SECTION IV

CNS Pharmacology

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Sedative-Hypnotic-Anxiolytic Drugs 1

Learning Objectives

- ❑ Answer questions related to benzodiazepines and barbiturates

- Drugs: **benzodiazepines** (BZs), **barbiturates**, and **alcohols**

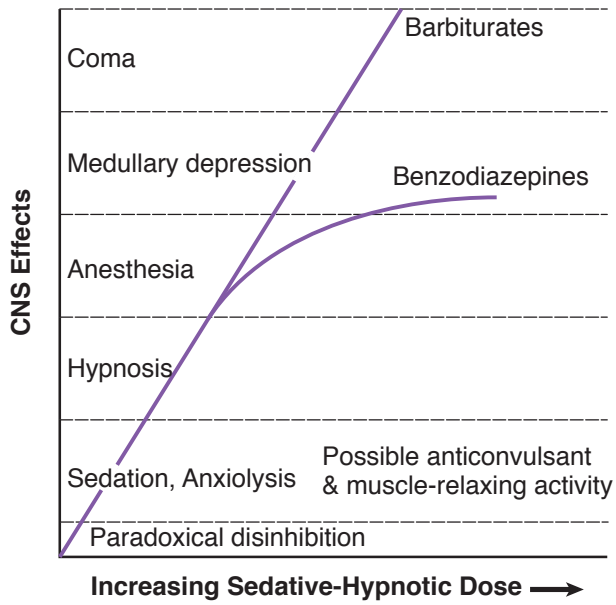

Figure IV-1-1. CNS Effects Associated with Increasing Doses of Sedative-Hypnotic (S-H) Drugs

- Cause dose-dependent CNS depression that extends from sedation to anesthesia to respiratory depression and death
- BZs reach a plateau in CNS depression; barbiturates and alcohol do not
- Mechanisms:

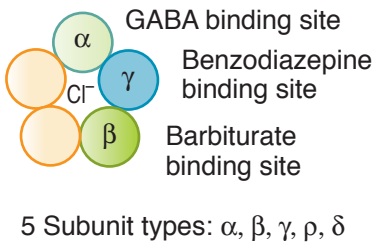

Figure IV-1-2. Site of Action of Drugs on the $GABA_A$ Complex

Clinical Correlate

Flumazenil

This nonspecifi BZ receptor antagonist is used to reverse the CNS depression caused by BZs used in anesthesia or in BZ overdose. Flumazenil cannot reverse the CNS depression caused by barbiturates and alcohols.

- $GABA_A$ activation ↑ Cl^- influx
- $GABA_B$ activation ↑ K^+ efflux
- Both mechanisms result in membrane hyperpolarization
  - Benzodiazepines:
    - Potentiate GABA
    - ↑ the frequency of Cl^- channel opening
    - Have no GABA mimetic activity
    - Act through BZ receptors
    - These receptors are part of the $GABA_A$ complex
    - BZ_1 mediates sedation
    - BZ_2 mediates antianxiety and impairment of cognitive functions
  - Barbiturates:
    - Prolong GABA activity
    - ↑ duration of Cl^- channel opening
    - Have GABA mimetic activity at high doses
    - Do not act through BZ receptors
    - Have their own binding sites on the $GABA_A$ complex
    - Also inhibit complex I of electron transport chain

- Uses of BZs:

Table IV-1-1. Uses of Various Benzodiazepines

Drug	Indications
Alprazolam	Anxiety, panic, phobias
Diazepam	Anxiety, preop sedation, muscle relaxation, withdrawal states
Lorazepam	Anxiety, preop sedation, status epilepticus (IV)
Midazolam	Preop sedation, anesthesia IV
Temazepam	Sleep disorders
Oxazepam	Sleep disorders, anxiety

- Pharmacokinetics of BZs:
  - Liver metabolites are also active compounds, except for oxazepam, temazepam, and lorazepam
- Uses of barbiturates:
  - Phenobarbital is used for seizures

- Pharmacokinetics of barbiturates:
  - Liver metabolized, sometimes to active compounds
  - General inducers of cytochrome P450s
  - Contraindication in porphyrias
- Tolerance to and dependence on sedative-hypnotics:
  - Chronic use leads to tolerance
  - Cross-tolerance occurs between BZs, barbiturates, and ethanol
  - Psychologic and physical dependence occur
  - But abuse liability of BZs is < ethanol or barbiturates
  - Withdrawal signs of BZs:
    - Rebound insomnia
    - Anxiety
    - Seizures when BZs were used as antiepileptic or in high doses
  - Withdrawal signs of barbiturates and ethanol:
    - Anxiety
    - Agitation
    - Life-threatening seizures (delirium tremens with alcohol)
  - Management of withdrawal: supportive and long-acting BZs
- Drug interactions
  - $GABA_A$ drugs are:
    - Additive with other CNS depressants (possible life-threatening respiratory depression), such as anesthetics, antihistamines, opiates, β-blockers, etc.
    - Barbiturates induce metabolism of most lipid-soluble drugs, such as oral contraceptives, carbamazepine, phenytoin, warfarin, etc.
- Non-BZ drugs:
  - Zolpidem and zaleplon
    - BZ_1 receptor agonist
    - Less effect on cognitive function (BZ_2-mediated)
    - Overdose reversed by flumazenil
    - Used in sleep disorders
    - Less tolerance and abuse liability (sleepwalking)
  - Buspirone
    - No effect on GABA
    - $5\text{-}HT_{1A}$ partial agonist
    - Used for generalized anxiety disorders
    - Nonsedative
    - Takes 1 to 2 weeks for effects

Chapter Summary

- Sedative-hypnotic-anxiolytic drugs include the benzodiazepines, barbiturates, and alcohols.
- S-H drugs ideally should reduce anxiety without affecting mental or motor function. However, most do affect mental or motor function. Figure IV-1-1 illustrates the relative effects on these functions of classes of S-H drugs at increasing concentrations.
- Most S-H drugs facilitate GABA action by binding to the $GABA_A$ receptor, which has one binding site for barbiturates and alcohol and another for benzodiazepines (Figure IV-1-2). The binding of these drugs at these sites leads to increased Cl^- influx, potentiating the inhibitory transmitter effects of GABA. The differences in action of the various S-H drugs relate to the differences in the binding site used. Further heterogeneity is introduced by the existence of two subtypes of benzodiazepine receptors, BZ_1 and BZ_2.
- The benzodiazepines are used to treat anxiety states and sleep disorders. Dose-dependent CNS depression does occur but can be reversed by flumazenil. Chronic use can lead to tolerance and dependency with rebound effects upon withdrawal. Table IV-1-1 summarizes the various benzodiazepines and their indications.
- Phenobarbital is used to treat seizures, and thiopental is used as an IV anesthetic. Barbiturates induce deep CNS depression at high doses, and there is no antidote.
- The barbiturates induce drug-metabolizing enzymes, including the P450 system, leading to potential drug interactions. They also stimulate heme synthesis and are contraindicated in porphyrias.
- Tolerance, dependence, and severe withdrawal symptoms are associated with chronic barbiturate use.
- Zolpidem and zaleplon are nonbenzodiazepines that bind to the BZ_1 receptors and therefore are more specific hypnotics. Buspirone is an anxiolytic that does not work through the GABA system. It is nonsedating and does not cause dependence but takes a week or two to show antianxiety effects.

Alcohols 2

Learning Objectives

- ❑ Answer questions about the mechanism of action and metabolism of alcohol

All alcohols cause CNS depression, in part through GABA mimetic activity. All alcohols cause metabolic acidosis.

Clinical Correlate

Alcohol and Pregnancy

Fetal alcohol syndrome is characterized by growth restriction, midfacial hypoplasia, microcephaly, and marked CNS dysfunction, including the frequent occurrence of mental retardation.

Note

Drugs that cause disulfi am-like effects:

- Metronidazole
- Griseofulvin

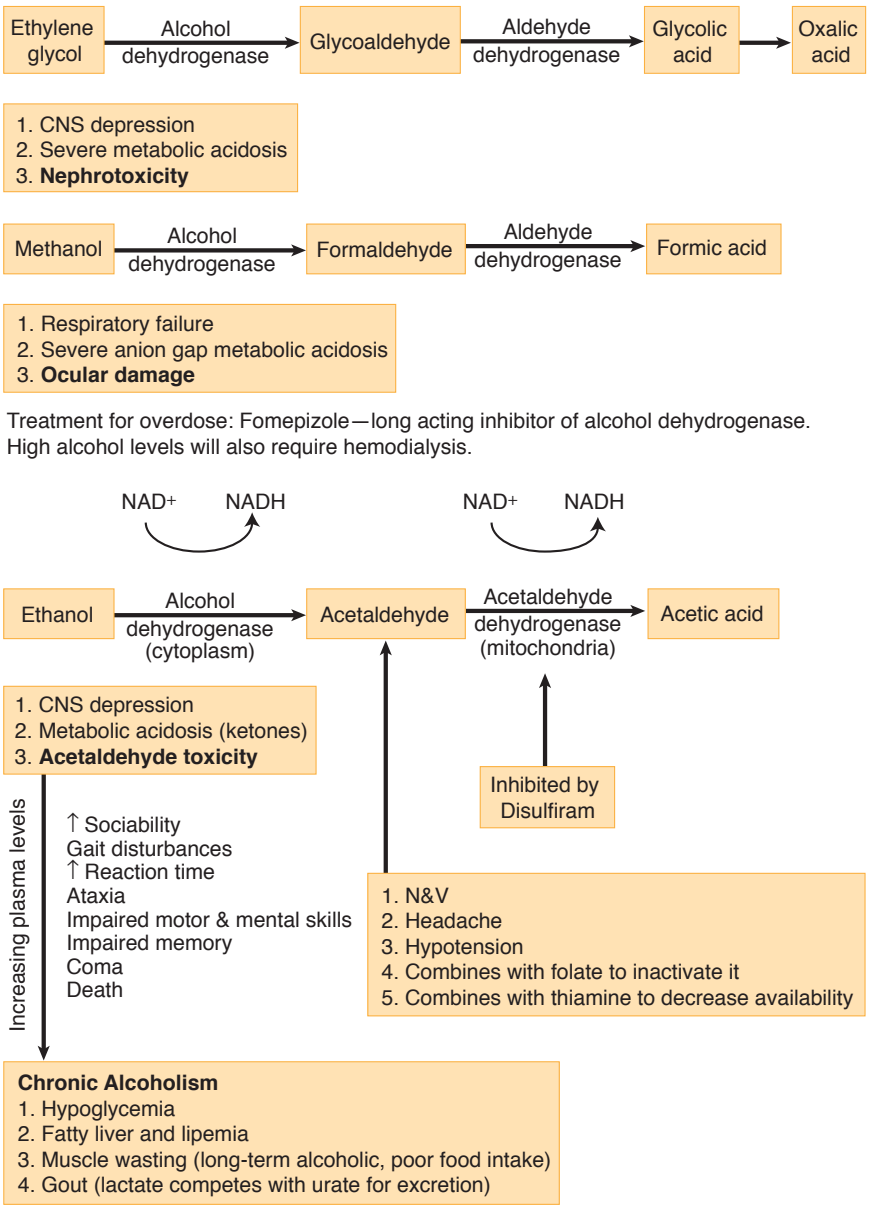

Figure IV-2-1. Metabolism and Pharmacologic Actions of the Alcohols

Drugs Used for Depression, Bipolar Disorders, and Attention Deficit Hyperactivity Disorder (ADHD)

3

Learning Objectives

- ❏ Explain information related to drugs used in depression bipolar disorders, and ADHD
- ❏ Solve problems related to the use of lithium

- "Amine hypothesis" of depression:
  - Reserpine: depletes NE, 5HT, DA, and causes severe depression
  - Acute mechanism of antidepressants: ↑ NE, ↑ 5HT
  - However, antidepressant effect takes several weeks to occur.

DRUGS USED IN DEPRESSION

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Drugs: **fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine**
- Mechanism: selective blockade of 5HT reuptake
- Uses:
  - Major depression
  - OCD
  - Bulimia
  - Anxiety disorders (chronic treatment/acute, benzodiazepines)
  - Premenstrual dysphoric disorder (PMDD)
- Side effects: anxiety, agitation, bruxism, sexual dysfunction, weight loss
- Toxicity: serotonin syndrome
- Drug interactions
  - ↑ 5HT: serotonin syndrome
    - Symptoms: sweating, rigidity, myoclonus, hyperthermia, ANS instability, seizures
    - Drugs: MAOIs, TCAs, and meperidine
  - Most inhibit cytochrome P450 enzymes (in particular, fluvoxamine and fluoxetine)
  - Important interaction includes increased levels of benzodiazepines in treatment of anxiety disorders
  - Citalopram is safer for interactions

Tricyclic Antidepressants (TCAs)

- Drugs: **amitriptyline, imipramine,** and **clomipramine**
- Mechanism: nonspecific blockade of 5HT and NE reuptake
- Uses:
  - Major depressions
  - Phobic and panic anxiety states
  - Obsessive-compulsive disorders (OCDs)
  - Neuropathic pain
  - Enuresis
- Side effects: muscarinic and α blockade
- Toxicity: the "3 Cs": coma, convulsions, and cardiotoxicity
- Drug interactions:
  - Hypertensive crisis with MAO inhibitors
  - Serotonin syndrome with SSRIs, MAO inhibitors, and meperidine
  - Prevent antihypertensive action of α_2 agonists

MAO Inhibitors

- Drugs: **phenelzine** and **tranylcypromine**
- Mechanism: irreversible inhibition of MAO_A and MAO_B
- Use: atypical depressions
- Drug interactions
  - Serotonin syndrome: SSRIs, TCAs, and meperidine
  - ↑ NE: hypertensive crisis
    - Symptoms: ↑ BP, arrhythmias, excitation, hyperthermia
    - Drugs: releasers (i.e., tyramine), tricyclic antidepressants (TCAs), α1 agonists, levodopa

Other Antidepressants

- Trazodone: associated with cardiac arrhythmias and priapism
- Venlafaxine: nonselective reuptake blocker devoid of ANS side effects
- **Bupropion:** dopamine reuptake blocker; used in smoking cessation
- Mirtazapine: α_2 antagonist, associated with weight gain

Clinical Correlate

Varenicline is a partial agonist of nicotinic receptors and is used in smoking cessation.

LITHIUM AND BIPOLAR DISORDERS

- **Lithium** remains DOC for bipolar disorders.
- Usually antidepressants/antipsychotics also required
- Mechanism:
  - Prevents recycling of inositol (↓ PIP_2) by blocking inositol monophosphatase
  - ↓ cAMP

- Side effects:
  - Narrow therapeutic index; requires therapeutic monitoring
  - Tremor, flu-like symptoms, life-threatening seizures
  - Hypothyroidism with goiter (↓ TSH effects and inhibition of 5′-deiodinase)
  - Nephrogenic diabetes insipidus (↓ ADH effect); manage with amiloride
- Teratogenicity: Ebstein's anomaly (malformed tricuspid valve)
- Other drugs used in bipolar disorders: valproic acid, carbamazepine

DRUGS USED IN ADHD

- **Methylphenidate:** amphetamine-like
  - Side effects: agitation, restlessness, insomnia, cardiovascular toxicity
- **Atomoxetine:** selective NE reuptake inhibitor
  - Side effects: See TCA section, above.

Chapter Summary

- The amine hypothesis of depression postulates that symptoms are caused by a functional deficiency of CNS NE and/or 5HT. This is based on the observation that most antidepressants affect the metabolism of these amines. Again, there are exceptions.
- The uses, drug interactions, and adverse effects of the monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and other antidepressants are discussed.
- Lithium, the mainstay for bipolar disorder treatment, often needs supplementation with antidepressant and/or sedative drugs. The uses, mechanisms of action, and adverse effects of lithium therapy as well as backup drugs used for treatment of bipolar disorder are considered.
- Atomoxetine and methylphenydate are used in the treatment of ADHD.

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Drugs Used in Parkinson Disease and Psychosis

4

Learning Objectives

- ❏ Answer questions about dopaminergic neural pathways
- ❏ Demonstrate understanding of dopamine receptors
- ❏ Compare and contrast the mechanism of action and side-effects for drugs used in Parkinson disease with antipsychotic drugs

DOPAMINERGIC NEURAL PATHWAYS

In the CNS, dopamine (DA) is a precursor to NE in diffuse noradrenergic pathways and is an inhibitory neurotransmitter in the following major dopaminergic pathways:

- Nigrostriatal tract
  - Cell bodies in the substantia nigra project to the striatum, where they release DA, which inhibits GABA-ergic neurons. In Parkinson disease, the loss of DA neurons in this tract leads to excessive ACh activity → extrapyramidal dysfunction.
  - DA receptor antagonists → pseudo-Parkinsonism (reversible).
  - DA agonists may cause dyskinesias.
- Mesolimbic-mesocortical tracts—cell bodies in midbrain project to cerebrocortical and limbic structures.
  - Functions include regulation of affect, reinforcement, cognitive functions, and sensory perception. Psychotic disorders and addiction are partly explained by ↑ DA in these pathways.
  - Drugs that ↑ DA functions → ↑ reinforcement and, at high doses, may cause psychoses.
  - DA antagonists → ↓ cognitive function.
- Tuberoinfundibular
  - Cell bodies in hypothalamus project to anterior pituitary and release DA → ↓ prolactin.
  - DA agonists are used in hyperprolactinemic states.
  - DA antagonists may cause endocrine dysfunction, including gynecomastia and amenorrhea/galactorrhea.
- Chemoreceptor trigger zone
  - Activation of DA receptors → ↑ emesis.
  - DA agonists (e.g., apomorphine) are emetic, and DA antagonists are antiemetic.

DOPAMINE RECEPTORS

- D_1-like: G_s coupled
- D_2-like: G_i coupled
  - D_{2A}: nigrostriatal
  - D_{2C}: mesolimbic

DRUGS USED IN PARKINSON DISEASE

- Signs and symptoms of Parkinson disease include:
  - Bradykinesia
  - Muscle rigidity
  - Resting tremor
- Pathology: degeneration of nigrostriatal dopamine tracts with imbalance between dopamine (↓) and ACh (↑)

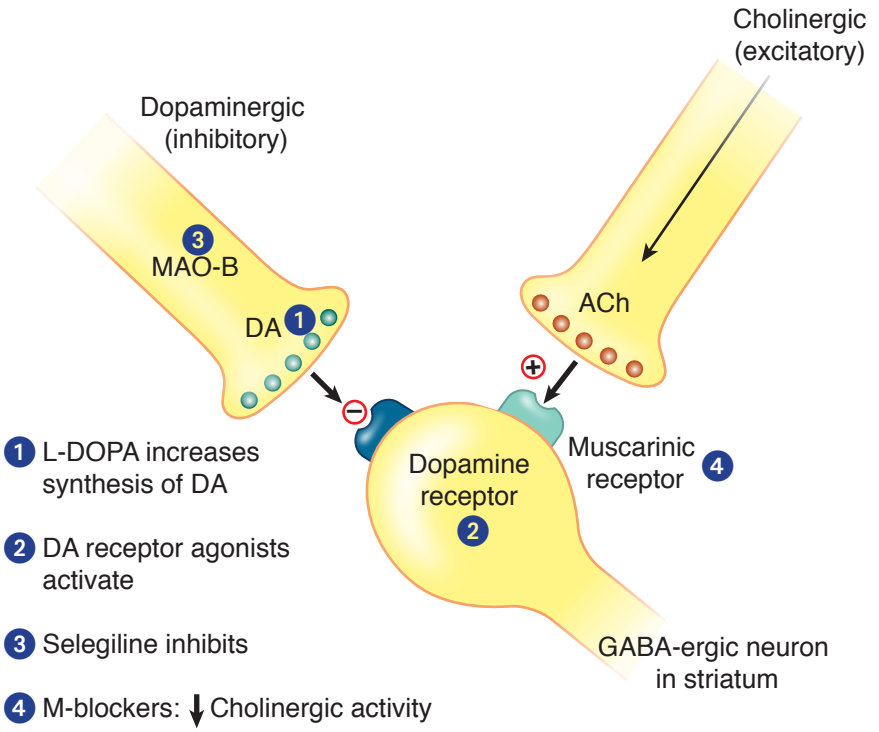

Figure IV-4-1. CNS Targets for Antiparkinsonian Drugs

- Pharmacologic strategy: restore normal dopamine and ↓ ACh activity at muscarinic receptors in the striatum
- Drugs increasing dopamine function:
  - **Levodopa**
    - Prodrug converted to dopamine by aromatic amino acid decarboxylase (AAAD)
    - Given with carbidopa

- Side effects:
  - Dyskinesias
  - "On-off" effects
  - Psychosis
  - Hypotension
  - Vomiting

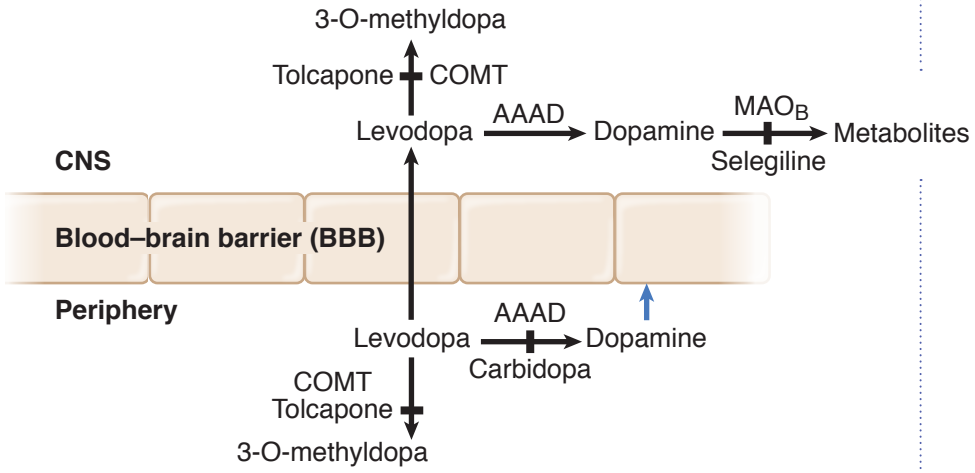

Figure IV-4-2. Inhibitors of Levodopa Metabolism

- **Tolcapone** and **entacapone**
  - COMT converts L-dopa to 3-O-methyldopa, a partial agonist at dopamine receptors.
  - These drugs inhibit COMT and enhance levodopa uptake and efficacy.
  - Tolcapone is hepatotoxic.
- **Selegiline**
  - MAO_B-selective inhibitor (no tyramine interactions)
  - Initial treatment and adjunct to levodopa
  - Side effects: dyskinesias, psychosis, insomnia (metabolized to amphetamine)

- Dopamine-receptor agonists:
  - **Bromocriptine**
    - Use: hyperprolactinemia and acromegaly
    - Side effects: dyskinesias and psychosis
  - **Pramipexole and ropinirole**
- Drugs decreasing ACh function:
  - Include **benztropine** and **trihexyphenidyl**, which are muscarinic blockers

- Actions: ↓ tremor and rigidity but have little effects on bradykinesia
- Side effects: atropine-like

- **Amantadine**
  - Antiviral, which block muscarinic receptors and ↑ dopamine release
  - Side effects: atropine-like and livedo reticularis

ANTIPSYCHOTIC DRUGS

Schizophrenia

- Positive symptoms:
  - Thought disorders
  - Delusions
  - Hallucinations
  - Paranoia
- Negative symptoms:
  - Amotivation
  - Social withdrawal
  - Flat affect
  - Poverty of speech
- "Dopamine hypothesis":
  - Symptoms arise because of excessive dopaminergic activity in mesolimbic system.
  - Dopamine agonists cause psychosis.
  - Dopamine antagonists have antipsychotic actions.
- Serotonin is increasingly seen as a part of the etiology of schizophrenia.
- Mechanism: blockade of dopamine and/or $5HT_2$ receptors
- Uses
  - Schizophrenia
  - Schizoaffective states
  - Bipolar disorder
  - Tourette syndrome and Huntington disease
  - Drug or radiation emesis
- Side effects from dopamine blockade:
  - Dyskinesias (extrapyramidal symptoms [EPS])
    - Acute EPS:

      Pseudoparkinsonism, dystonia, akathisia

      Management: antimuscarinic drugs (benztropine or diphenhydramine)
    - Chronic EPS:

      Tardive dyskinesia (TD)

      Management: discontinuation/switch to atypical
  - Dysphoria
  - Endocrine dysfunction:
    - Temperature regulation problems (neuroleptic malignant syndrome [NMS], treated with dantrolene and bromocriptine) (see chapter 6)

- ↑ prolactin (galactorrhea, amenorrhea, gynecomastia)
- ↑ eating disorders (weight gain)

- Side effects from muscarinic blockade (particularly tachycardia and ↓ seizure threshold)
- Side effects from alpha blockade (particularly hypotension)

Table IV-4-1. Characteristic Properties of Antipsychotic Drugs

Drug Group Examples	EPS*	M Block	Sedation	Alpha Block	Other Characteristics
Typicals					
Chlorpromazine	++	++	+++	+++	NA
Thioridazine	+	+++	+++	+++	• Cardiotoxicity (torsades—"quinidine-like") • Retinal deposits
Fluphenazine	+++	+	+	+	NA
Haloperidol	+++	+	+	+	Most likely cause of neuroleptic malignant syndrome (NMS) and TD
Atypicals					
Clozapine	+/–	++	+	+++	• Blocks D_{2c} and $5HT_2$ receptors • No TD • Agranulocytosis—(weekly WBC count) requirement for weekly blood test, weight gain • Increased salivation ("wet pillow"syndrome) • Seizures
Olanzapine	+/–	+	+	++	Blocks $5HT_2$ receptors, improves negative symptoms
Risperidone	+	+/–	++	++	Blocks $5HT_2$ receptors, improves negative symptoms
Aripiprazole	+	+/–	+/–	+/–	Partial agonist of D_2 receptor; blocks $5HT_2$ receptors
Other atypicals: quetiapine, ziprasidone					

*Extrapyramidal symptoms

Clinical Correlate

Parenteral formulations of certain antipsychotic drugs (e.g., fluphe azine, haloperidol) are available for rapid initiation of treatment and for maintenance therapy in noncompliant patients. Depot forms of both drugs exist.

Chapter Summary

Dopaminergic Neural Pathways

- Dopamine (DA) in the nigrostriatal tract helps regulate kinesis by inhibiting GABA-ergic and cholinergic neurons. The loss of DA neurons in this tract leads to excessive ACh activity and Parkinsonism. DA receptor antagonists cause a reversible pseudo-Parkinsonism; agonists may cause dyskinesis.
- DA neurons in the midbrain projecting into the cerebrocortical and limbic regions regulate affect, reinforcement, psychomotor function, and sensory perception. DA agonists enhance psychomotor activity and reinforcement and at high doses may cause psychoses. DA antagonists decrease psychomotor function.
- In the hypothalamus, DA released into the pituitary decreases prolactin release. DA agonists (e.g., bromocriptine) are used to treat hyperprolactinemia; antagonists may cause endocrine dysfunction.
- The activation of DA receptors in the chemoreceptor trigger zone increases emesis; thus, DA agonists are emetic, and antagonists are antiemetic.

Antiparkinsonian Drugs

- Parkinsonism is due to an imbalance between DA and ACh activity in the nigrostriatal tract. Drugs attempt to restore this balance either by increasing DA or decreasing ACh levels. Figure IV-4-1 illustrates the CNS sites targeted in antiparkinsonism therapy.
- Drugs used to increase DA function are levodopa, tolcapone, entacapone, bromocriptine, pramipexole, and selegiline. Drugs that decrease ACh function are benztropine, trihexyphenidyl, and amantadine. The properties of each are described.

Antipsychotic Drugs

- Although the prevailing concept is that schizophrenia is due to hyperdopaminergic activity in the CNS, not all antischizophrenic drugs act as DA antagonists; some instead modify serotonin function.
- The typical antipsychotic drugs (e.g., chlorpromazine, thioridazine, fluphenazine, and haloperidol) act primarily as DA antagonists, blocking D_{2A} receptors. Side effects include the induction of pseudo-Parkinsonism, akathisia, and/or acute dystonic effects. Their use and symptom management are discussed, as are other adverse effects including toxicity, tardive dyskinesia, and neuroleptic malignant syndrome.
- Atypical antipsychotics (e.g., clozapine, risperidone, and olanzapine) act as antagonists at $5HT_2$ receptors and seem to have fewer adverse effects. Aripiprazole is a D_2 partial agonist.
- Table IV-4-1 summarizes the characteristics of the antipsychotic drugs.

Anticonvulsants 5

Learning Objectives

- ❏ Describe the mechanism of action and unique features of the commonly used anticonvulsants
- ❏ Provide an overview of which anticonvulsants are used for which types of seizures

Seizures result from episodic electrical discharges in cerebral neurons associated with prolonged depolarization, during which sustained, high-frequency, repetitive fi ing (SHFRF) occurs, followed by prolonged hyperpolarization. The goal of drug management is restoration of normal patterns of electrical activity.

- Mechanisms of action:
  - ↓ axonal conduction by preventing Na^+ influx through fast Na channels—carbamazepine, phenytoin
  - ↑ inhibitory tone by facilitation of GABA-mediated hyperpolarization—barbiturates, benzodiazepines
  - ↓ excitatory effects of glutamic acid—lamotrigine, topiramate (blocks AMPA receptors); felbamate (blocks NMDA receptors)
  - ↓ presynaptic Ca^{2+} influx through type-T channels in thalamic neurons—ethosuximide and valproic acid

Table IV-5-1. Seizure States and Effective Drugs

Seizure Type	Effective Drugs
Partial—simple or complex	Valproic acid, phenytoin, carbamazepine, lamotrigine
General—tonic-clonic	Valproic acid, phenytoin, carbamazepine, lamotrigine
General—absence	Ethosuximide, valproic acid
Status epilepticus	Lorazepam, diazepam, phenytoin, or fosphenytoin*

*IV fosphenytoin is more water soluble.

- Primary anticonvulsants
  - **Phenytoin**
    - Blocks axonal Na^+ channels in their inactivated state
    - Prevents seizure propagation
    - Uses: seizure states
    - Pharmacokinetics:
      - Variable absorption
      - Nonlinear kinetics
      - Induction of cytochrome P450s
      - Zero-order kinetic of elimination
    - Side effects:
      - CNS depression
      - Gingival hyperplasia
      - Hirsutism
      - Osteomalacia (↓ vitamin D)
      - Megaloblastic anemia (↓ folate)
      - Aplastic anemia (check hematology lab results)
    - Teratogenicity: cleft lip and palate
  - **Carbamazepine**
    - Mechanism identical to phenytoin
    - Uses:
      - Seizure states
      - DOC for trigeminal neuralgia
      - Bipolar disorder
    - Pharmacokinetics: induces cytochrome P450, including its own metabolism
    - Side effects:
      - CNS depression
      - Osteomalacia
      - Megaloblastic anemia
      - Aplastic anemia
      - Exfoliative dermatitis
      - ↑ ADH secretion (dilutional hyponatremia)
    - Teratogenicity:
      - Cleft lip and palate
      - Spina bifida
  - **Valproic acid**
    - Mechanism:
      - Similar to phenytoin
      - But also inhibition of GABA transaminase
      - Blockade of T-type Ca^{2+} channels

- Uses:
  - Seizure states
  - Mania of bipolar disorders
  - Migraine prophylaxis
- Pharmacokinetics: inhibits cytochrome P450s
- Side effects:
  - Hepatotoxicity (from toxic metabolite)
  - Thrombocytopenia
  - Pancreatitis
  - Alopecia
- Teratogenicity: spina bifida

– **Ethosuximide**
- Mechanism: blockade of T-type Ca^{2+} channels in thalamic neurons
- Use: absence seizures

– **Lamotrigine**
- Blocks Na^+ channels and glutamate receptors
- Used in various seizures
- Side effects: Stevens-Johnson syndrome

– **Levetiracetam**
- Mechanism unclear
- Used in focal-onset and generalized tonic-clonic seizures

– **Topiramate**
- Blocks Na^+ channels and glutamate receptors and enhances GABA activity
- Used in focal seizures in adults and children > age 2; also used in migraine prophylaxis
- Side effects: weight loss

• General features of anticonvulsant drug use:
– Anticonvulsants are additive with other CNS depressants
– Avoid abrupt withdrawal, which may precipitate seizures
– ↓ efficacy of oral contraceptives via induction of cytochrome P450

• Other anticonvulsant drugs
– **Felbamate**
- Block Na^+ channels and glutamate receptors
- Used in seizure states (often adjunct therapy)
- Side effects: Aplastic anemia

– **Gabapentin**
- May affect calcium channels and neurotransmitter release, GABA effects
- Used in seizure states, neuropathic pain (such as postherpetic neuralgia)

Chapter Summary

- Seizures are caused by episodic electrical discharges in cerebral neurons. These trigger repetitive firing and prolonged hyperpolarization. The goal of drug management is to restore normal electrical patterns. Different classes of drugs do this by acting on different receptor/transmitter systems, which are listed.
- Table IV-5-1 summarizes the drugs of choice available to treat each of the several types of seizures.
- The mechanisms of action, metabolism, and the adverse effect of the primary anticonvulsant drugs (phenytoin, carbamazepine, ethosuximide, valproic acid, and the barbiturates and benzodiazepines) are discussed.
- Anticonvulsive drugs in general have additive depressive effects when used with other depressant drugs, cause a precipitation of seizures upon abrupt withdrawal, and decrease the efficiency of oral contraceptives.
- Other anticonvulsants listed are felbamate, gabapentin, and lamotrigine.

Drugs Used in Anesthesia 6

Learning Objectives

- ❏ Demonstrate understanding of general anesthetics
- ❏ Explain information related to local anesthetics
- ❏ Use knowledge of skeletal muscle relaxants to solve problems

GENERAL ANESTHETICS

Inhaled Anesthetics

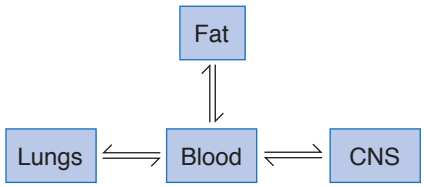

Figure IV-6-1. Compartmentalization of Anesthetics in the Body

Table IV-6-1. Properties of Specifi Inhaled Anesthetics

Anesthetic	MAC Value	Blood–Gas Ratio	CV Effects	Specifi Characteristics
Nitrous oxide	104%	0.5	Minimal	Rapid onset and recovery, no metabolism Diffusional hypoxia Spontaneous abortions
Sevoflu ane	2%	0.6	Minimal	
Desflu ane	6%	0.5	Minimal	

- Anesthesia protocols include several agents in combinations.
- Inhaled anesthetics have varying potency in proportion to their lipid solubility.
- A MAC (minimal alveolar anesthetic concentration) is defined as the concentration of inhaled anesthetic, as a % of inspired air, at which 50% of patients do not respond to a surgical stimulus.
  - MAC is a measure of potency: ED50.
  - The more lipid soluble the anesthetic, the lower the MAC and the greater the potency.
  - MAC values are additive.
  - MAC values are lower in the elderly and in the presence of opiates or sedative-hypnotics.
- Rates of onset and recovery depend on the blood–gas ratio:
  - The more soluble the anesthetic in the blood, the slower the anesthesia.
  - Anesthetics with high blood–gas ratios are associated with slow onset.
  - Anesthetics with high blood–gas ratios are associated with slow recovery.
  - Anesthetics with low blood–gas ratios have fast onset and recovery.

Intravenous Anesthetics

- Midazolam
  - Benzodiazepine used for:
    - Preoperative sedation
    - Anterograde amnesia
    - Induction
    - Outpatient surgery
  - Depresses respiratory function
- Propofol
  - Used for induction and maintenance of anesthesia
  - Antiemetic
  - CNS and cardiac depressant
- Fentanyl
  - Opiate used for induction and maintenance of anesthesia
  - Depresses respiratory function
  - *See* Opioid Analgesics, chapter 7 in this section
- Ketamine
  - Dissociative anesthetic
  - NMDA-receptor antagonist
  - Induction of anesthesia
  - Emergent delirium, hallucinations
  - Cardiovascular stimulation
  - ↑ intracranial pressure

LOCAL ANESTHETICS

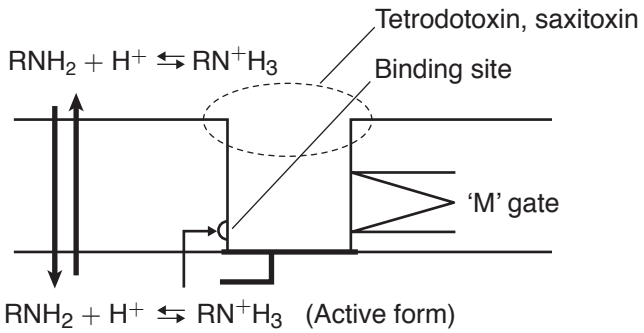

Figure IV-6-2. Mode of Action of Local Anesthetics

- Local anesthetics provide regional anesthesia.
- Drugs:
  - **Esters:** procaine, cocaine, benzocaine are metabolized by plasma and tissue esterases
  - **Amides:** lidocaine, bupivacaine, mepivacaine are metabolized by liver amidases
- Mechanisms:
  - Nonionized form crosses axonal membrane
  - From within, ionized form blocks the inactivated Na^+ channel
  - Slows recovery and prevents propagation of action potentials
- Nerve fiber sensitivity:
  - Nerve fibers most sensitive to blockade are of smaller diameter and have high firing rates
  - The order of sensitivity is:

$$\text{type B and C} > \text{type } A_\delta > \text{type } A_\beta \text{ and } A_\gamma > \text{type } A_\alpha$$

  - Recovery is in reverse order
- Absorption:
  - Coadministration of α_1 agonists:
    - ↓ local anesthetic absorption into the systemic circulation
    - Prolong effects and ↓ toxicity
- Side effects:
  - Neurotoxicity
  - Cardiovascular toxicity
  - Allergies (esters via PABA formation)

Note

Na^+ Channel Toxins

- Tetrodotoxin (from puffer fish) and saxitoxin (algae toxin, "red tide")
  - Block activated Na^+ channels
  - ↓ Na^+ influ
- Ciguatoxin (exotic fish) and batrachotoxin (frogs)
  - Bind to activated Na^+ channels
  - Cause inactivation
  - Prolong Na^+ influ

Note

Esters and Amides

Local anesthetics that are esters have just one "i" in their names (e.g., procaine, cocaine); amide local anesthetics have more than one "i" (e.g., lidocaine, bupivacaine).

Note

Cocaine intrinsically causes vasoconstriction by blocking norepinephrine uptake.

SKELETAL MUSCLE RELAXANTS

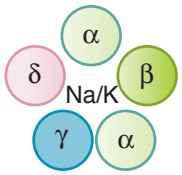

Figure IV-6-3. Nicotinic ACh Receptor of the Neuromuscular Junction

- Nicotinic receptors have five subunits.
- Two ACh bind each to two α subunits in order to open the Na^+ channel.
- This depolarizes the muscle.
- Used mainly in anesthesia protocols or in the ICU to afford muscle relaxation and/or immobility.
- Muscle relaxants interact with nicotinic ACh receptors at the neuromuscular junction.
- Drugs:
  - **Nondepolarizing (competitive)**
    - Nicotinic antagonists
    - d-Tubocurarine prototype
    - Reversible with AChE inhibitors
    - Progressive paralysis (face, limbs, respiratory muscle)
    - No effects on cardiac and smooth muscle
    - No CNS effects
    - Specific drugs:

      Atracurium

      * Rapid recovery
      * Safe in hepatic or renal impairment
      * Spontaneous inactivation to laudanosine
      * Laudanosine can cause seizures
  - **Depolarizing (noncompetitive)**
    - Nicotinic agonist
    - Specific drug: **succinylcholine**
    - Two phases:

      Phase I: depolarization, fasciculation, prolong depolarization, flaccid paralysis

      Phase II: desensitization
    - AChE inhibitors ↑ phase I; may reverse phase II
    - Rapidly hydrolyzed by pseudocholinesterase: short duration

- Cautions:
  - Atypical pseudocholinesterase
  - Hyperkalemia
  - Malignant hyperthermia

Centrally Acting Skeletal Muscle Relaxants

- Benzodiazepines through $GABA_A$ receptors
- Baclofen through $GABA_B$ receptors
- Use: spasticity

Chapter Summary

Drugs Used in Anesthesia

- The more lipid soluble the inhalation anesthetic, the greater its potency (lower MAC value). The more soluble an inhalation anesthetic in the blood (higher blood:gas ratio), the slower will be the onset to anesthesia and the slower will be the recovery.
- Thiopental, midazolam, propofol, fentanyl, and ketamine are intravenous anesthetics that are discussed.
- Local anesthetics (weak bases) infiltrate and anesthetize nerve bundles near sites of injection by binding to inactive Na^+ channels in their ionized forms. However, to get to the channel they must diffuse through the lipid bilayer in an unionized form. Thus, their effects are influenced by pH.
- The smaller and most rapidly firing nerve fibers are the most sensitive to blockade.
- The coadministration of alpha adrenoceptor agonists decreases local anesthetic absorption into the systemic circulation, prolonging their effects and potentially decreasing their toxicity.
- The adverse effects of local anesthetics are given.

Sodium Channel Toxins

- Tetrodotoxin, saxitoxin, ciguatoxin, and batrachotoxin are sodium-channel toxins found in various fish, frogs, or dinoflagellates.

Skeletal Muscle Relaxants

- The skeletal muscle relaxants provide muscle relaxation and/or immobility via N-receptor interactions. Most, including D-tubocurarine and atracurium, are competitive and nondepolarizing and can be reversed by AChE inhibitors. Succinylcholine is a depolarizing, noncompetitive agonist.
- Spasmolytics reduce excess muscle tone or spasm in injury or CNS dysfunction. They may act in the CNS, the spinal cord, or directly on the muscle. Benzodiazepines and baclofen reduce the tonic output of spinal motor neurons. Dantrolene blocks Ca^{2+} release from the muscle sarcoplasm reticulum.

Bridge to Pathology/Genetics

Malignant Hyperthermia

A life-threatening syndrome characterized by muscle rigidity, hyperthermia, hypertension, acidosis, and hyperkalemia. Associated with the use of skeletal muscle relaxants, especially succinylcholine, used in anesthesia regimens. Genotypic susceptibility may be related to mutations in the genes encoding ryanodine receptors and/or a protein component of the L-type calcium channel in skeletal muscle.

Treatment

Dantrolene acts directly on skeletal muscle to decrease contractility by blocking Ca^{2+} release from the sarcoplasmic reticulum. It is used in states that include extreme muscle rigidity, such as malignant hyperthermia associated with inhaled anesthetics and skeletal muscle relaxants or neuroleptic malignant syndrome associated with antipsychotics.

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Opioid Analgesics 7

Learning Objectives

- ❑ Describe the site of action, effects, and common complications associated with morphine use
- ❑ Differentiate between mu-receptor agonists, antagonist, and mixed agonist-antagonist
- ❑ Describe the appropriate use of these medications in the treatment of pain, opiate withdrawal, and drug abuse

- Endogenous opiate peptides represented by endorphins, enkephalins, and dynorphins
- Three receptor families: μ, κ, and δ
- Presynaptic and postsynaptic inhibition through G_i coupling
- Mu pharmacology most important
- Morphine is the prototype μ agonist
- Pharmacology of **morphine**:
  - Analgesia: ↑ pain tolerance and ↓ perception and reaction to pain
  - Sedation
  - Respiratory depression: ↓ response to ↑ pCO_2 (do not give O_2; give naloxone)
  - Cardiovascular: minimal effects on heart, but vasodilation (avoid in head trauma)
  - Smooth muscle
    - Longitudinal relaxes
    - Circular constricts

      GI: ↓ peristalsis, constipation, cramping

      GU: urinary retention, urgency to void

      Biliary: ↑ pressure

      Pupils: miosis
  - Cough suppression: antitussive action, independent of analgesia and respiratory depression
  - Nausea and vomiting: stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema
  - ↑ histamine release

Clinical Correlate

Contraindications and Cautions for Opioids

- Head injuries (possible increased intracranial pressure)
- Pulmonary dysfunction (except pulmonary edema)
- Hepatic/renal dysfunction (possible accumulation)
- Adrenal or thyroid defi iencies (exaggerated responses)
- Pregnancy (possible neonatal depression or dependence), except meperidine which does not inhibit uterine contractions in delivery and causes less respiratory depression in the newborn

- Pharmacokinetics of morphine:
  - Glucuronidation
  - Morphine-6-glucuronide is highly active
  - Caution in renal dysfunction
- Other opioids and analgesics (*see* Table IV-7-1).

Table IV-7-1. Other Opioids and Analgesics

Receptor Action	Drug	Characteristics
Full agonists	Meperidine	• Also antimuscarinic No miosis Tachycardia No spasm GI/GU/gallbladder • Metabolized by cytochrome P450 to normeperidine, a serotonin reuptake inhibitor; normeperidine may cause serotonin syndrome and seizures
	Methadone	• Used in maintenance of opiate addict
	Codeine	• Cough suppressant • Analgesia • Used in combination with NSAIDs
Partial agonist	**Buprenorphine**	**• Precipation of withdrawal**
Mixed agonist-antagonists	Nalbuphine, pentazocine	• κ agonist spinal analgesia dysphoria • μ antagonist precipitation of withdrawal
Antagonists	Naloxone	• IV, reversal for respiratory depression
	Naltrexone	• PO, ↓ craving for alcohol and used in opiate addiction
	Methylnaltrexone	• Treatment of opioid-induced constipation (does not cross BBB and won't precipitate withdrawal)

- Side effects of opioid analgesics:
  - Acute toxicity: classic triad
    - Pinpoint pupils
    - Respiratory depression
    - Coma
  - Management of acute toxicity:
    - Supportive
    - IV naloxone

Clinical Correlate

Seizures caused by meperidine cannot be treated with opioid antagonists; use benzodiazepines

- Abuse liability of opioid analgesics:
  - Tolerance: pharmacodynamic; occurs to all effects, except miosis and constipation
  - Dependence: physical and psychologic
  - Withdrawal:
    - Yawning
    - Lacrimation, rhinorrhea, salivation
    - Anxiety, sweating, goose bumps
    - Muscle cramps, spasms, CNS-originating pain
  - Management of withdrawal:
    - Supportive
    - Methadone
    - Clonidine
- Opiate-related drugs with specific indications
  - Loperamide: diarrhea
  - Dextromethorphan: cough

Chapter Summary

- Opioid agonists and/or antagonists act in part by binding to the receptors for the endogenous opiopeptides. These are G-protein–linked, multisubunit structures to which the various opioids bind as full or partial agonists or as antagonists. The resultant complex array of potential mechanisms, sites of action, types of effects, kinetics, and contraindications are discussed.
- Table IV-7-1 summarizes the receptor actions and other relevant characteristics of 8 opioid drugs.

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Drugs of Abuse 8

Learning Objectives

- ❏ Provide an overview of the main classes of medications that are abused and controlled
- ❏ Give examples of drugs in each class and describe their effect, toxicity, and withdrawal response

Table IV-8-1. Properties of Drugs of Abuse

CNS Stimulants	Cocaine	Amphetamines
Neurotransmitters involved	NE, DA, 5HT	
Mechanism(s) of action	Blocks DA, NE, and 5HT reuptake in CNS; local anesthetic action from Na+ channel blockade	Blockade of reuptake of NE and DA, release amines from mobile pool, weak MAO inhibitors
Effects	1. Increase NE: sympathomimetic effect with increased heart rate and contractility, blood pressure changes, mydriasis, and central excitation, hyperactivity 2. Increase DA: psychotic episodes, paranoia, hallucinations, possible dyskinesias, and endocrine disturbances 3. Increase 5HT: behavioral changes, aggressiveness, dyskinesias, and decreased appetite	
Toxicity	1. Excess NE: cardiac arrhythmias, generalized ischemia with possible MI and strokes; acute renal and hepatic failures 2. Excess DA: major psychosis, cocaine delirium 3. Excess 5HT: possible serotonin syndrome 4. All of the above: convulsion, hyperpyrexia, and death	
Withdrawal	Craving, severe depression, anhedonia, anxiety; manage with antidepressants	
CNS Depressants	**Benzodiazepines**	**Barbiturates and Ethanol**
Neurotransmitters involved	GABA	
Mechanism of action	Potentiation of GABA interaction with $GABA_A$ receptors involves BZ_1 and BZ_2 binding sites	Prolongation of GABA, GABA mimetic at high doses, on $GABA_A$ receptors
Effects	Light to moderate CNS depression	Any plane of CNS depression
Toxicity	Sedation, anterograde amnesia; in severe OD (or IV use), reverse with **flu azenil**	Severe CNS depression, respiratory depression, and death
Withdrawal	Rebound insomnia, rebound anxiety	Agitation, anxiety, hyperrefl xia, and life-threatening seizures + in ethanol withdrawal delusions/ hallucinations—delirium tremens (DTs)

Table IV-8-1. Properties of Drugs of Abuse (continued)

Opioids	**Morphine, Heroin, Methadone, Fentanyls, Other Opioids**	
Neurotransmitters involved	NE, DA, 5HT, GABA, and many others	
Mechanism of action	Activate opioid μ, κ, and δ receptors. Potent μ receptor activators have the most intense abuse and dependence liability, possibly effected via an increase in dopaminergic transmission in the mesolimbic tracts	
Effects	Euphoria, analgesia, sedation, cough suppression, and constipation; strong miosis (except meperidine)	
Toxicity	Severe respiratory depression (reverse with **naloxone**), nausea, vomiting	
Withdrawal	Lacrimation, yawning, sweating, and restlessness, rapidly followed with centrally originating pain, muscle cramping, and diarrhea; not life-threatening	
Hallucinogens	**Marijuana**	**Hallucinogens**
Neurotransmitters involved	Many	5HT
Mechanism of action	Interaction of THC with CB_1 and CB_2 cannabinoid receptors in CNS and periphery	Interaction with several subtypes of 5HT receptors
Effects	Sedation, euphoria, ↑ HR, conjunctival irritation, delusions, hallucinations	Hallucinogen, sympathomimetic, causes dysesthesias
Toxicity	Associated with smoking, possible fl shbacks	Poorly described, fl shbacks likely
Withdrawal	Irritability, anxiety	Poorly characterized

Miscellaneous Abused Drugs

1. PCP: NMDA-receptor antagonist; extremely toxic, horizontal and vertical nystagmus, paranoia, rhabdomyolysis; overdose is common, with convulsions and death
2. Ketamine: similar to but milder than PCP, with hallucinations, glutamate-receptor antagonist
3. Anticholinergics: scopolamine, atropine-like
4. MDMA ("Ecstasy"), MDA, MDEA: amphetamine-like with strong 5HT pharmacology and therefore hallucinogenic; generally neurotoxic
5. Inhalants: solvent abuse, multiple organ damage; see Toxicology, section XI

Chapter Summary

- Table IV-8-1 summarizes the properties of drugs of abuse. These include the CNS stimulants (cocaine and amphetamines), the CNS depressants (benzodiazepines, barbiturates, and ethanol), the opioids (morphine, heroin, methadone, fentanyl, and others), the hallucinogens (marijuana and other hallucinogens), PCP, ketamine, anticholinergics (scopolamine), MDMA-MDA-MDEA (all amphetamine-like), and inhalants.

CNS Drug List and Practice Questions

9

Table IV-9-1. CNS Drug List

Sedative-Hypnotics	Anticonvulsants
Barbiturates: phenobarbital Benzodiazepines: alprazolam, diazepam, lorazepam, oxazepam	Carbamazepine, ethosuximide, valproic acid, phenytoin, diazepam, lorazepam, gabapentin, lamotrigine, felbamate, topiramate, tiagabin, vigabatrin
	Anesthetics (Inhaled)
Others: buspirone, zolpidem, zaleplon BZ receptor antagonist: flu azenil	Desflu ane, sevoflu ane, nitrous oxide
Anesthetics (IV)	**Neuromuscular Blocking Agents**
Fentanyl, ketamine, midazolam, propofol, thiopental	Depolarizing: succinylcholine Nondepolarizing: atracurium, tubocurarine
Local Anesthetics	**Skeletal Muscle Relaxants**
Lidocaine, bupivacaine, mepivacaine, procaine, cocaine	Depolarizing: succinylcholine Nondepolarizing: D-tubocurarine, atracurium
Opioid Analgesics	**Antipsychotics**
Full agonists: morphine, meperidine, methadone, fentanyl, and heroin Partial agonists: buprenorphine, codeine Mixed agonist-antagonists: nalbuphine Antagonists: naloxone, naltrexone, methylnaltrexone	Typicals: Chlorpromazine, fluphe azine, thioridazine, haloperidol Atypicals: clozapine, risperidone, olanzapine, aripiprazole, quetiapine, ziprasidone
Antiparkinsonian Drugs	**Antidepressants**
DA agonists: levodopa, bromocriptine, pramipexole MAO-B inhibitor: selegiline AAAD inhibitor: carbidopa M blockers: benztropine, trihexiphenidyl COMT inhibitor: tolcapone DA releaser and M blocker: amantadine	MAOIs: phenelzine, tranylcypromine TCAs: amitriptyline, imipramine, clomipramine SSRIs: flu xetine, paroxetine, sertraline Others: bupropion, mirtazapine, trazodone, venlafaxine
Bipolar Disorder	**ADHD**
Lithium	Methylphenydate Atomoxetine

1. Lorazepam can be safely used as a preanesthetic medication in a patient undergoing liver transplantation without fear of excessive CNS depression because the drug is

   A. excreted in unchanged form
   B. actively secreted into the GI tract
   C. conjugated extrahepatically
   D. a selective anxiolytic devoid of CNS depressant actions
   E. reversible by naloxone

2. Midazolam is an effective anesthetic because it acts by

   A. increasing functional activity at $GABA_B$ receptors
   B. enhancing the actions of dopamine
   C. blocking the NMDA glutamate receptor subtype
   D. acting as a partial agonist at 5HT receptors
   E. facilitating GABA-mediated increases in chloride ion conductance

3. Which one of the following is an established clinical use of morphine?

   A. Management of generalized anxiety disorders
   B. Relief of pain associated with biliary colic
   C. Pulmonary congestion
   D. Treatment of cough associated with use of ACE inhibitors
   E. Suppression of the ethanol withdrawal syndrome

4. A 40-year-old man was given a drug that binds to a subunit of the $GABA_A$ receptor. When used at a high dose, the drug can open Cl^- channels independent of GABA. What drug was the man given?

   A. Diazepam
   B. Ethanol
   C. Phenobarbital
   D. Baclofen
   E. Dronabinol

5. Which one of the following is characteristic of both phenytoin and carbamazepine?

   A. Inhibition of hepatic cytochrome P450
   B. First-order elimination at high therapeutic doses
   C. Enhances the effects of oral contraceptives
   D. Safe to use in pregnancy
   E. Prevent sodium influx through fast sodium channels

6. A patient comes to the ER with a painful stab wound. The ER resident administers pentazocine for the pain. Soon after administration the patient experiences sweating, restlessness, and an increase in pain sensations. What is the most likely explanation for his symptoms?

   A. The patient is probably tolerant to pentazocine.
   B. The patient is a heroin addict.
   C. Pentazocine is an ineffective analgesic.
   D. Pentazocine was used at the wrong dose.
   E. Pentazocine doesn't cross the blood-brain barrier.

7. The data shown in the table below concern the effects of drugs on transmitter function in the CNS. Which one of the drugs is most likely to alleviate extrapyramidal dysfunction caused by typical antipsychotics? (The + signs denote intensity of drug actions.)

Drug	Activation of DA Receptors	Activation of GABA Receptors	Block of ACh M Receptors
A.	++++	0	0
B.	++	++	0
C.	0	0	++++
D.	0	+++++	0
E.	+	+	0

8. Tricyclic antidepressants

   A. have anticonvulsant activity
   B. should not be used in patients with glaucoma
   C. may increase oral absorption of levodopa
   D. are sometimes used as antiarrhythmics

9. Which one of the following statements about lithium is accurate?

   A. It causes symptoms of mild hyperthyroidism in up to 25% of patients.
   B. Plasma levels are increased by a high-Na diet.
   C. Adverse effects include acne, polydipsia, and polyuria.
   D. Spina bifida is major concern in fetal development.
   E. Sedative actions calm manic patients within 24 h.

10. Ingestion of methanol in wood spirits would cause which of the following to happen?

    A. The formation of formaldehyde
    B. Nephrotoxicity
    C. Hypotension and vomiting
    D. The production of glycolic acids
    E. Inhibition of aldehyde dehydrogenase

11. What Is the rationale for combining levodopa with carbidopa?

    A. Carbidopa stimulates dopamine receptors
    B. Carbidopa increases levodopa entry into the CNS by inhibiting peripheral dopa decarboxylase
    C. Carbidopa enhances levodopa absorption
    D. Carbidopa enhances the peripheral conversion of levodopa to dopamine
    E. Carbidopa blocks peripheral COMT

12. A 29-year-old male patient is being treated with an antidepressant drug, and his mood is improving. However, he complains of feeling "jittery" and agitated at times, and if he takes his medication in the afternoon he finds it difficult to get to sleep at night. He seems to have lost weight during the 6 months that he has been taking the drug. He has been warned not to take other drugs without consultation because severe reactions have occurred with opioid analgesics including meperidine. This patient is probably taking

    A. alprazolam
    B. chlorpromazine
    C. paroxetine
    D. amitriptyline
    E. trazodone

13. The ability of several drugs to inhibit the reuptake of CNS amine neurotransmitters is shown in the table below (number of arrows ↓ indicates the intensity of inhibitory actions). Which one of the drugs is most likely to have therapeutic effectiveness in the management of both obsessive-compulsive disorders (OCD) and major depressive disorders?

Drug	DA Reuptake	NE Reuptake	5HT Reuptake	GABA Reuptake
A.	↓↓	0	0	↓↓
B.	0	↓↓↓↓	↓	0
C.	0	0	↓↓↓↓	0
D.	0	0	↓	↓↓↓↓
E.	↓↓↓↓	↓↓	0	0

14. A patient suffering from attention deficit hyperactivity disorder is placed on atomoxetine. A drug that has a similar mechansim of action to atomoxetine is

    A. methylphenidate
    B. botulinum toxin
    C. clonidine
    D. amitriptyline
    E. entacapone

15. A patient suffering from generalized anxiety disorder (GAD) has a history of drug dependence that includes the illicit use of secobarbital ("reds") and a variety of other drugs. Psychotherapy is indicated, but the physician also prescribes a drug that can be helpful in GAD and that has the advantage of no abuse liability. The drug prescribed was most likely to have been

    A. bupropion
    B. buspirone
    C. baclofen
    D. buprenorphine
    E. phenobarbital

16. A patient has been diagnosed has having "long QT syndrome." The patient is experiencing significant pain following a bout with shingles. What would be an appropriate drug for his pain?

    A. Amitriptyline
    B. Fentanyl
    C. Acyclovir
    D. Diazepam
    E. Gabapentin

17. A habitual user of a schedule-controlled drug abruptly stops using it. Within 8 h, she becomes anxious, starts to sweat, and gets severe abdominal pain with diarrhea. These symptoms intensify over the next 12 h, during which time she has a runny nose, is lacrimating, and has uncontrollable yawning and intensification of muscle cramping and jerking. Assuming that these are withdrawal symptoms in the patient due to her physical dependence, the drug most likely to be involved is

    A. alprazolam
    B. amphetamine
    C. ethanol
    D. meperidine
    E. secobarbital

18. A 57-year-old patient, living at home, has severe pain due to a metastatic carcinoma that is being managed with fentanyl, delivered transdermally from a patch. He should also be taking, or at least have on hand

A. apomorphine
B. docusate
C. loperamide
D. morphine
E. naloxone

19. A hospital nurse is taking imipramine for a phobic anxiety disorder, and her patient is being treated with chlorpromazine for a psychotic disorder. Which of the following adverse effects is likely to occur in both of these individuals?

A. Excessive salivation
B. Pupillary constriction
C. Orthostatic hypotension
D. Seizure threshold
E. Weight loss

20. Which one of the following pairs of "drug/mechanism of action" is most accurate?

A. Carbamazepine/facilitation of the actions of GABA
B. Ethosuximide/blocks Na channels in axonal membranes
C. Phenelzine/inhibits dopa decarboxylase
D. Procaine/blocks Ca channels (type T) in thalamic neurons
E. Lithium/inhibits recycling of inositol

21. A 30-year-old male patient is brought to the ER with the following symptoms attributed to a drug overdose: HR and BP, mydriasis, behavioral excitation, aggressiveness, paranoia, and hallucinations. Of the following drugs, which one is most likely to be responsible for these symptoms?

A. Amphetamine
B. Ethanol
C. Fentanyl
D. Flunitrazepam
E. Marijuana

22. Which one of the following CNS receptors is directly coupled to an ion channel so that the effects of its activation do not involve second messenger systems?

A. N (ACh)
B. α (NE)
C. D_{2A} (DA)
D. μ (beta endorphin)
E. $5HT_2$ (serotonin)

Answers

1. **Answer: C.** Most benzodiazepines are metabolized by liver cytochrome P450. In a patient lacking liver function, benzodiazepines that are metabolized via extrahepatic conjugation (e.g., lorazepam, oxazepam) are safer in terms of the possibility of excessive CNS depression. Lorazepam is metabolized, probably in the lungs, via glucuronidation. Although benzodiazepine actions can be reversed, the drug that acts as an antagonist is flumazenil, not naloxone.

2. **Answer: E.** Benzodiazepines interact with components of the GABA receptor–chloride ion channel macromolecular complex. Binding of BZs leads to an increase in the frequency of chloride ion channel opening elicited by the inhibitory transmitter GABA. Benzodiazepines do not act on $GABA_B$ receptors; baclofen, a centrally acting muscle relaxant, is an agonist at these receptors. Buspirone, the selective anxiolytic, may be a partial agonist at 5HT receptors.

3. **Answer: C.** Morphine continues to be used in pulmonary congestion, in part because of its sedative (calming) and analgesic effects and also because of its vasodilating actions, which result in favorable hemodynamics in terms of cardiac and pulmonary function. Similarly, morphine is of value in an acute MI, especially its ability to relieve pain. However, morphine is not suitable for pain of biliary origin because it causes contraction of the sphincters of Oddi, leading to spasms. None of the other proposed indications are appropriate.

4. **Answer: C.** Benzodiazepines, barbiturates, and ethanol all modulate the actions of the $GABA_A$ receptor, while baclofen works at the $GABA_B$ receptor, and dronabinol works on cannabinoid receptors. Of the $GABA_A$ drugs, only barbiturates have GABA-mimicking activity and this occurs at high doses. This is one of the reasons why barbiturates are a more dangerous group of drugs than benzodiazepines since benzos lack GABA-mimicking activity.

5. **Answer: E.** Phenytoin has the unusual characteristic of following first-order elimination kinetics at low doses but zero-order kinetics at high doses because of saturation of the liver enzymes involved in its metabolism. Carbamazepine, like most drugs, follows first-order kinetics. Both drugs are P450 inducers and can increase the metabolsim of oral contraceptives making them less effective. Both drugs are teratogenic, causing structural abnormalities during fetal development including cleft palate. Both drugs block inactivated sodium channels, preventing sodium entry, thereby prolonging the time to recovery.

6. **Answer: B.** Pentazocine is an agonist at κ (kappa) opioid receptors and an antagonist at μ opioid receptors. Mixed agonist-antagonists can displace μ receptor agonists such as heroin from receptors, resulting in the rapid development of symptoms of withdrawal in patients who are physically dependent on such drugs—"precipitated withdrawal." Symptoms include yawning, lacrimation, salivation, restlessness, anxiety, sweating, goosebumps, muscle cramps, and pain.

7. **Answer: C.** Muscarinic receptor antagonists such as benztropine, trihexyphenidyl, and diphenhydramine are used to manage the reversible extrapyramidal dysfunction (e.g., pseudo-Parkinsonism) that results from treatment with drugs that block DA receptors in the striatum (typical antipsychotics). Drugs that activate DA receptors, although theoretically possible, require doses that are toxic and exacerbate psychoses. Because the actions of DA in the striatum lead to inhibition of GABA-ergic neurons, drugs that activate GABA receptors are unlikely to be effective in this situation, although they may well have both anxiolytic and anticonvulsant properties.

8. **Answer: B.** In addition to blocking reuptake of NE and 5HT, pharmacodynamic actions of the tricyclic antidepressants include block of peripheral adrenergic and muscarinic receptors—the former resulting in postural hypotension and the latter, via mydriasis, exacerbating glaucoma. TCAs may cause arrhythmias in overdose. They have no effect on the absorption of levodopa.

9. **Answer: C.** Lithium causes goiter in a significant number of patients; however, thyroid dysfunction does not occur in all such patients, and when it does it presents as hypothyroidism (not hyper-T). High-Na diets increase lithium elimination; low Na increases lithium plasma levels. Uncoupling of vasopressin receptors is characteristic of lithium, leading to a nephrogenic diabetes insipidus. Although potential teratogenicity is a concern during pregnancy, lithium does not cause neural tube defects but may cause abnormalities in heart valves. Lithium takes 10 to 20 days for effectiveness, and in acute mania it is often necessary to calm the patient with parenteral antipsychotic drugs such as fluphenazine or haloperidol.

10. **Answer: A.** Methanol is metabolized by alcohol dehydrogenase to formaldehyde and then further metabolized to formic acid by aldehyde dehydrogenase. Its major toxicity is severe vision damage. Ethylene glycol Ingestion is associated with nephrotoxicity, while ethanol ingestion causes nausea, vomiting, and hypotension.

11. **Answer: B.** Carbidopa inhibits peripheral dopa decarboxylase which enhances uptake of levodopa into the CNS and therefore, its conversion to dopamine. Carbidopa doesn't cross the blood-brain barrier and therefore has no direct benefit at dopamine receptors.

12. **Answer: C.** The patient is probably taking an SSRI such as paroxetine. SSRIs rarely cause sedation and commonly cause agitation and the "jitters," which sometimes necessitates concomitant use of drugs that are strongly sedating, such as trazodone. SSRIs are best taken in the morning to avoid problems of insomnia, and they appear to cause weight loss, at least during the first 12 months of treatment. Severe drug interactions leading to the "serotonin syndrome" have been reported when SSRIs have been used together with MAO inhibitors, tricyclics, and the opioid meperidine.

13. **Answer: C.** Drug C appears to be a selective inhibitor of the reuptake of serotonin, and existing drugs of this class (SSRIs) are approved for use in both major depressive and obsessive-compulsive disorders. The tricyclic antidepressant clomipramine, a potent inhibitor of 5HT reuptake, was formerly the drug of choice for OCD until replaced by the SSRIs. Drugs A and E may have value in the treatment of Parkinson disease because they block the reuptake of DA. Drug D may be effective in anxiety and seizure states because it is an effective blocker of GABA reuptake.

14. **Answer: D.** Atomoxetine is used in attention deficit hyperactivity disorder (ADHD) and works by blocking the reuptake of norepinephrine into nerve terminals. This mechanism is how both cocaine and the tricyclic antidepressants such as amitriptyline work. Amphetamines such as methylphenidate are also commonly used in ADHD and work by displacing norepinephrine from the mobile pool.

15. **Answer: B.** Buspirone has selective anxiolytic activity that is slow in onset. The drug has no abuse liability and will not suppress withdrawal symptoms in patients who have become physically dependent on barbiturates, benzodiazepines, or ethanol. Bupropion is an antidepressant, also approved for management of dependence on nicotine. Baclofen is a spinal cord muscle relaxant that activates $GABA_B$ receptors. Buprenorphine is a long-acting opioid analgesic with no effectiveness in GAD, and phenobarbital is a barbiturate that may cause dependence.

16. **Answer: E.** The patient is experiencing postherpetic neuralgia. While acyclovir is effective at eradicating the herpes virus it is ineffective against the pain of shingles. Appropriate drugs are TCAs like amitriptyline and gabapentin. Patients with long QT syndrome have a genetic flaw in cardiac inward rectifying K current, leading to increased APD. Drugs that accentuate this by inhibiting the repolarizing K current (phase 3), which include thioridazine and the tricyclic antidepressants, are likely to have enhanced cardiotoxic potential in such patients. As a result, this patient should be placed on gabapentin.

17. **Answer: D.** The signs and symptoms described are typical of withdrawal from physical dependency on an opioid that has efficacy equivalent to a full agonist—in this case, meperidine. Although anxiety, agitation, and even muscle jerking may occur in withdrawal from dependence on sedative-hypnotics such as alprazolam and secobarbital, the symptoms of GI distress, rhinorrhea, lacrimation, and yawning are not characteristic (seizures are more typical). Symptoms of withdrawal from high-dose use of CNS stimulants such as amphetamine or cocaine include lassitude and severe depression of mood. The phrase "schedule-controlled" refers to FDA classifications of drugs that have abuse liability, including both licit and illicit drugs.

18. **Answer: B.** Fentanyl is a full agonist at opioid receptors and provides analgesia in cancer pain equivalent to morphine, so there is no good reason to have morphine on hand, and it would be a danger to the patient in terms of accidental overdose. Apomorphine is an emetic, hardly appropriate given the stimulatory effects of opioids on the emetic center. Likewise, loperamide is used in diarrheal states, and patients on strong opioids are almost certain to be constipated; for this reason, a stool softener like docusate should be available to the patient. The opioid antagonist naloxone is used IV in overdose situations but would not be provided to the patient for use PRN.

19. **Answer: C.** Orthostatic hypotension occurs with both tricyclic antidepressants and phenothiazines because both types of drug can block alpha-adrenergic receptors in venous beds. Their ability to block M receptors leads to xerostomia (not salivation) and mydriasis (not miosis). Tricyclics and phenothiazines also share a common tendency to decrease seizure threshold and cause weight gain (not loss).

20. **Answer: E.** Lithium inhibits the dephosphorylation of IP_2 (needed for the recycling of inositol), leading to depletion of membrane PIP_2. Consequently, the activation of receptors by neurotransmitters such as ACh, NE, and 5HT fails to release the second messengers IP_3 and DAG. Carbamazepine and the local anesthetic procaine block axonal Na channels; ethosuximide may block Ca channels in thalamic neurons. Phenelzine is a nonselective inhibitor of MAO.

21. **Answer: A.** The signs and symptoms are characteristic of a CNS stimulant that facilitates the activity of amines in both the CNS and the periphery. Amphetamines promote the release of NE from sympathetic nerve endings, causing CV stimulation and pupillary dilation. In the CNS, they enhance the actions of DA, NE, and 5HT, causing behavioral excitation and a psychotic state that may be difficult to distinguish from schizophrenia. Ethanol, marijuana, fentanyl, and flunitrazepam (a benzodiazepine that has been used in "date rape") are all CNS depressants.

22. **Answer: A.** ACh receptors in the CNS are present on less than 5% of the neuronal population. Most of them are of the muscarinic subtype, M_1 (excitatory) and M_2 (inhibitory), via G-protein coupled changes in cAMP. Nicotinic receptors are excitatory via direct coupling to cation channels (Na/K), and their activation does not initiate second messenger pathways. Other CNS transmitter receptors that are directly coupled to ion channels include those for GABA and glutamic acid. Almost all CNS receptors for DA, NE, 5HT, and opioid peptides are coupled to ion channels via second messenger systems.