Psychiatry

Chapter 3
Pharmacology

3. Pharmacology

Objectives

» Understand the different DEA schedules of drugs and provide examples of drugs in each schedule. Outline the signs and symptoms of intoxication and withdrawal from several depressants, stimulants, and hallucinogens.

» Describe the signs, symptoms, and treatment of pharmacological emergencies involving psychiatric medications including serotonin syndrome, neuroleptic malignant syndrome, and hypertensive crisis.

» Define the mechanism of action, uses, adverse effects, and give examples of the various psychiatric medication classes (including stimulants, antipsychotics, and antidepressants).

» Describe four medications used to treat opioid or alcohol use disorder.

Drugs, substances, and certain chemicals used to make drugs are classified into different categories (called schedules) in the United States by the Drug Enforcement Agency (DEA). The schedules are as follows:

- Schedule I: Substances with no currently accepted medical use and a high potential for abuse. Examples include heroin, marijuana, and lysergic acid diethylamide (LSD).
- Schedule II: Substances with a high potential abuse leading to severe psychological or physical dependence. Examples include cocaine, methamphetamine, methadone, and hydromorphone.
- Schedule III: Substances with a moderate to low potential for physical and psychological dependence. Examples include ketamine, anabolic steroids, testosterone.
- Schedule IV: Substances with a low potential for abuse and low risk of dependence. Examples include alprazolam, diazepam, lorazepam, and zolpidem.
- Schedule V: Substances with lower potential for abuse than schedule IV. Examples include pregabalin, Lomotil (diphenoxylate and atropine), and robitussin (dextromethorphan and guaifenesin).

Substances may be reclassified into new schedules if research provides evidence of the substance's medical benefit, or if a substance is found to have more addictive properties than it was previously believed to have.

a. Psychoactive Substances, Intoxication and Withdrawal

Psychoactive substances are any substances that affect the mind. When taken in excess these substances cause intoxication; when taken in excess for a period of time and then not taken, these substances often cause withdrawal. Symptoms of intoxication and withdrawal vary depending on the substance and are helpful in recognizing signs and symptoms of intoxication or withdrawal in order to provide appropriate treatment. Several commonly abused substances and their intoxication and withdrawal findings are presented in the table below.

Class	Drug	Intoxication Findings	Withdrawal Findings
Depressants	Alcohol	Slurred speech, ataxia, emotional lability. With higher amounts black-outs and coma occur. Testing: elevated serum gamma-glutamyl transferase (GGT). Alcohol-induced liver damage is indicated by elevated serum AST and ALT and an AST/ALT ratio over 2. *For metabolism of ethanol, see biochemistry notes.	Symptom progression by hours since last drink: 3-12: anxiety, insomnia, nausea, abdominal pain, tremors. 8-48: seizures 12-48: hallucinations (usually visual) 48-96: global confusion, autonomic hyperactivity (leading to possible cardiovascular collapse), diaphoresis, hallucinations (altogether called **delirium tremens**). Treatment: thiamine, magnesium, benzodiazepines.
	Barbiturates	Respiratory depression. Narrow therapeutic index.	Onset 2-4 days after last dose. Anxiety, restlessness, insomnia, dizziness. Severe symptoms include hyperthermia and cardiovascular collapse.
	Benzodiazepines	Dizziness, confusion, drowsiness, blurred vision, hypotension, ataxia, respiratory depression (less than barbiturates). Treatment: flumazenil (with caution as it can precipitate withdrawal seizures).	Anxiety, irritability, confusion, seizures, sleep disorders. Severe symptoms include delirium, psychosis.
	Opioids	Altered mental status, confusion, delirium, respiratory and CNS depression, pupillary constriction (miosis), seizures, decreased gag reflex. Treatment: naloxone. Most common cause of drug overdose deaths.	Agitation, anxiety, muscle cramps, insomnia, rhinorrhea, lacrimation, dilated pupils (mydriasis), piloerection, abdominal cramping and diarrhea, nausea/vomiting. Generally start within 12-30 hours of last use. Treatment: methadone, buprenorphine.

Class	Drug	Intoxication Findings	Withdrawal Findings
	Inhalants	Euphoria, dizziness, disorientation, ataxia, diplopia, stupor or coma. Most commonly abused by teenagers.	Irritability, dysphoria, sleep disturbance, appetite and mood changes, headache.
Stimulants	Amphetamines	Euphoria, grandiosity, decreased need for sleep, agitation, paranoia, dyskinesias, disorientation, headache, chest pain and palpitations, dry mouth, diaphoresis, GI upset, mydriasis. Can be injected, inhaled, snorted, or ingested orally (skin findings consistent with IV use). Dental decay and caries common from vasoconstrictive effects and poor dental hygiene.Methamphetamine-associated cardiomyopathy is a growing cause of heart failure (systolic dysfunction and LV dilation).	Somewhat vague symptoms of fatigue, depression, increased appetite, irritability, anxiety, and sometimes psychosis.
	Caffeine	Dizziness, diarrhea, insomnia, headache, irritability, tremor.	Headache, fatigue, irritability, difficulty concentrating, nausea, vomiting, muscle pain/stiffness.
	Cocaine	Euphoria, restlessness, over-excitement, muscle tremors, mydriasis, tachycardia and hypertension, hallucinations, paranoia, angina and MI. Can be snorted, injected, or smoked (snorting can lead to nasal septum perforation). Treatment: benzodiazepines. Pure beta blockers can result in blocked B2 vasodilation and resulting alpha stimulation-->increased blood pressure and possible worsening coronary vasoconstriction).	Agitation, restlessness, depression, fatigue, increased appetite, vivid and unpleasant dreams.

Class	Drug	Intoxication Findings	Withdrawal Findings
Stimulants	Nicotine	Restlessness, decreased appetite, short term increased blood pressure.	Difficulty concentrating, headache, insomnia, irritability, depression, increased appetite. Treatment: nicotine replacement therapy, bupropion, varenicline.
Hallucinogens	Lysergic Acid Diethylamide	Intensification of moods (either positive or negative), mood lability, changes in consciousness, visual illusions, synesthesia, disorientation, persistent psychosis (up to years) is possible but rare. Effects peak around 2-4 hours. Treatment: supportive; if severely agitated, benzodiazepines can be used.	Withdrawal symptoms are uncommon. Some people may experience cravings, depressed mood, fatigue, insomnia, and flashbacks of hallucinations (rare). Treatment: supportive; clonidine can decrease flashback severity.
	Marijuana	Relaxation, euphoria, sleepiness, decreased short-term memory, dry mouth, red eyes (conjunctival injection), impaired perception and motor skills, panic, paranoia, acute psychosis, increased appetite. Cannabinoid hyperemesis syndrome may occur after frequent, long-term use and results in uncontrollable vomiting, nausea, cramping, and abdominal pain. Symptoms are often temporarily relieved with a hot shower and cease after about 2 days if marijuana use is stopped.	Irritability, depression, insomnia, anxiety, flu-like symptoms, decreased appetite.

Class	Drug	Intoxication Findings	Withdrawal Findings
Hallucinogens	MDMA	Euphoria, loss of inhibition, increased feelings of closeness/empathy, sensuality, anxiety, hyperactivity, increased thirst, bruxism, distortion of time, hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome. Treatment: supportive; treat hyperthermia with dantrolene, serotonin syndrome with cyproheptadine or benzodiazepines.	Fatigue, depression, anxiety, irritability, sleep disturbances, difficulty concentrating.
	Phencyclidine (PCP)	Hallucinations, agitation, altered consciousness, catatonia, coma, convulsions, hypertension, tachycardia, horizontal nystagmus (although can be vertical or rotatory), psychosis, delirium, seizures.	Depression, fasciculations, cravings, agitation, anxiety, irritability, headache, muscle breakdown, hyperthermia. Develop within about 8 hours of abstinence.

b. Central Nervous System Stimulants

Examples: Methylphenidate, atomoxetine, dextroamphetamine, methamphetamine, lisdexamfetamine, modafinil, varenicline

Uses: ADHD, narcolepsy.

Action: Increase catecholamine levels in the synaptic cleft.

Side Effects: Anxiety, agitation, tachycardia, hypertension, nervousness, and weight loss.

c. Typical antipsychotics

Examples: Chlorpromazine, prochlorperazine, thioridazine, fluphenazine, haloperidol, pimozide, thiothixene

Uses: Schizophrenia (primarily positive symptoms), psychosis, bipolar disorder, Tourette syndrome, Huntington disease, OCD.

Action: Competitive blockade of Dopamine D2 receptors. This class is lipid soluble and therefore is stored in adipose tissues; as a result, these medications are slowly removed from the body.

» Low potency (chlorpromazine, prochlorperazine, thioridazine): more anticholinergic, antihistamine, anti-α_1 effects.

» High Potency (fluphenazine, haloperidol, pimozide, thiothixene): more neurologic side effects (extrapyramidal effects).

Side Effects: This class is used infrequently due to debilitating side effects. Side effects include: galactorrhea, oligomenorrhea, gynecomastia (from dopamine antagonism leading to hyperprolactinemia), dyslipidemia, weight gain, hyperglycemia, dry mouth, constipation, sedation, orthostatic hypotension, QT prolongation. Chlorpromazine can cause corneal deposits. Thioridazine can cause retinal deposits.

Extrapyramidal Symptoms (EPS): Drug-induced movement disorders that progress in severity over time. If these develop, a dose reduction or medication change may be necessary.

Hours to days: acute dystonia (muscle spasms, stiffness, oculogyric crisis). Treatment is with benztropine or diphenhydramine.

Days to months: Akathisia (motor restlessness, treat with beta-blockers, benztropine, benzodiazepines). Parkinsonism (bradykinesia, treat with benztropine or amantadine).

Months to years: Tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs). Treat with atypical antipsychotics, valbenazine, deutetrabenazine.

Neuroleptic Malignant Syndrome: A potentially fatal reaction to antipsychotic (neuroleptic) drugs characterized by muscle rigidity, fever, altered mental status, stupor, labile blood pressure, increased creatinine kinase, and myoglobinemia. Treatment: discontinue the neuroleptic agent and treat with dantrolene or bromocriptine (dopamine agonist).

d. Atypical Antipsychotics

Examples: Aripiprazole, clozapine, olanzapine, quetiapine, paliperidone, risperidone, ziprasidone.
Uses: Schizophrenia (positive and negative symptoms), bipolar, OCD, anxiety, depression, mania, Tourette syndrome. Clozapine is effective for treatment-resistant schizophrenia.
Action: Primarily act as D2 and 5-HT2 receptor antagonists with varied effects on H1 receptors; complete mechanisms of actions are not fully understood. Aripiprazole is a partial D2 agonist.
Side Effects: This class is more frequently used than the typical antipsychotics due to fewer severe side effects (EPS, anticholinergic effects). All medications in this class may cause prolonged QT interval. Olanzapine (and others with -apine suffix) are notorious for causing weight gain and metabolic syndrome. Risperidone may cause hyperprolactinemia. Perhaps the most serious: clozapine may cause agranulocytosis (frequent laboratory monitoring required).

e. Lithium

Uses: Bipolar disorder (mood stabilizer).
Action: Exact mechanism is not known. Narrow therapeutic index requires frequent laboratory monitoring of serum levels. Renally excreted (reabsorbed at PCT by Na+ channels).
Side Effects: Hypothyroidism, nephrogenic diabetes insipidus, tremor. Mild teratogen (may cause Ebstein anomaly if taken by pregnant woman). Due to renal excretion, co-administration of medications affecting renal clearance can result in lithium toxicity; examples include thiazides, NSAIDs, ACE inhibitors.

f. Buspirone

Uses: Generalized anxiety disorder. Commonly used in addition to SSRIs or SNRIs rather than as first-line treatment. Requires 1-2 weeks to begin to show effects.
Action: 5-HT1A Agonist
Side Effects: Few side effects. Overdose presents with miosis, nausea/vomiting, dizziness, drowsiness, decreased consciousness.

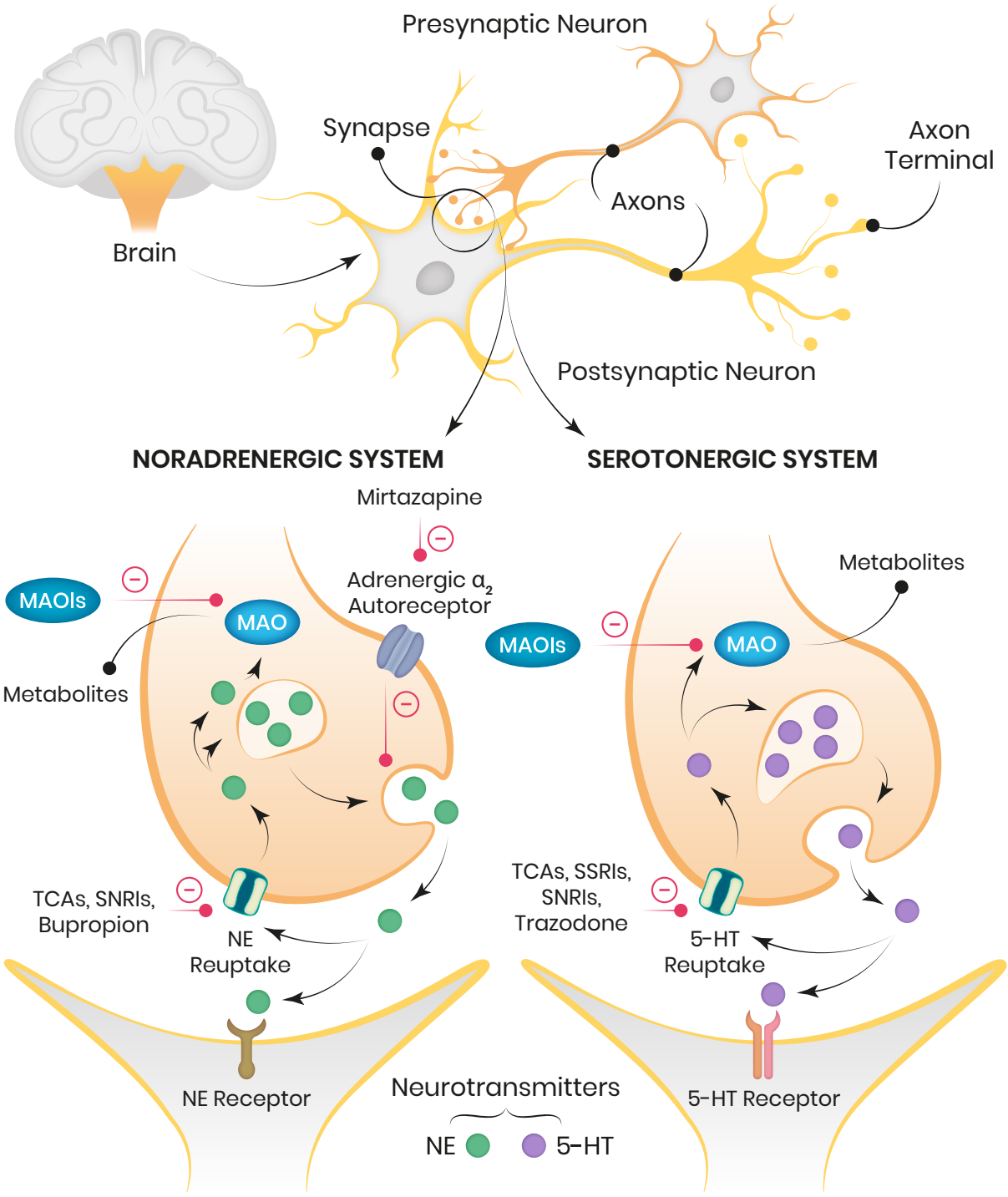
g. Antidepressants

Many antidepressants work by increasing the amount of serotonin. Any medications that increase serotonin in the synaptic cleft (e.g., SSRIs, SNRIs, MAOIs, several atypical antidepressants, tramadol, ondansetron, triptans) carry a risk of serotonin syndrome, a psychiatric medication-related emergency.
Serotonin Syndrome: A condition caused by increased levels of serotonin (5-HT) in the body. Diagnostic criteria are based around a triad of cognitive-behavioral, neuromuscular, and autonomic derangements. Characteristic signs and symptoms include confusion, agitation, altered level of consciousness, myoclonus, hyperreflexia, hypertonia, seizures, hyperthermia, hypertension, tachycardia, diaphoresis, mydriasis. Treatment: Cyproheptadine (serotonin antagonist).

While characteristics of neuroleptic malignant syndrome and serotonin syndrome overlap, it is important to differentiate the two; several key differences are displayed in the table below.

	Personality Disorder	Neuroleptic Malignant Syndrome
Precipitant	Serotonergic agents	Dopamine antagonists
Onset	Abrupt>gradual	Gradual>abrupt
Vital Signs	Hypertension, tachycardia, tachypnea, hyperthermia	
Course	Rapidly resolving	Prolonged
Skin	Diaphoretic	
Muscles	Increased tone, tremors, choreoathetoid movements	Diffuse rigidity
Reflexes	Hyperreflexia, clonus	Decreased
Pupils	Mydriasis	Normal
Bowel Sounds	Hyperactive	Normal-decreased

Antidepressants Figure 9



Mechanism of action of the antidepressants.

i. Selective Serotonin Reuptake Inhibitors (SSRIs)

Examples: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

Uses: Depression, anxiety, OCD, eating disorders, PTSD

Action: Inhibit reuptake of 5-HT; require 4-8 weeks to have therapeutic effect.

Side Effects: Nausea/vomiting, GI upset, SIADH, sexual dysfunction (decreased libido and anorgasmia). Most dangerous side effect is serotonin syndrome.

ii. Serotonin-norepinephrine Reuptake Inhibitors

Examples: Duloxetine, venlafaxine, desvenlafaxine, milnacipran, levomilnacipran.

Uses: Depression, anxiety, diabetic neuropathy. Certain agents are also indicated for other specific disorders: venlafaxine is used for social anxiety disorder, panic disorder, PTSD, OCD; duloxetine and milnacipran are used to treat fibromyalgia.

Action: Inhibit reuptake of 5-HT and norepinephrine. Require 4-8 weeks to have a therapeutic effect.

Side Effects: Decreased appetite, fatigue, nausea, increased blood pressure, sexual dysfunction (although less than TCAs), and serotonin syndrome.

iii. Tricyclic Antidepressants

Examples: Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline.

Uses: Less frequently used due to side effect profile and widespread availability of SSRIs and SNRIs. Major depressive disorder, peripheral neuropathy, chronic neuropathic pain, migraine prophylaxis. Clomipramine is used to treat OCD; Imipramine is sometimes used for enuresis.

Action: Inhibit reuptake of serotonin and norepinephrine.

Side Effects: α1 antagonistic effects (orthostatic hypotension), anticholinergic side effects (tachycardia, urinary retention, dry mouth), sedation, QT prolongation. Tertiary TCAs (amitriptyline) have more anticholinergic effects than secondary (nortriptyline). Most serious side effects: seizures, coma, arrhythmia (due to sodium channel inhibition), respiratory depression, hyperthermia. Due to anticholinergic effects, TCAs should be used sparingly among older adults. Treatment of toxicity: sodium bicarbonate ($NaHCO_3$).

iv. Monoamine Oxidase Inhibitors (MAOIs)

Examples: Phenelzine, selegiline, tranylcypromine, isocarboxazid.

Uses: Infrequently used due to side-effect profile. Atypical depression, anxiety. Selegiline is used to treat Parkinson disease.

Action: Nonselective inhibition of MAO (MAO degrades neurotransmitters; result of inhibition is increased levels of norepinephrine, serotonin, and dopamine).

Side Effects: Dry mouth, nausea, headache, insomnia, orthostatic hypotension, CNS stimulation. Because MAOIs also inhibit degradation of tyramine; consumption of tyramine containing foods (wines, cheeses, cured meats) can lead to hypertensive crisis. MAOI toxicity or serotonin syndrome can result when they are taken with any drugs that increase monoamine concentrations; therefore MAOIs are contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan, linezolid. MAOIs should be discontinued for at least 2 weeks before starting any other serotonergic medications.

Hypertensive crisis: A severe increase in blood pressure that can lead to a stroke or other end-organ damage (>180 systolic or >120 diastolic). MAOI reaction with tyramine-containing foods is not the only cause (others include chronic uncontrolled hypertension, other medication reactions, pheochromocytomas). When this occurs with MAOIs, it is due to tyramine displacing neurotransmitters in the synaptic cleft, leading to increased sympathetic stimulation. Treatment of MAOI-caused crisis: Phentolamine (non-selective alpha blockade, leads to lowered blood pressure).

v. Atypical Antidepressants

Bupropion: Dopamine and norepinephrine reuptake inhibitor. Used as an antidepressant and for smoking cessation. Adverse effects: tachycardia, insomnia, headache. Contraindicated in bulimia and anorexia nervosa (due to lowering the seizure threshold).

Mirtazapine: α2-antagonist (increases release of serotonin and norepinephrine), 5-HT2 and 5-HT3 receptor antagonist. Primary use is as an antidepressant in patients who may benefit from weight gain. Adverse effects: sedation, increased appetite (weight gain), dry mouth.

Trazodone: 5-HT2, α1, and H1 antagonist. Primary use is for insomnia (higher doses required for antidepressant effects). Adverse effects: sedation, nausea, priapism, orthostatic hypotension.

Varenicline: Nicotinic acetylcholine receptor partial agonist. Primary use is for smoking cessation. Adverse effects: insomnia, nausea, vivid dreams, depression, and suicidal ideation.

Vilazodone: 5-HT reuptake inhibitor, 5-HT1A receptor partial agonist. Primary use is for depression. Adverse effects: diarrhea, nausea, vomiting, sexual dysfunction, insomnia, fatigue, weight change, anticholinergic effects.

Vortioxetine: 5-HT reuptake inhibitor, 5-HT1A receptor agonist, 5-HT3 receptor antagonist. Primary use is for depression. Adverse effects: nausea, vomiting, diarrhea, sexual dysfunction, anticholinergic effects.

h. Medications for Opioid Intoxication and Medication-Assisted Treatment

i. Methadone:

A synthetic, orally effective opioid that produces less euphoria, has a longer duration of action, and is equally as potent as morphine.

Uses: Used for analgesia as well as in controlled withdrawal of dependent heroin abusers and for long-term maintenance therapy for heroin abusers.

Action: μ-opioid receptor agonist.

Side Effects: Can produce physical dependence, headache, dry mouth, sleep changes, constipation, respiratory depression.

ii. Buprenorphine

Uses: Used in a sublingual form to treat opioid use disorder

Action: μ-opioid receptor partial agonist; kappa- and delta-opioid receptor antagonist.

Side effects: Constipation, headache, fatigue.

iii. Naloxone

Uses: Used to rapidly reverse opioid overdose.

Action: Competitive antagonist of μ,κ,σ opioid receptors. Short acting.

Side effects: Myalgias, fever, diaphoresis, restlessness, irritability, GI upset.

iv. Naltrexone

Uses: Treatment for alcohol use disorder and opioid use disorder. Taken long term (over 12 weeks) to prevent relapse. Must be started after detoxification to prevent relapse. Naltrexone and acamprosate are both first-line treatments for alcohol use disorder with similar rates of efficacy.

Action: Competitive antagonist of μ,κ,σ opioid receptors. Long acting.

Side effects: Nausea (most common), headache, constipation, dizziness, irritability, insomnia, myalgias.