

# VOLUME C

## Pharmacological Treatment for Drug Use Disorders

## Drug Treatment for Special Populations



## Module 2

# Basics of opioid dependence Pharmacotherapy options



Opioids:  
Definition,  
effects and  
treatment  
implications



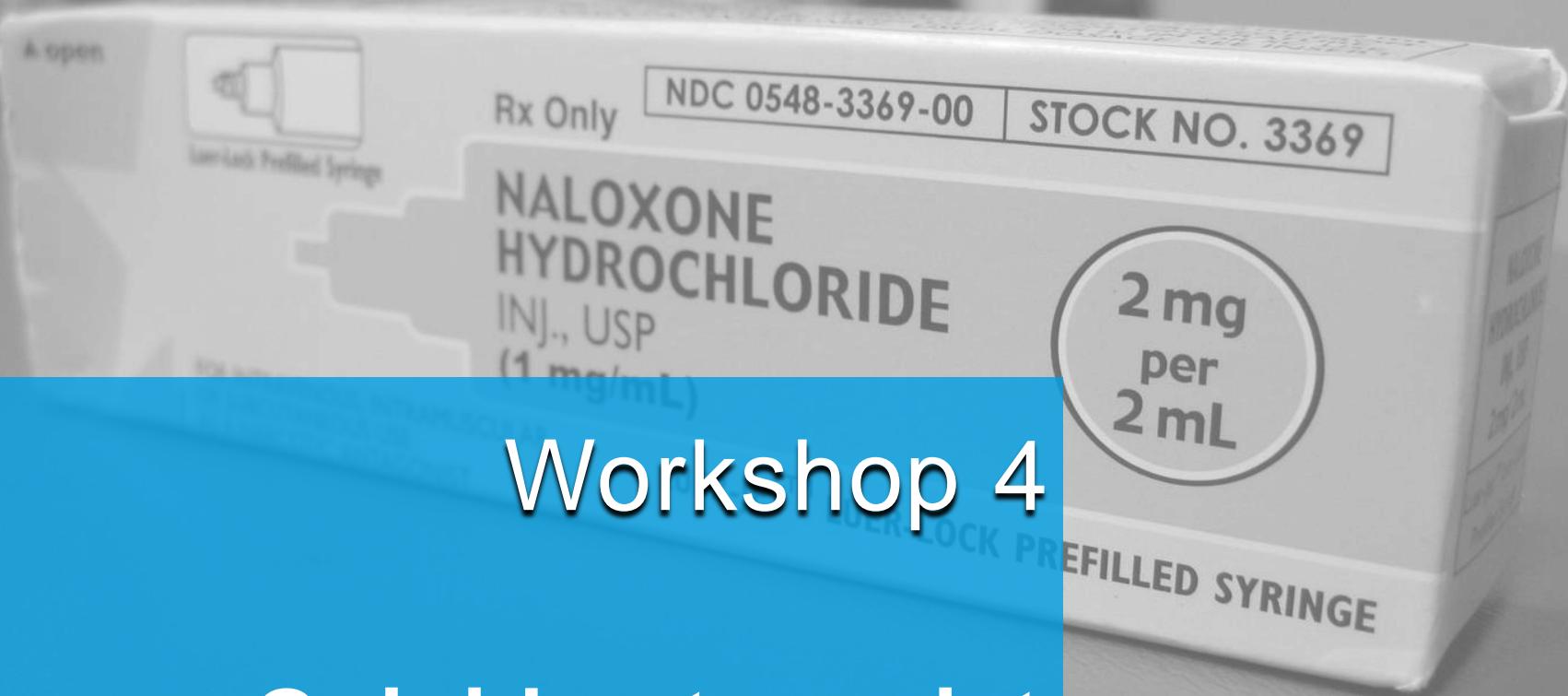
Opioid  
dependence  
treatment with  
Methadone



Opioid  
dependence  
treatment with  
Buprenorphine



Opioid  
antagonist  
treatment



# Workshop 4

## Opioid antagonist treatment

# Training objectives

**At the end of this workshop you will be able to:**

- ▶ Understand the neurobiology conditioning, underpinning opioid relapse
- ▶ Identify the rationale for the use of Naloxone for opioid overdose
- ▶ Understand the rationale for the use of Naltrexone for relapse prevention
- ▶ Explain the challenges and limitations of Naltrexone treatment





# Naloxone for opioid overdose

## Let's reflect!



Have you ever witnessed an opioid overdose and what did you do? Share your experience!

# Naloxone for opioid overdose

- ▶ Naloxone is a medication used to counter the effects of opioid overdose, for example heroin and morphine overdose
- ▶ Specifically, Naloxone is used in opioid overdoses for countering life-threatening depression of the central nervous system and respiratory system
- ▶ It is marketed under trade names including Narcan®, Nalone® and Narcanti®

# Naloxone pharmacology

- ▶ The drug is derived from Thebaine and has an extremely high affinity for  $\mu$ -opioid receptors in the central nervous system
- ▶ Naloxone is a  $\mu$ -opioid receptor competitive antagonist, and its rapid blockade of those receptors often produces rapid onset of withdrawal symptoms

# Naloxone pharmacology

- ▶ Naloxone, administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC) has been used in opioid overdose management for over 40 years, with minimal adverse effects beyond the induction of opioid withdrawal symptoms
- ▶ It also carries no potential for abuse
- ▶ Recently, a first intranasal (IN) Naloxone spray has become commercially available in North America
- ▶ The drug acts after about two minutes, and its effects may last about 45 minutes



# Opioid overdose



# Signs of opioid overdose



Opioid overdose is identified by a combination of three signs and symptoms referred to as the “opioid overdose triad”. The symptoms of the triad are:

- ▶ Pinpoint pupils
- ▶ Unconsciousness
- ▶ Respiratory depression

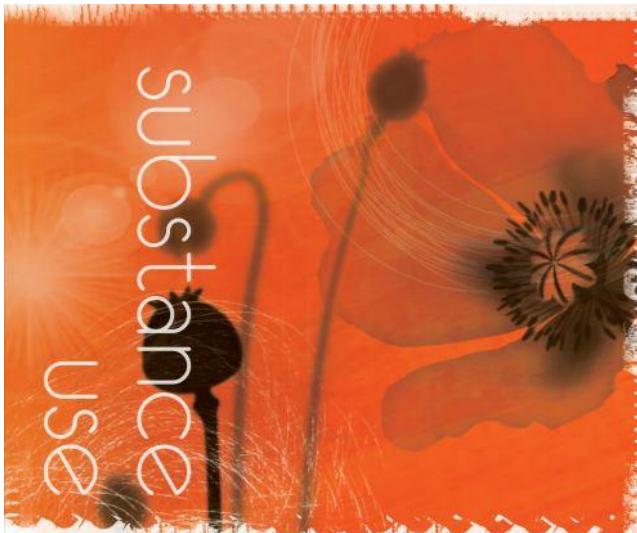
Treatment of overdose should be initiated if the person is not rousable and the respiratory rate is visibly slowed (i.e., less than 10 breaths per minute).

# Naloxone for opioid overdose

## World Drug Report 2014

- ▶ A number of countries have implemented community-based programmes that make Naloxone more readily available to appropriately trained opioid users, their peers and family members
- ▶ In the USA, there were 188 local opioid overdose prevention programmes distributing Naloxone in 2010
- ▶ Between 1996 and 2010, those programmes reported 10,171 opioid overdose reversals through use of Naloxone

# Naloxone for opioid overdose: WHO recommendation



- ▶ Deaths from opioid overdose are preventable by reducing opioid dependency, restricting supply & by reversing the effects of opioids after an overdose has occurred
- ▶ Naloxone is recommended by the WHO to immediately reverse the effects of an opioid overdose
- ▶ It is highly effective and safe and has no significant side effects and no potential for misuse

# Management of opioid overdose



# Management of opioid overdose

- ▶ Treatment should be initiated if the person is not rousable & respiratory rate < 10 bpm
- ▶ Primary focus should be to address respiration and oxygenation
- ▶ For the treatment (reversal) of opioid overdose, WHO recommends using Naloxone
- ▶ In the case of suspected opioid overdose, any respiratory arrest should be managed with assisted breathing and / or oxygen while waiting for Naloxone to be administered and take effect. Naloxone is fast-acting, and adequate respiration will typically resume within 3-7 minutes of intramuscular administration of Naloxone

# Dose of Naloxone to treat known or suspected opioid overdose

- ▶ An initial dose of 1 – 2 mg should be given to patients with Apnoea or in cardiovascular arrest. Signs of improvement - increase in respiratory rate and pupillary dilation – should occur within 2-3 minutes following IV administration
- ▶ If no response is seen during this time, a higher (1-2 mg) repeated doses should be given 2 -3 minute intervals while ventilation and oxygenation is maintained
- ▶ Higher doses of Naloxone may be required for Buprenorphine, methadone or fentanyl overdose

# Dose of Naloxone to treat known or suspected opioid overdose

- ▶ The primary goal of Naloxone is to restore adequate ventilation (above 12 respirations/minute) and oxygenation (above 92%) rather than full alertness
- ▶ Administering higher doses of Naloxone can precipitate opioid withdrawal and cause difficult to control agitation
- ▶ An acute lung injury (with hypoxia, rales and mouth frothing) can be seen in rapid overdose reversals in patients with marked hypoventilation.
- ▶ If intravenous administration is impracticable, Naloxone may be administered by the intramuscular or subcutaneous route

# Opioid overdose: Steps to take

- ▶ The ideal dose of Naloxone improves respiration without inducing opioid withdrawal
- ▶ If in doubt, error on the side of too large a dose
- ▶ If there is access to injecting equipment and adequate patient ventilation, smaller amounts can be given in repeated dose, until breathing rate > 10 bpm
- ▶ Naloxone's effect last for 30-90 min, which is usually sufficient to prevent death
- ▶ Naloxone may be administered as IV, IM, s/c or as a spray into the nose using an atomizer

# Opioid overdose: Steps to take

- ▶ If Naloxone not available, overdose can be treated with respiratory support
- ▶ Ideally, patient should then be transported to the hospital for observation for at least 1 hr.
- ▶ If patient refuses observation for an hr. & is able to walk and speak coherently, the risk of reverting to potentially fatal sedation when the Naloxone wears off is relatively small I (1 in 600)
- ▶ A medical professional/caregiver stay with patient for several hours, counsel them not to use more opioids and keep the individual active

# Opioid overdose: Steps to take

- ▶ In Overdoses of long-acting opioids, the duration of the sedation may outlast the effects of Naloxone
- ▶ The safest method of treating the overdose of a long-acting opioid is ventilation
- ▶ Patients can also be managed with repeated boluses of Naloxone or Naloxone infusions
- ▶ However, death can occur if there is an unnoticed interruption to the Naloxone infusion or if the patient wakes up and prematurely discharges him/herself from medical care. This is rare event

# Opioid overdose: Steps to take

- ▶ The aftermath of an OD should include discussion of ongoing drug or pain treatment after the effects of the Naloxone have worn off
- ▶ All people using opioids, should receive education on the factors ↑ the risk of overdose and on recognition of overdose symptoms, as well as on the need for respiratory support and medical assistance in cases of overdose
- ▶ In addition, negative health outcomes associated with non-fatal overdose, such as respiratory infections, may develop later
- ▶ Individuals should thus be advised to seek a basic health screening in the days following an overdose

# Where are we so far?



- ▶ What are the signs of opioid overdose?
- ▶ What is Naloxone and what are its properties?
- ▶ What are the key steps to take in case of opioid overdose?
- ▶ What is the most effective strategy to reduce the frequency of overdose?

1 x 10 Table

NALTREXONE HYDROCHLORIDE  
TABLETS USP 50 mg

NALTREXONE  
50 mg  
Naltrexone for  
relapse prevention

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INTAS

# Naltrexone in relapse prevention

Naltrexone is an opioid Antagonist used in Relapse management of

- ▶ Opioid dependence
- ▶ Alcohol dependence



It is available as

- ▶ Oral preparation
- ▶ Implants
- ▶ Long acting injections

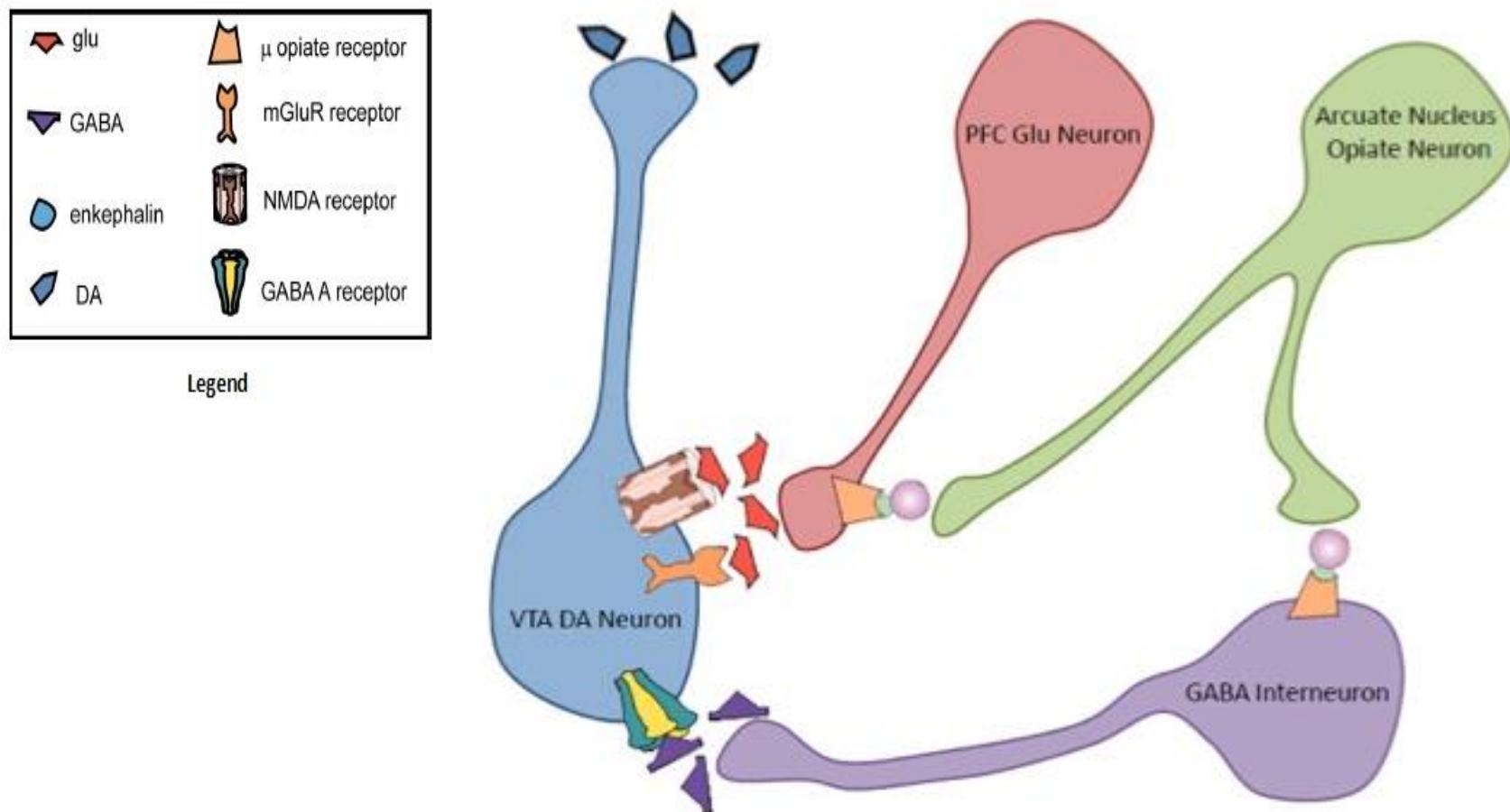
# Naltrexone for opioid relapse prevention

Naltrexone is an opioid antagonist which, when taken regularly, blocks a former opiate user from experiencing the effects of opiates. It can be helpful following detoxification in enabling a patient to maintain abstinence.

# Naltrexone

<b>What it does</b>	Naltrexone, and its active metabolite 6-β-Naltrexol, are competitive antagonists at $\mu$ - and $\kappa$ -opioid receptors, and also at $\delta$ -opioid receptors. This blockade of opioid receptors is the basis of its action in the management of opioid dependence – it reversibly blocks or attenuates the effects of opioids.
<b>Commence</b>	After at least 7-10 opioid free days. May be initiated 2-3days post buprenorphine detoxification in specialist inpatient setting. Patients are to have urine screen negative for opioid prior to commencing.
<b>Treatment time</b>	Initially, for period of 3 months. Extended treatment may be necessary as time to full recovery in opioid dependence is variable.
<b>Side effects</b>	Nausea, vomiting, abdominal pain, diarrhea, constipation, reduced appetite, increased thirst, chest pain, anxiety, sleep disorders, headache etc.
<b>Contra-indications</b>	Currently dependent on opioid, severe hepatic impairment, acute hepatitis, hepatic failure, severe renal impairment, lactation
<b>Cautions</b>	LFTS before and during treatment. Pregnancy (use only if benefit outweighs risk). Avoid concomitant use of Opioid but increased dose of opioid analgesic may be required for pain. Warn patients of risk of acute opioid intoxication if they over-dose in attempt to overcome opioid receptor blockade.

# Naltrexone: Mechanism of action



## Naltrexone: Mechanism of action

- ▶ Naltrexone, and its active metabolite 6- $\beta$ -naltrexol, are competitive antagonists at  $\mu$ - and  $\kappa$ -opioid receptors, and to a lesser extent at  $\delta$ -opioid receptors
- ▶ This blockade of opioid receptors is the basis behind its action in the management of opioid dependence – it reversibly blocks or attenuates the effects of opioids

# Naltrexone for opioid relapse prevention

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## Side effects

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- Acute opioid withdrawal precipitated (e.g., lethargy, aches, cramps, low energy)
- Depression, irritability
- Anxiety, nervousness
- Sleeping difficulties
- Skin rash
- Poor appetite
- Dizziness

## Precautions

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- If Naltrexone ceased and opioid use reinstated, reduced tolerance to opioids increases risk of overdose and death
- Precipitates withdrawals in opioid-dependent patients



# Naltrexone: Clinical properties

# Naltrexone for opioid relapse prevention

- ▶ Naltrexone will cause withdrawal symptoms in people who are physically dependent on narcotics
- ▶ Naltrexone treatment is started after an individual is no longer dependent on narcotics
- ▶ It is important for an individual to be fully withdrawn from opioids
- ▶ If Naltrexone is taken by individuals who are incompletely detoxified from opioids, it can precipitate a rapid and unpleasant withdrawal syndrome

# Naltrexone precipitated withdrawal

- ▶ Ingestion of Naltrexone in opioid dependent people will result in an acute block of opioid receptors and may precipitate a severe opioid withdrawal reaction if opioids are present
- ▶ Withdrawal can appear after 20 – 30 minutes after ingestion and may last up to 48 hrs
- ▶ Symptoms include confusion, agitation, hallucinations, sweating, tachycardia, abdominal pain and episodes of profuse vomiting and/or diarrhoea, which may result in significant fluid losses

# Starting Naltrexone

- ▶ Before starting Naltrexone or during the course of treatment it is important to conduct blood test and monitor liver enzymes. Naltrexone can be given unless liver enzymes are elevated  $> 5$  times upper limit of normal
- ▶ If uncertain whether the patient has used opioids, it may be necessary to conduct a Naloxone dose challenge before administering Naltrexone. If opioids have been used then severe and prolonged withdrawal symptoms will result if Naltrexone is administered



# Starting Naltrexone:

## Naloxone / Naltrexone challenge

Following a negative urine test for opioids, the patient is given:

- ▶ First Naltrexone dose of 6-12 mg orally or Naloxone 0.8 mg or higher
- ▶ If the patient does not experience any withdrawal symptoms after a few hours, a 50 mg tablet of Naltrexone can be given
- ▶ Patients can be commenced on Naltrexone within a few days of finishing a buprenorphine detoxification
- ▶ The usual maintenance dose is then 50 mg a day

# Starting Naltrexone after withdrawal from Methadone

- ▶ Patient must be methadone free for at least 7-10 days prior to commencing Naltrexone treatment, due to the long half-life of methadone
- ▶ Once a satisfactory Naloxone challenge is achieved, Naltrexone treatment can be commenced
- ▶ Patient may experience opioid withdrawal symptoms for several days after commencing Naltrexone treatment

## Starting Naltrexone after withdrawal from

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- ▶ A negative Naloxone challenge of withdrawal symptoms when a patient treated with buprenorphine is initiated on Naltrexone
- ▶ This is why Naloxone dose should be higher, usually 1.2 mg is sufficient to assure negative challenge
- ▶ This could be due the higher affinity of buprenorphine to the opioid receptor
- ▶ Therefore a drug screen to test for the presence of opioids should also be carried out
- ▶ Reduce buprenorphine dose to 400 micrograms per day
- ▶ Wait at least for 4-5 days after the last dose of buprenorphine before commencing Naltrexone therapy

# Maintenance dose of Naltrexone for opioid relapse prevention

- ▶ After Day 1 of starting treatment with Naltrexone, the maintenance dose is 50 mg/day
- ▶ The usual weekly dose is 350 mg/week
- ▶ The weekly dose may be divided up according to one of the following schedules:
  - 50 mg every day
  - 100 mg every other day
  - 50 mg/day during the week and 100 mg on Saturday
  - 100 mg on Monday, Wednesday & 150 mg on Friday
  - 150 mg every three days

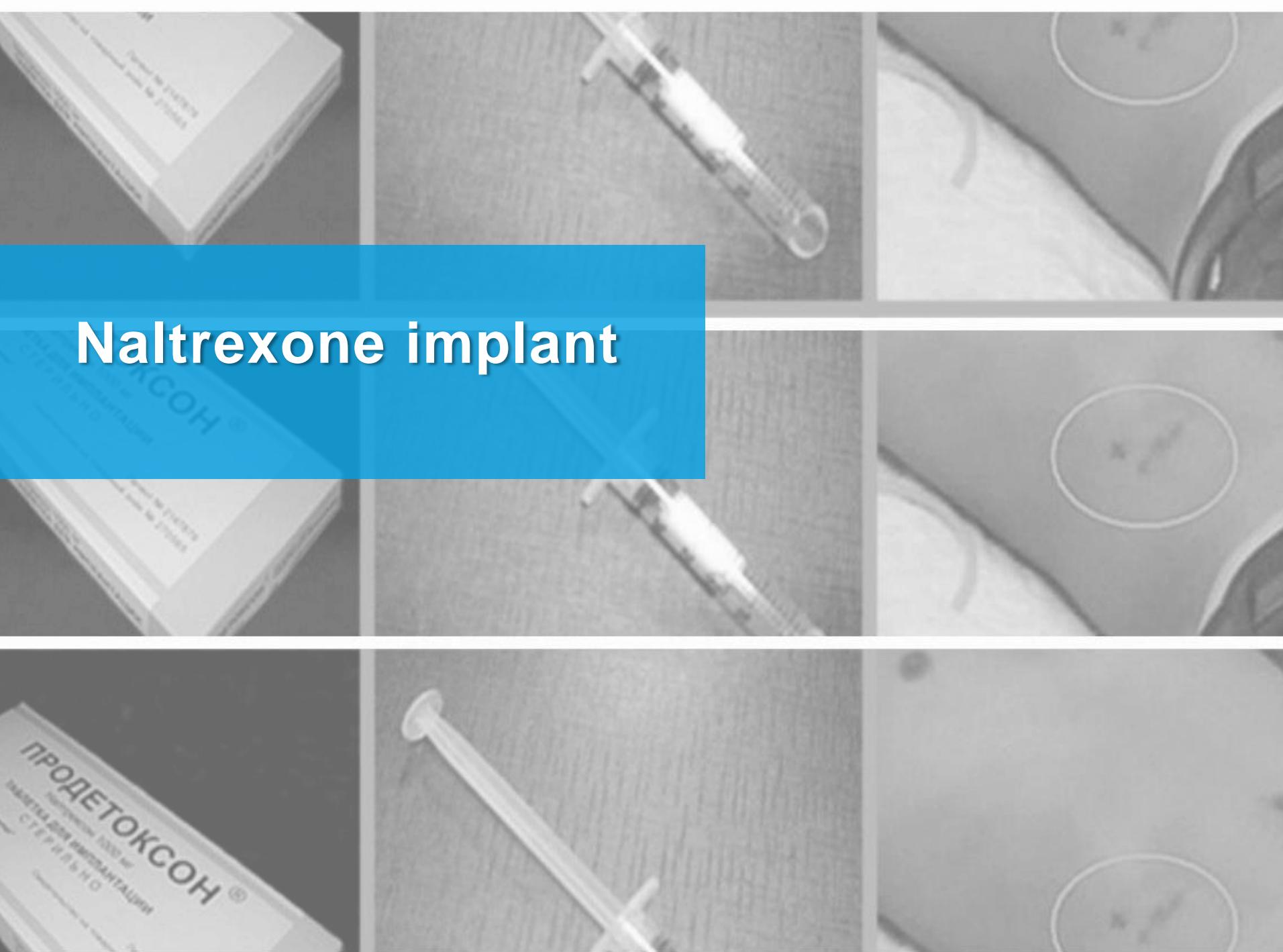
## Naltrexone for relapse management outcome

- ▶ The outcome of Naltrexone treatment is improved by a programme of supervision, which can involve carers to ensure compliance with the regimen
- ▶ Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care

# Naltrexone with psychosocial intervention

- ▶ Positive results when Naltrexone is combined with cognitive behavioural therapy and treatment with the Matrix Model
- ▶ Contingency management produces large increases in retention on Naltrexone
- ▶ Family therapy promotes successful treatment with Naltrexone
- ▶ Using legal pressure (individuals sentenced to treatment by courts) to mandate people to take Naltrexone can greatly increase retention on Naltrexone and outcome success

# Naltrexone implant



# Naltrexone implant

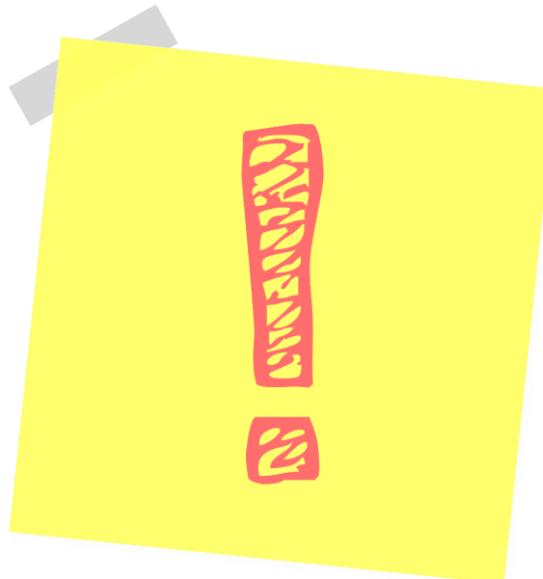
## “A Bulwark Against Ambivalence”

- ▶ To succeed with Naltrexone therapy, patients must consistently choose to take the next dose of medication rather than satisfy urges to re-experience effects of drugs
- ▶ However, Naltrexone does not reliably suppress drug craving, and many patients waver in their resolve to remain abstinent
- ▶ The rationale for extended-release Naltrexone formulations is to provide sustained, long-lasting protection against such ambivalence

# Naltrexone implant for opioid relapse prevention

- ▶ Naltrexone can be administered as a low-dose implant. These implants can remain effective for 30-60 days. They dissolve slowly and are usually put in under a local anaesthetic in the left iliac fossa
- ▶ This implant procedure has not been shown scientifically to be successful in "curing" the patient of their addiction, although it does provide a better solution than oral Naltrexone for medication compliance reasons

# Conclusion: Naltrexone for opioid dependence



- ▶ Naltrexone, nonselective opioid antagonist
- ▶ Induction issues
- ▶ Retention
- ▶ Depot preparation
- ▶ Better outcomes with specific therapies or legal interventions



# Naltrexone for alcohol relapse prevention

# Naltrexone for alcohol dependence: Pharmacology

- ▶ Alcohol produces some of its reinforcing properties by releasing the body's own **opiate-like** substance (endorphin)
- ▶ Naltrexone can block endorphin effects
- ▶ A person with alcohol dependence, who is maintained on Naltrexone will not experience endorphin-mediated alcohol-induced euphoria
- ▶ Maintenance on Naltrexone will reduce alcohol use

# Naltrexone in alcohol dependence: Pharmacology

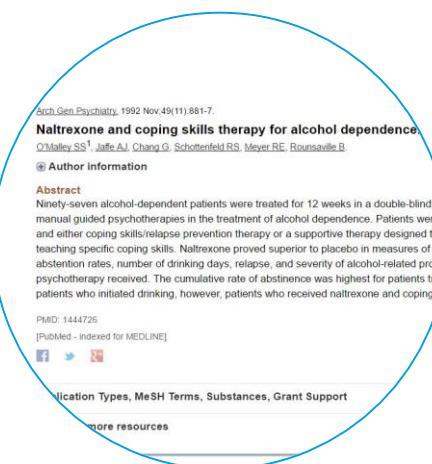
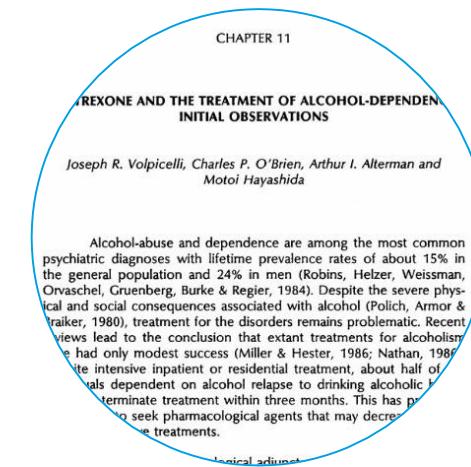
- ▶ The  $\mu$ -opioid receptor modulates dopaminergic cell firing in the ventral tegmental area and therefore blocking the  $\mu$ -opioid receptor with Naltrexone prevents any increase in dopaminergic activity
- ▶ Consequently, Naltrexone reduces alcohol's rewarding effects and also motivation to drink or 'craving'

# Naltrexone for alcoholism evidence

Two landmark studies documented that Naltrexone can be an effective treatment for treating alcoholics:

- ▶ **“Naltrexone in the Treatment of Alcohol Dependence”** by Volpicelli, W., Alterman, A., Hayashida, M., O’Brien, C.
- ▶ **“Naltrexone and Coping Skills Therapy for Alcohol Dependence”** by O’Malley, S., Jaffe, A., Chang, G., Schottenfeld, R., Meyer, R., Rounsville, B.

O’Malley et al. demonstrated that if Naltrexone is used with coping skills therapy, relapses are reduced and the severity of the relapse is reduced.



# Naltrexone in alcohol dependence: Evidence

“There have been several meta-analyses and systematic reviews which broadly have the same conclusion that oral Naltrexone significantly reduces return to heavy drinking, probably by reducing ‘lapse to relapse’, but does not necessarily improve cumulative or continuous abstinence rates.”

*Lingford-Hughes AR, 2012*

## Naltrexone for relapse prevention: Summary

- ▶ Opioid antagonist, Naltrexone can be beneficial in relapse management of both opioid and alcohol dependence
- ▶ The compliance with Naltrexone treatment is improved by a programme of supervision, which can involve carers
- ▶ It is most effective when delivered as part of a programme of psychosocial intervention and supportive care



## Let's think!



Discuss with your colleagues:

- ▶ Who are the best candidates for treatment with Naltrexone for relapse prevention?

A photograph of a woman with blonde hair and glasses, looking thoughtfully at a wall covered in numerous large blue question marks. She is wearing a white shirt. The background is a light-colored wall.

Questions

# Wrap-up

- 
- ▶ Why and how use Naloxone for opioid overdose?
  - ▶ How to use of Naltrexone for relapse prevention?
  - ▶ What are the challenges and limitations of Naltrexone treatment?

# Post-assessment



Thank you for your time!  
End of module 2

