

## CATEGORY III – COMMUNICATION, TREATMENT & PREVENTION INTERVENTIONS PHARMACOLOGY OF ADDICTIONS

### 1.0 Introduction

Medications are used in the treatment of drug, alcohol and nicotine dependence to manage withdrawal during detoxification, stabilisation and substitution as well as for relapse prevention, in addition to the symptomatic management or treatment of co-occurring conditions. The pharmacological option should always be part of psychosocial interventions in the context of a care plan.

#### LEARNING OUTCOMES

Medical students will gain knowledge in

1. Understanding the pharmacological basis of medications used to manage dependence.
2. Recognising how pharmacological agents are used to treat drug and alcohol dependence.
3. Understanding that different medications are needed in the different phases of the addiction cycle.
4. Describing the medications commonly prescribed in opioid and alcohol dependence.

### 2.0 Context

The substance dependence syndrome consists of both physical and psychological components:

**Physical dependence:** Physical dependence is a condition in which the body has adjusted to the presence of a drug, resulting in symptoms of withdrawal when its use stops. In extreme cases, the effect of rapid withdrawal can be life threatening because the body has become dependent on the drug so that it interferes with normal body processes.

**Psychological dependence:** This is characterized by emotional and mental preoccupation with the drug's effects and by a persistent craving for it. The symptoms displayed are not physical symptoms.

The pharmacological interventions discussed here are used to treat the physical dependence and emergencies as a result of substance misuse as follows:

- Emergencies e.g. overdose, seizures, dehydration, hypothermia/hyperthermia and acute confusional state including delirium tremens.
- Detoxification and withdrawal syndromes. e.g. diazepam, chlorthalidone, lofexidine, methadone, buprenorphine.
- Substitution e.g. methadone, buprenorphine, nicotine replacement therapy, bupropion.
- Relapse prevention e.g. naltrexone, acamprosate, disulfiram.
- Treatment of vitamin deficiency.
- Co-morbid psychiatric disorders, e.g. depression, anxiety, psychosis.

- Co-morbid physical disorders e.g. HIV, hepatitis C, diabetes, hypertension.

### 3.0 Special issues

- People who misuse drugs, alcohol and tobacco should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals.
- If service users do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines on consent for examination or treatment.
- Special groups will need their treatment regimes managed appropriately and safely with greater monitoring and supervision. Account MUST be taken of the age of the patient when prescribing. Lower doses need to be considered for young and older people as well as those who are physically ill.
- Psychosocial interventions must be part of the treatment package.

### 4.0 Assessment

Medication as part of treatment can play an important role in the alleviation of withdrawal symptoms (detoxification);- in substitute prescribing to treat dependence; and as part of relapse prevention. A full and detailed assessment is required before commencing any pharmacological interventions and this should be corroborated by biological screening such as saliva, urine or blood to ensure the presence of the substance is identified or observations of objective signs of withdrawal are being elicited.

### 5.0 Treatments

#### 5.1 Types of medication

Medications may be antagonists at the post-synaptic receptor; that is, they block synaptic transmission at the receptor level. Alternatively, they may stimulate the receptor; full agonists have strong or 100% action on the receptor, whereas partial agonists induce less effect i.e.<100% even when all receptors are fully occupied. Partial agonists will act like an antagonist if there is a full agonist present.

#### 5.2 Drugs used in opioid dependence

##### 1. Methadone

It is a long-acting opioid used as a substitute. It has a half-life of approximately 24 hours so the majority of patients

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can be maintained on once daily dosing. It is widely used as a heroin substitute in maintenance treatment as well as detoxification when it can be reduced slowly over a period of several weeks. As a full opioid agonist it has similar effects as heroin, but less euphoria due to its slow onset of action. It has side effects such as respiratory depression and lethargy at high dosages (especially dangerous when misused with alcohol or benzodiazepines), constipation, reduced saliva (contributing to poor dental hygiene).

### 2. Buprenorphine

This is a partial agonist at the opioid receptor. It has a long half-life (>24 hours) and is usually dispensed on a once daily basis, sublingually. It is increasingly being prescribed as an alternative substitute to methadone in maintenance and detoxification treatment. It produces less euphoria, sedation and positive reinforcement than full agonists as well as causing less respiratory depression if taken alone. Buprenorphine has a high affinity for opioid receptors. As a result it prevents heroin and other opioids from binding to the receptors and thus attenuates their effects. There may be a particular subset of individuals who might benefit more than others from buprenorphine. The reverse is also true, with methadone suggested as more useful in those with high levels of dependency. Buprenorphine should not be used simply instead of methadone but as a further treatment option that seeks to increase access to services for a greater number, and a more diverse, range of patients.

### 3. Opioid receptor antagonists

These medications block the effects of heroin or other opioid agonists. Naltrexone is prescribed when a patient has achieved abstinence. An oral dose is taken daily and acts as a safety net, preventing the euphoria and reinforcing effects of opioid agonists. Naloxone is short-acting opioid antagonist that is administered parentally in emergency situations such as in the treatment of an acute opioid overdose. Take-home packs of naloxone are distributed to individuals at risk of opioid overdose (or their partners, carers) by drug services in order to reduce overdose deaths.

### 4. Lofexidine

This is used in detoxification from opioids because it improves many of the symptoms of opioid withdrawal (via inhibition of noradrenergic transmission). Lofexidine is an adjunctive medication prescribed for symptom management and are therefore not in the same category as substitutes such as methadone or buprenorphine. Its major side effect is hypotension.

### 5.3 Adjunctive medication

When prescribing adjunctive medications, such as anti-inflammatory, antiemetics, anti-depressants, and ie anxiolytics and hypnotics during opioid detoxification, healthcare professionals should:

- only use them when clinically indicated, such as when agitation, nausea, insomnia, pain and/or diarrhoea are present
- use the minimum effective dosage and number of drugs

needed to manage symptoms

- be alert to the risks of adjunctive medications (particularly benzodiazepines), as well as interactions between them and with the opioid agonist (NICE, 2007).

### 5.4 Pain management for substance misusers

Palliative care and anaesthesia and surgery factsheets cover these matters.

### 5.5 Drugs used in alcohol dependence

**1. Benzodiazepines-** (e.g. chlordiazepoxide or diazepam)-these are effective at reducing symptoms of withdrawal as well as reducing the rate of occurrence of delirium tremens and seizures. They are used in the short-term (7-12 days) detoxification process but are often misused and can lead to dependence. Side effects include sedation and respiratory depression which is especially dangerous if a patient continues to drink or is also using opioids.

**2. Disulfiram-** is used once a patient is abstinent from alcohol. It inhibits aldehyde dehydrogenase, a key enzyme involved in the metabolism of alcohol. This leads to an accumulation of acetaldehyde after drinking alcohol, which causes unpleasant effects such as nausea and vomiting, headache, flushing, palpitations and hypotension. The consumption of large amounts of alcohol on top of disulfiram can lead to collapse and death. Fear of these aversive reactions is an important aspect of its efficacy.

**3. Acamprosate-** is usually started once a patient is abstinent from alcohol and some evidence shows it can improve rates of abstinence. The pharmacology underlying its clinical efficacy is still unclear but it is hypothesised that it works by reducing craving and the urge to drink.

**4. Naltrexone-** has also been shown to be better than placebo at reducing risk of a lapse becoming a full blown relapse.

### 5.6 Drugs used in nicotine dependence

Medication can be used as substitutes, e.g. nicotine gum or patches, or to help reduce and stop smoking, e.g. bupropion or varenicline. The evidence base is becoming established as to their effectiveness. There is currently a lively debate about the use of e-cigarettes as a means to reduce/stop the user's nicotine dependence levels.

### 5.7 Drugs used in stimulant dependence

No pharmacological agents have been shown to be effective as substitute agents, in the withdrawal phase or in maintaining abstinence from stimulant dependence.

### 5.8 Drugs used in cannabis dependence

No pharmacological agents have been shown to be effective as substitute agents, but studies have shown that Motivational Enhanced Therapy (MET), Cognitive Behavioural Therapy (CBT) and Contingency Management (CM) have shown benefits in changing behaviour, using behavioural techniques.

### 5.9 Other medications

Substance misusers do present to services with a range of other physical and mental health problems and may require medication for the treatment of other conditions:

- Vitamin deficiency, e.g. Vitamin K and thiamine for alcohol users
- Mental health conditions
- Physical health conditions

### 5.10 Special populations

**Young people:** rarely present with dependence syndrome and therefore rarely require substitute medication. Most pharmacological preparations are not licensed for adolescents and the initiation of pharmacological treatment for young people, should generally be offered by specialist addiction psychiatrists or specially qualified doctors in primary care (Crome, 2009). Sometimes young people will require supportive symptomatic medication. Non-pharmacological responses such as brief interventions, motivational interviewing, cognitive and family therapies do lead to positive outcomes.

**Older people:** consideration needs to be given when prescribing for older people as pharmacokinetic and pharmacodynamic considerations mean that there will need to be a dosage reduction and careful monitoring (Royal College of Psychiatrists, 2018). The treatment of substance misuse in older people also needs to take account of co-morbid physical problems such as neuropsychiatric disorders and hepatic complications (e.g. alcoholic liver disease and hepatitis C), and potential contraindications with other medications as well as respiratory complications such as chronic obstructive pulmonary disease (COPD).

### 6.0 Referral/networks/services

Pharmacological treatment is one part of an integrated treatment plan in which a range of professional staff will be involved in providing different components of the intervention package. For example, initiation of opioid substitution therapy (methadone or buprenorphine) involves titration of the dose (slowly increasing the dose over a number of days until the patient's withdrawal symptoms are controlled) to avoid overdose or over-sedation. Additionally, consumption is supervised (at the drugs service or pharmacy) daily, for several months, in order to reduce diversion and accidental poisoning. Hence, it is crucial to ensure a co-ordinated approach to prescribing for those with substance dependence to avoid patients seeking drugs from a range of different GPs, hospitals or doctors. It is also necessary to involve a pharmacist to consult and discuss pharmacological issues e.g. choice of treatment, initiation of medication, dosing regime, interactions with other medications.

### 7.0 References and useful resources

- Canidate, S.S., Carnaby, G.D., Cook, C.L., & Cook, R.L. (2017). A systematic review of naltrexone for attenuating alcohol consumption in women with alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, Mar; 41(3), 466-472. doi: 10.1111/acer.13313.
- Crome I.B (2009) Substance misuse and addiction in adolescence – issues for the practising GP in *Care of Children and young people for the MRCGP* (ed K.Mohanna). London. Royal College of General Practitioners.
- Department of Health and the devolved administrations.(2017) Drug Misuse and Dependence: UK Guidelines on Clinical Management. London: Department of Health, the Scottish Government, Welsh Assembly Government and Northern Ireland Executive  
<https://www.gov.uk/government/publications/drug-misuse-and-dependence-uk-guidelines-on-clinical-management>
- EMCDDA ( 2016) Preventing opioid overdose deaths with take-home naloxone [http://www.emcdda.europa.eu/publications/insights/take-home-naloxone\\_en](http://www.emcdda.europa.eu/publications/insights/take-home-naloxone_en)
- Luty, J., (2015) Drug and alcohol addiction: new pharmacotherapies. *B J Psych Advances* (21), 33-41 doi: 10.1192/apt.bp.114.013367
- NICE (2007) *Drug Misuse: naltrexone for the management of opioid dependence (NICE technology appraisal, TA115)* <http://www.nice.org.uk/guidance/TA115>
- NICE (2007) *Drug misuse: methadone and buprenorphine maintenance (NICE technology appraisal, TA114)* <http://www.nice.org.uk/guidance/TA114>
- NICE (2007) *Drug misuse: opioid detoxification (NICE clinical guideline, CG52)* <http://www.nice.org.uk/CG52>
- NICE (2007) *Drug misuse: psychosocial interventions (NICE clinical guideline, CG51)* <http://www.nice.org.uk/CG51>
- NICE (2010) *Alcohol-use disorders: physical complications (NICE clinical guideline, CG100)* <http://guidance.nice.org.uk/CG100>
- NICE (2011) *Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (NICE clinical guideline, CG115)* <http://guidance.nice.org.uk/CG115>
- Rang H. J; Ritter J.M; Flower R.J and Henderson G. (2016) Rang and Dale's pharmacology (8th edn) Edinburgh : Churchill Livingstone
- Royal College of Psychiatrists (2018) Our Invisible Addicts (2nd edition) <https://www.rcpsych.ac.uk/usefulresources/publications/collegereports/cr/cr211.aspx>
- Society for the Study of Addiction: Naloxone Conference 2017 Presentations <https://www.addiction-ssa.org/knowledge-hub/topic/test-topic>
- Tay J (2016) Naloxone training in General Practice <http://www.rcgp.org.uk/clinical-and-research/resources/bright-ideas/naloxone-training-in-general-practice.aspx>

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**Table 1: mechanism of action of medicatons used in the treatment of substance misuse**

	Antagonist	Full agonist	Partial agonist	Other targets
Opioids (e.g. heroin)	Naltrexone Naloxone	Methadone	Buprenorphine	Lofexidine
Alcohol	-	Benzodiazepines	Benzodiazepines	Acamprosate Disulfiram Naltrexone
Nicotine	Mecamylamine	Nicotine gum, patch, lozenge, or inhalant	Varenicline	Bupropion
Stimulants (e.g. cocaine)	-	Amphetamine, methylphenidate	-	Vaccine Aripiprazole

**Table 2: Medications used in the treatment of substance misuse**

Drug type	Clinical indication	Evidence source
<b>Naltrexone</b>	Recommended as a treatment option for people who have been opioid dependent but who have stopped using opioids, and who are highly motivated to stay free from the drugs in an abstinence programme. To avoid precipitated withdrawal, it is generally recommended that naltrexone be initiated 3-5 days after the last dose of buprenorphine.	<a href="http://www.nice.org.uk/TA115">http://www.nice.org.uk/TA115</a>
<b>Methadone and buprenorphine</b>	For the treatment of opiate dependence and can be given as a tablet or a liquid are recommended as treatment options.	<a href="http://www.nice.org.uk/TA114">http://www.nice.org.uk/TA114</a>
<b>Acamprosate calcium</b>	Acamprosate is used in alcohol dependence. It works by reducing the desire or craving to drink alcohol. It is only given to people who have successfully stopped drinking.	<a href="http://www.nice.org.uk/TA115">http://www.nice.org.uk/TA115</a>
<b>Chlordiazpoxide</b>	Recommended for alcohol detoxification.	<a href="http://guidance.nice.org.uk/CG100">http://guidance.nice.org.uk/CG100</a> <a href="http://www.nice.org.uk/TA115">http://www.nice.org.uk/TA115</a>
<b>Lofexidine</b>	An alternative choice to methadone or buprenorphine, often used in patients who are lower doses of opioid drugs.	<a href="http://www.nice.org.uk/CG52">http://www.nice.org.uk/CG52</a>
<b>Diazepam</b>	Diazepam is used to help reduce alcohol withdrawal symptoms. It relieves anxiety and tension and aids sleep. Diazepam can also prevent fits.	

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**Table 3: Suggested protocol for titrated fixed-dose chlordiazepoxide for treatment of alcohol withdrawal (Ghodse et al., 1998; South West London and St George’s Mental Health NHS Trust, 2010) as cited in NICE 2011**

Typical recent daily consumption	15-20 units		30-49 units		50-60 units
Severity of alcohol dependence	Moderate **SADQ score 15-25		Severe SADQ score 30-40		Very severe SADQ score 40-60
Starting dose of chlordiazepoxide	15-25mgs qds		30-40mgs qds		50mg qds
Day 1 (starting dose)	15 qds	25 qds	30 qds	40 qds*	50 qds*
Day 2	10 qds	20 qds	25 qds	35 qds	45 qds
Day 3	10 tds	15 qds	20 qds	30 qds	40 qds
Day 4	5 tds	10 qds	15 qds	25 qds	35 qds
Day 5	5 bd	10 tds	10 qds	20 qds	30 qds
Day 6	5 nocte	5 tds	10 tds	15 qds	25 qds
Day 7		5 bd	5 tds	10 qds	20 qds
Day 8		5 nocte	5 bd	10 tds	10 qds
Day 9			5 nocte	5 tds	10 qds
Day 10				5 bd	10tds
Day 11				5 nocte	5 tds
Day 12					5 bd
Day 13					5 nocte

\*\*SADQ is a short, self-administered, 20-item questionnaire designed by the World Health Organisation to measure severity of dependence on alcohol.

**Note.** \* Doses of chlordiazepoxide in excess of 30 mg q.d.s. should only be prescribed in cases where severe withdrawal symptoms are expected and the patient’s response to the treatment should always be regularly and closely monitored. Doses in excess of 40 mg q.d.s.

should only be prescribed where there is clear evidence of very severe alcohol dependence.

Such doses are rarely necessary in women and never in the elderly or where there is severe liver impairment.

**Qds** = Quater die sumendus: four times a day

**Tds** = ter die sumendum: three times a day

**Bd** = bis die: twice a day

**Nocte**: at night

### Table 4: Regime for detoxification using diazepam

**Withdrawal should be gradual** (dose tapering, such as 5–10% reduction every 1–2 weeks, or an eighth of the dose fortnightly, with a slower reduction at lower doses), and titrated according to the severity of withdrawal symptoms.

This may take 3–4 months to a year or longer. Some people may be able to withdraw in less time.

### Approximate Equivalent Doses of Benzodiazepines

Diazepam 5mg is equivalent to	15mg chlordiazepoxide
	0.5mg to 1mg loprazolam
	0.5mg lorazepam
	0.5 to 1mg lormetazepam
	5mg nitrazepam
	15mg oxazepam
	10mg temazepam