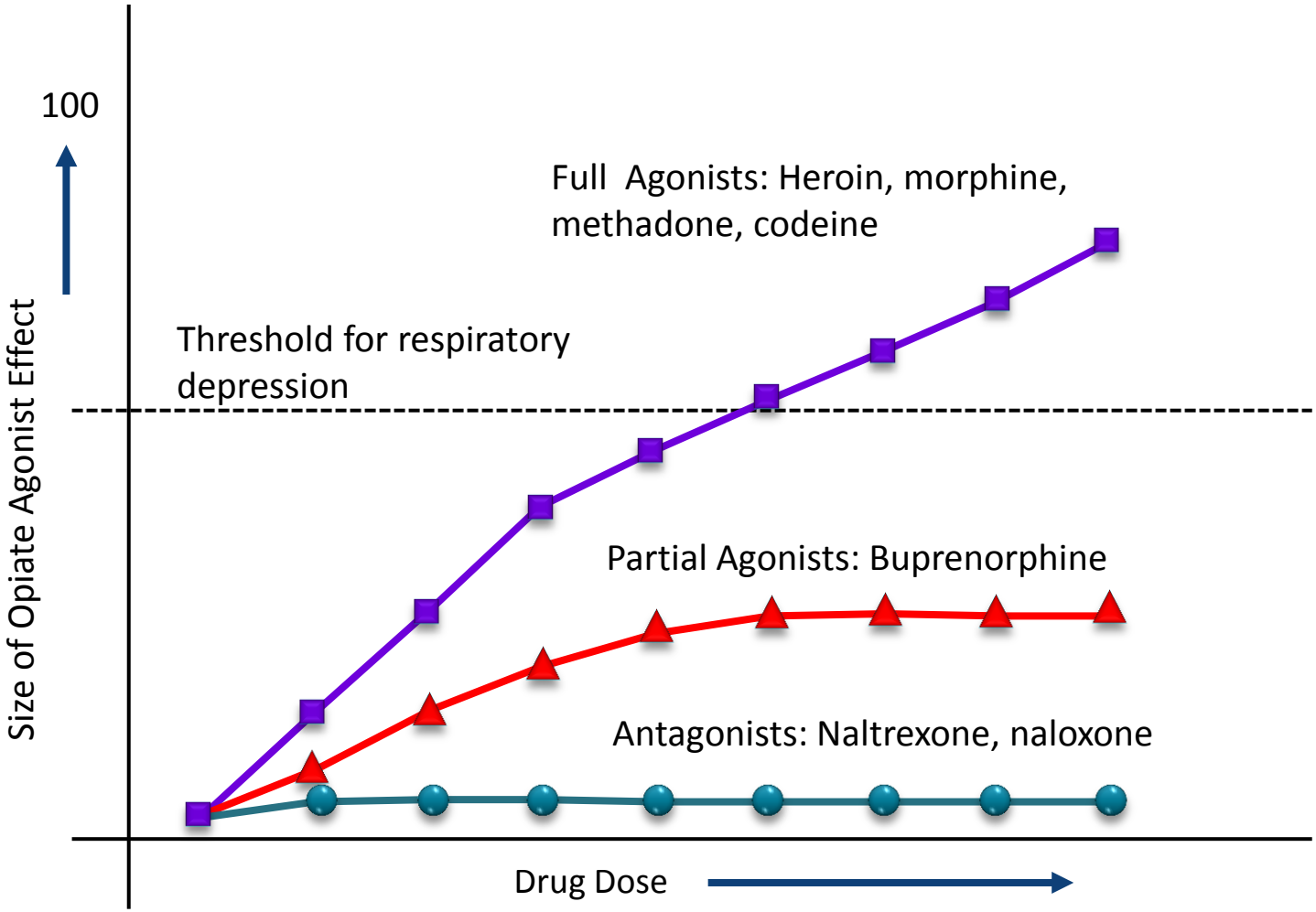
# Antagonists

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

# Partial Agonists

- Activates the receptor at lower levels
- Is relatively less reinforcing
- Is a less abused opioid type
- Includes buprenorphine
- At higher doses, even when partial agonist binds all mu receptors, maximal agonist effect is never achieved

# Opioid dose-response effects



# Principles of Harm Minimization

- Treatment Focus on
  - Reducing use
  - Reducing risk of infectious disease and mortality
  - Improving physical and psychological health
  - Reducing criminal behaviour
  - Re-integration in work/educational process
  - Improve social functioning

Without necessarily ceasing drug use

# Choice of agents

- Agonist
- Antagonist

# Antagonists

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

# Pharmacokinetics

- Absorbed following oral administration
- Reached 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

# Pharmacokinetics

- Fist pass metabolism in the liver via glucoronic acid conjugation with transformation to the active metabolite 6-beta naltrexol

# Pharmacodynamics

- Non-specific opiate antagonist and binds to al three receptors-mu, kappa, sigma
- Pharmacological duration longer than predicted by plasma kinetics
- Plasma half-life is 4 hours but duration of opiate receptor blockade is higher
- 50 mg dosage blocks for 24 hours and 100 mg for 48 hours and 150 mg for 72 hours (25 mg heroin)

# Indications

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

# Rationale

- 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

# Guidelines for Use of Naltrexone

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

# Administration of Naltrexone

- 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
- After 1-2 weeks-thrice/week
- DOT

# Progress in Treatment

- Multiple outcome measures
- 6-12 months at least
- 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 every 3-6 months then

*Caution in liver or renal impairment*
*Risk of 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 still under study

# 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

# Agonist Maintenance Treatment

# Agonist Maintenance Treatment…

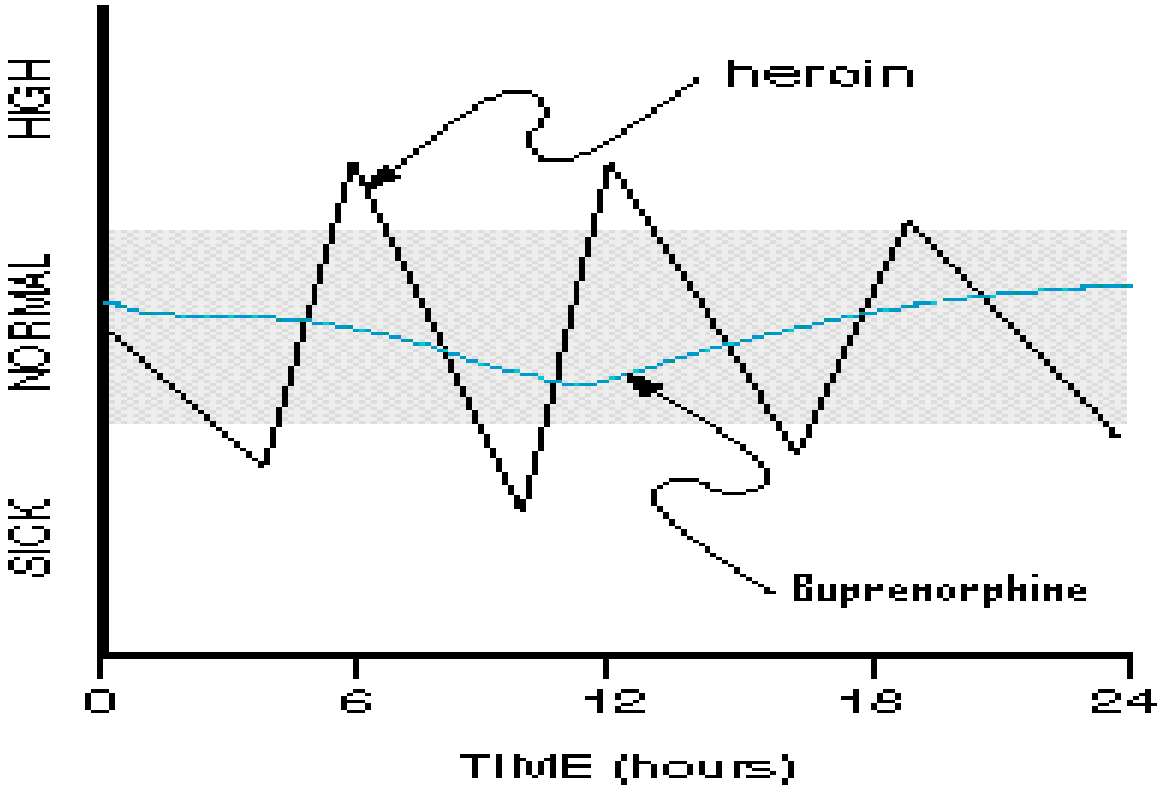
## Compounds available:

- Methadone
- Buprenorphine
- Oral sustained release morphine
- Buprenorphine & Naloxone combination

# What kind of medications are suitable for agonist maintenance?

- Ability to control withdrawal symptoms and craving
- Attenuate acute effects of externally administered opiates
- Long acting (so that frequent dosing is not required)
- Easy to administer Be orally active
- Low euphoria – low dependence potential
- Have low long term toxicity/side effects
- Have high therapeutic index
- Economical
- Easily available

# Rationale for agonist maintenance or substitution treatment



# Indications

- Opioid Dependence
  - Long duration of drug use
  - IDU
  - Multiple failed abstinence attempts
  - Occupational or family instability
- Most patients suitable for agonist maintenance

# Risks

- Overdose
- Diversion

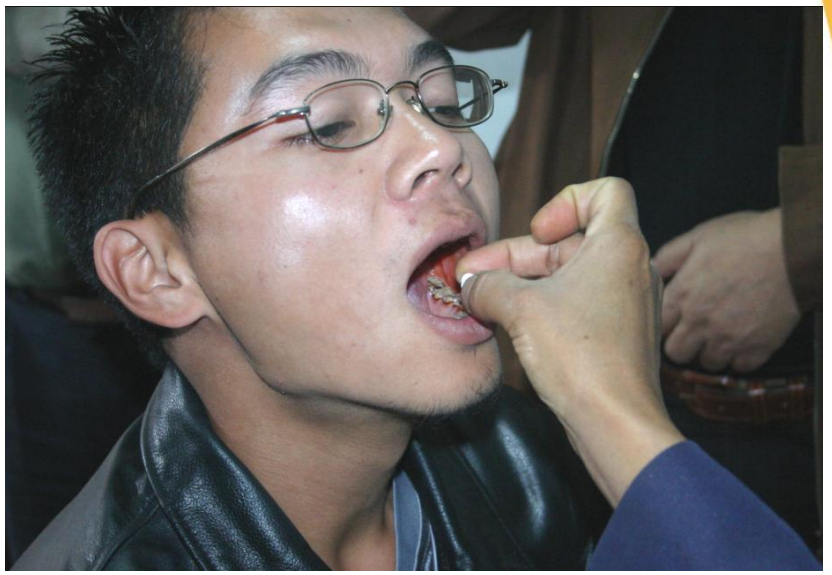
# Factors Related to Outcome

- Adequate dosage, duration and continuity of treatment
- Accompanying medical and psychosocial services

# Substitution or Maintenance therapy

- Treatment is administered by accredited professionals in the framework of recognized medical practice
- Appropriate clinical monitoring

# Presbytarian Hospital, Aizawl, Mizoram



# Buprenorphine

# Buprenorphine; Pharmacodynamics

- Partial agonist at the m opiate receptor
  - Low intrinsic activity partially activates receptors
- High affinity for the m receptor
  - Affinity for 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 withdrawl.

# Buprenorphine: Pharmacokinetics

- Buprenorphine undergoes extensive first-pass metabolism in the liver, and is therefore unsatisfactory for oral use.
- It is available therefore 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%).

# Buprenorphine: 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
- Available in India (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 displacing residual illicit opioid agonists from receptors and because its partial agonist activity reduces the stimulation of receptors.***

# Drug interactions-Medications Metabolized by Cytochrome P450 3A4

- Buprenorphine levels are increased by:
  - Erythromycin or clarithromycin
  - Itraconazole or ketoconazol
  - Rifampin
- Buprenorphine levels are decreased by:
  - Phenytoin (Dilantin)
  - Carbamazepine (Tegretol)
  - phenobarbital

# Drug interactions

- *Opioid Agonists*–in 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.

# 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

- When the buprenorphine-naloxone tablet is used by opiate addicts by the intended route (sublingual)- the patient will experience a predominant buprenorphine effect.
- However, if the buprenorphine-naloxone tablets were 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).

# Buprenorphine- naloxone combination

- Thus, the innovative buprenorphine-naloxone combination (2mg+0.5mg) sublingual tablet has been shown to effectively treat opioid dependence or block the effects of illicit opioids without noticeable negative effects of naloxone
- Such a tablet is also likely provide for greater patient autonomy in the form of biweekly or weekly (as opposed to daily or alternate-daily) visits to the treatment center and make a provision for `take-home' medications, thus providing patients with more time for vocational/ rehabilitative activities

# Buprenorphine-Limitations

- Water soluble
- Can be diverted and injected
- Abusable compound -However abuse potential lower than that of full agonists
- Being partial agonist, abuse potential is low-moderate

# MYTH #1: Patients are still addicted

**FACT:** Addiction is pathologic use of a substance 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 heroin or other opioids

**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: Patients are still getting high

**FACT:** When taken sublingually, buprenorphine is slower acting, and does not provide the same “rush” as heroin.

- Buprenorphine has a ceiling effect resulting in lowered experience of the euphoria felt at higher doses.

# METHADONE

# Efficacy of Methadone

- The benefits of the methadone maintenance treatment include the following:
- An adequate maintenance dose of methadone does not make the patient feel “high” or drowsy, so the patient can generally carry on a normal life. Daily drug-seeking to “feed a habit” ceases.
- Methadone can be taken once daily by mouth without the use of injection needles, which limits exposure to diseases like hepatitis and HIV. Methadone’s gradual, long lasting effects eliminate drug hunger or craving.

- It relieves symptoms associated with withdrawal from opiates
- There is little 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
- 6 months' supply
- 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

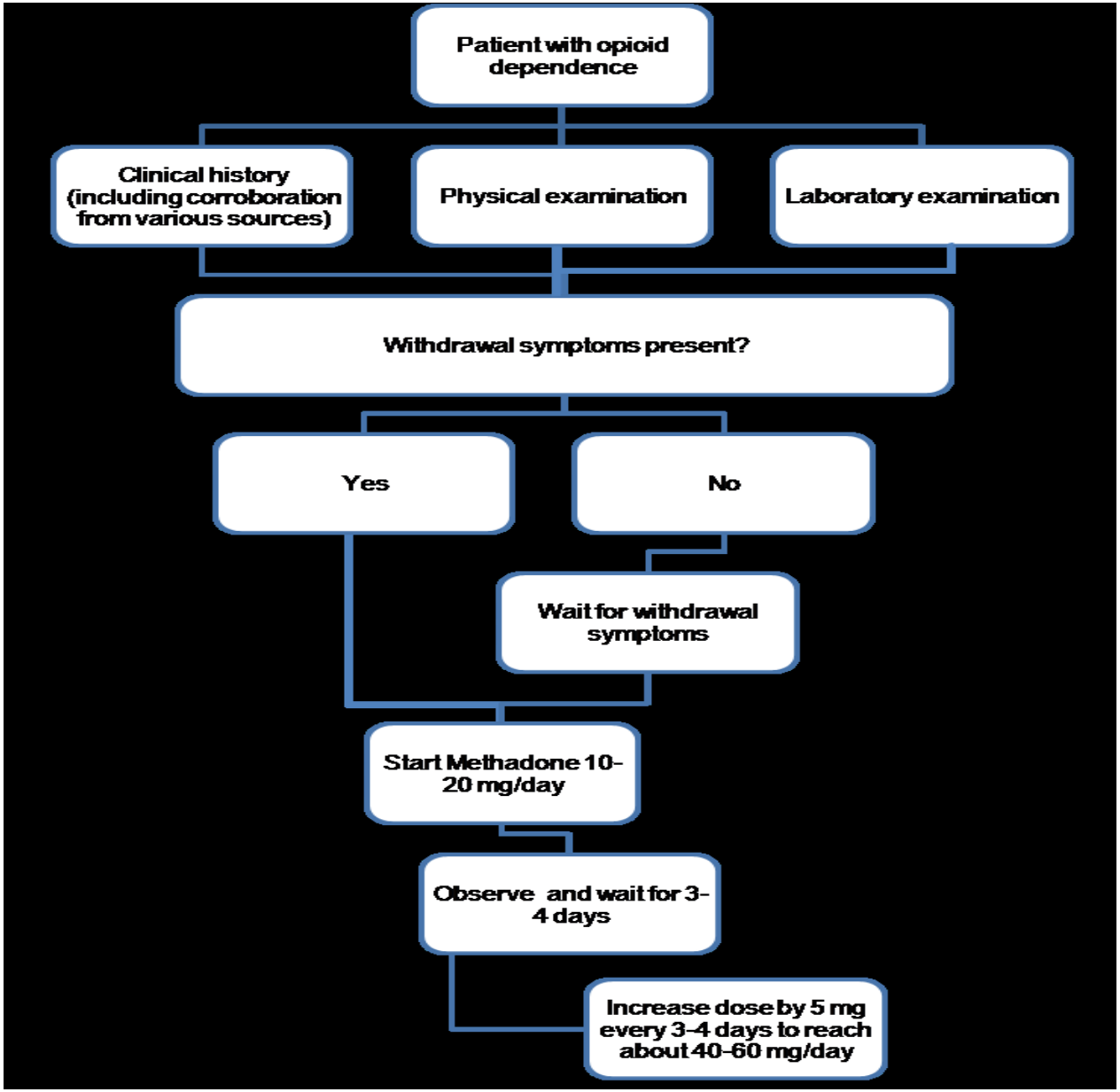
- Sugar may cause tooth decay in long-term users
- Storage difficult due to volume
- Causes vein damage if injected
- May attract children
- May interfere with control of diabetes
- Large volume to take – especially for people on high doses

# 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

# The typical pattern of prescribing could be

- 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

# Missed Doses

- In general the following schedule can be presumed to be safe and effective.
- If the patient has missed,
- **One day:** No change in dose
- **Two days:** If no evidence of intoxication administer normal dose
- **Three days**: Administer half dose in discussion with the prescribe.
- **Four days:** Patient must see prescriber. Recommence at 40mg or half dose whichever is the lower
- **Five days or more:** regard as a new induction

# Deferred dispensing

- Patients should not receive Methadone if they appear to be intoxicated, particularly with alcohol; patients may be asked to wait to be reassessed some hours later prior to administration of Methadone.

**Replacement of vomited doses**

- A physician or pharmacist may replace a vomited dose provided the vomiting was observed by a responsible individual e.g.: pharmacist or nurse. The following schedule must be followed:
- The vomiting occurred **less than 15 minutes** (2) after ingestion: full replacement
- The vomiting occurred **between 15 and 30 minutes**: ½ the dose would be replaced
- The vomiting occurred **after 30 minutes**: no replacement is to be given

# Management of Methadone overdose

## The signs and symptoms of Methadone overdose include:

- Pinpoint pupils
- Nausea
- Dizziness
- Feeling intoxicated
- Sedation/ nodding off
- Unsteady gait, slurred speech
- Snoring
- Hypotension
- Slow pulse (bradycardia)
- Shallow breathing (hypoventilation)
- Frothing at the mouth (Pulmonary Oedema)
- Coma

Emergency Room
Inj Naloxone 0.4 mg IV

# Management of common side effects

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

# Summary

- Important to provide long term pharmacotherapy
- Range of Options-Antagonist, agonist
- 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

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