Pharmacology of the Central Nervous System: Clinical Implications

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Online Course: www.dentalcare.com/en-us/professional-education/ce-courses/ce539

Disclaimer: Participants must always be aware of the hazards of using limited knowledge in integrating new techniques or procedures into their practice. Only sound evidence-based dentistry should be used in patient therapy.

Introduction
The objectives of the course are to identify therapeutic agents prescribed for the treatment of central nervous system (CNS) disorders, present their mechanisms of action and indications for their use.

Conflict of Interest Disclosure Statement
• Dr. Whittingham reports no conflicts of interest associated with this course.
• Dr. Terézhalmy has done consulting work for Procter & Gamble and has served on the dentalcare.com Advisory Board.

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Overview
This continuing dental education course is intended to provide a clinical frame of reference when patients present in the oral healthcare setting with a history of taking drugs for the treatment of CNS disorders. Based on the Top 300 Prescription Drugs dispensed by U.S. Community pharmacies common CNS disorders are identified and discussed, including implications to clinical dentistry.

Learning Objectives
Upon completion of this course, the dental professional should be able to:
• Discuss the relevance of the top 300 drugs dispensed by U.S. community pharmacies.
• Discuss the basis of CNS pharmacology.
• Identify common CNS drugs.
• Discuss the mechanism of action of CNS drugs and indications for their use.
• Discuss prevalent CNS disorders with reference to the practice of dentistry.

Introduction
A patient's overall health status determines the patient's ability to undergo dental care. Consequently, patient-specific problems that may interfere with the clinical process must be identified. In determining perioperative risk, clinicians must consider past and present illnesses, major hospitalizations, drug allergies and other adverse drug reactions (ADRs), dietary supplements and special diets, and medications taken by the patient.¹

In the U.S. there are approximately 500 FDA-approved active ingredients (therapeutic agents) in several thousand different formulations. ClinCalc DrugStats provides prescription drug utilization data estimates based on the Medical Expenditure Panel Survey (MEPS) conducted annually.² The list of Top Prescription Drugs of 2017 reflects data collected in 2014 and is based on more than 3 billion out-patient prescriptions.²

The Top 200 Prescription Drugs dispensed by U.S. community pharmacies represent 40% of the available 500 active ingredients and comprise 90% of all drugs taken by ambulatory patients.² The Top 300 Prescription Drugs represent 60% of the available 500 active ingredients and comprise 97% of all drugs taken by ambulatory patients.² These data are invaluable in identifying patient-specific risks factors in ambulatory settings.

The Top 300 Drugs of 2017 include 64 agents, prescribed primarily by physicians, for the treatment of conditions affecting the central nervous system (CNS). In relation to these drugs, minimum competency by oral healthcare providers assumes knowledge in the following four areas: (1) recognition of drugs by name (brand/generic); (2) indications for their use; (3) familiarity with potential ADRs; and (4) the use of informational resources.

DailyMed is the official repository for FDA-approved package inserts, i.e., for individual drug-related, clinically relevant data.³ The information is the most recent submitted to the FDA by pharmaceutical companies and includes strengthened warnings undergoing FDA review. The information is accurate; whenever possible it is based on human experience, and does not contain promotional or misleading information such as implied claims.

The Basis of CNS Pharmacology
The nervous system, comprised of two major components, i.e., the peripheral nervous system (PNS) and the central nervous system (CNS), has three main functions: sensory input, integration of data, and motor output.⁴ The PNS is subdivided into sensory (afferent) and motor (efferent) divisions. Afferent sensory neurons conduct signals from the PNS to the CNS. Efferent motor neurons conduct signals from the CNS to the PNS.
The efferent motor division of the PNS is subdivided into somatic and autonomic systems. The somatic nervous system controls voluntary movements. The autonomic nervous system (ANS) controls involuntary responses. The sympathetic division of the ANS mobilizes body systems and is responsible for “fight or flight” responses. The parasympathetic division of the ANS conserves energy and is responsible for responses related to “calm and relaxation.”

The CNS has three functional levels: neocortical, limbic, and vegetative (Figure 1). The vegetative or lowest level consists of the brain stem and the reticular activation system that connect the brain to the spinal cord. The mid-level is the limbic system or the emotional center of the brain responsible for the biochemical events that constitute the stress response. The highest and most sophisticated level of the brain is the neocortex.

The neocortex consists of grey matter surrounding the white matter of the cerebrum. The cerebral hemispheres, which contain the cerebral cortex and basal ganglia, are connected by a bundle of nerve fibers called the corpus callosum. The cerebral cortex is responsible for high-level functions, such as sensory perception, generation of motor commands, spatial reasoning, conscious thought, and in humans, language.

The basal ganglia consist of three deep nuclei of gray matter and include the caudate and putamen nuclei - known as the striatum, and the globus pallidus. They help initiate and control cortical functions. These actions include intended movement, behavior, and certain aspects of cognition. Regions of the basal ganglia responsible for movement ensure that intended actions are carried out and irrelevant movements are inhibited.

The cerebral cortex contains parts of, and interacts with, elements of the limbic system. Significant structures of the limbic system include the cingulate gyrus, amygdala, hippocampus, thalamus, and hypothalamus. The cingulate gyrus coordinates smells and sights with pleasant memories of previous emotions and participates in the emotional reaction to pain and the regulation of aggressive behavior.

The hippocampus is involved in learning memory, i.e., the conversion of temporary...
memories into permanent memories; helps to analyze and remember special relationships essential for accurate movements; and facilitates the use of memory to modify behavior. The amygndala connects with the hippocampus, the septal area, and the thalamus and mediates such feelings as friendship, affection, and expression of mood.

Various nuclei of the thalamus link sensory pathways from the periphery to the cortex and structures of the limbic system and is associated with changes in emotional activity. The hypothalamus controls mood (e.g., expression of emotions such as pleasure, rage, aversion, and displeasure); motivated behaviors such as sexuality and hunger; regulates thirst and body temperature; and via the pituitary gland, controls hormonal processes.

The cerebellum receives information related to spatial positioning; and sends signals to the motor areas of the cortex via the thalamus and down the spinal cord to regulate proprioception. The cerebellum coordinates skeletal muscle activity in space and time; maintains balance; controls eye movement; and influences motor learning (e.g., eye-hand coordination) and cognitive functions (e.g., timing of repetitive events and language).

The brainstem (medulla, pons and midbrain) connects the spinal cord to the thalamus and the cortex. The medulla and pons contain control centers that direct the autonomic nuclei that regulate heart rate, respiration, digestive functions, and reflex reactions (e.g., coughing and vomiting). In the midbrain, neurons in the periaqueuductal gray send descending projections to the spinal cord and modulate pain perception.

The spinal cord is organized into white and gray matter. White matter consists of fiber tracts that connect the periphery and spinal cord to more rostral areas of the CNS. Gray matter consists of dorsal and ventral horns. The dorsal horn relays sensory information from the periphery to the CNS. The ventral horn relays signals from central motor areas to skeletal muscle. Interneurons connect sensory and motor neurons and mediate reflexes.

Distant areas of the nervous system connect to one another and relay signals between the PNS and the CNS via long-tract neurons. Local circuit neurons maintain connectivity within a localized area of the CNS and modulate signal transmission. Single-source divergent neurons originate in various nuclei of the brainstem, hypothalamus, and basal forebrain and innervate broad areas of the CNS (Figures 2-7).

Neurons communicate with one another and with other cells through the release of neurotransmitters. Neurotransmitters are synthesized by cytoplasmic enzymes and are stored in neuronal vesicles. When a nerve is stimulated its resting potential changes and the action potential generated causes an influx of Ca$^{2+}$ ions into the presynaptic nerve terminal and the content of neurotransmitter-filled vesicles exocytose into the synaptic cleft.

The released neurotransmitter diffuses across the synaptic cleft and on the postsynaptic axonal membrane binds either to a neurotransmitter-gated ionotropic receptor and/or to a metabotropic receptor (e.g., a G protein-coupled receptor). Ionotropic receptor activation modulates ion channel function directly, while metabotropic receptor activation leads mainly to cAMP-dependent modulation of other ion channels.

A neurotransmitter may be excitatory or inhibitory and in some cases both (as a function of receptor subtypes). Excitatory neurotransmitters induce a net inward current by opening cation-specific ion channels, e.g., Na$^+$ and Ca$^{2+}$ ion channels; or by closing K$^+$ ion “leak channels.” The net influx of Na$^+$ and Ca$^{2+}$ ions and the reduced outward flow of K$^+$ ions across the neuronal membrane results in axonal membrane depolarization.

Inhibitory neurotransmitters induce a net outward current by opening K$^+$ ion channels or Cl$^-$ ion channels and induce K$^+$ efflux or Cl$^-$ influx, respectively. The loss of intracellular cations (i.e., K$^+$ ions) and the gain of intracellular anions (i.e., Cl$^-$ ions) moves the membrane potential away from its threshold value, reduces the ability of inward current to depolarize the membrane, and results in neuronal membrane hyperpolarization.
Figure 2. Glutamatergic neurons are found throughout the brain - most densely concentrated in the cerebral cortex, the hippocampus, the amygdala, the basal ganglia, the brain stem, and the spinal cord.

Figure 3. GABAergic neurons are found throughout the brain - most highly concentrated in the substantia nigra and globus pallidus of the basal ganglia, the cerebellum, the hypothalamus, interneurons throughout the brain, the periaqueductal gray, and the spinal cord.
Figure 4. Dopaminergic neurons arise in the substantia nigra and the ventral tegmental area and project to the striatum and the cerebral cortex, and to the amygdala and the hippocampus of the limbic system.

Figure 5. Cholinergic neurons arise in the pedunculopontine nucleus, the nucleus basalis, and the medial septal nuclei and project widely throughout the brain (hippocampus), and the spinal cord.
Figure 6. Serotonergic neurons arise in the raphe nuclei and project to the limbic system, the basal ganglia; and via the basal forebrain, to the cerebral hemispheres as well as the cerebellum and the spinal cord.

Figure 7. Noradrenergic neurons arise in the locus coeruleus and the lateral tegmental area and project widely throughout the cerebral cortex, the hypothalamus, the brain stem, cerebellum, and the spinal cord.
Termination of ionotropic neurotransmission at postsynaptic neurons is accomplished by two mechanisms: (1) degradation of the neurotransmitter by enzymes in the synaptic cleft and/or by (2) neurotransmitter uptake into the presynaptic terminal by specific transporters allowing the neurotransmitter to be recycled into synaptic vesicles for storage. Termination of signaling by a G protein-coupled neurotransmitter also involves intracellular enzymes.

Neurotransmitters in the CNS include acetylcholine, amino acids, monoamines, and a number of neuroactive peptides and purines (Table 1). Major amino acids neurotransmitters include glutamate, gamma-aminobutyric acid (GABA), and others such as glycine and aspartate. Major monoamine neurotransmitters include the catecholamines dopamine and norepinephrine; and the indoleamine serotonin.⁴⁻¹¹

CNS Drugs in the Top 300 Prescription Drugs
Since excitatory and inhibitory neurotransmitters are implicated in several pathological processes affecting the CNS, altering neurotransmitter kinetics and dynamics provides a mechanism for pharmacological intervention. CNS drugs in the Top 300 dispensed in 2017 include receptor modulators, direct receptor agonists or antagonists, inhibitors of neurotransmitter degradation, and inhibitors of neurotransmitter reuptake (Tables 2-7).²

Prevalent CNS Disorders
Based on the mechanisms of action of CNS drugs in the Top 300 Prescription Drugs of 2017 dispensed by U.S. community pharmacies, the most common major CNS disorders encountered in an ambulatory patient population include generalized anxiety disorder, major mood disorders, schizophrenia (psychosis), seizure disorders, Alzheimer's disease, Parkinson's disease, and attention-deficit/hyperactivity disorder.

Generalized Anxiety Disorder
Fear and anxiety normally reflect adaptive responses to stress. Biological responses to stress activate the hypothalamic-pituitary-adrenal axis and the central noradrenergic system. These neurochemical systems subserve important adaptive functions in preparing the organism to respond to a treat or stress by increasing vigilance, modulating memory, mobilizing energy stores, and elevating cardiovascular function.

Acute stress increases CRH, ACTH, cortisol, and central norepinephrine release. In addition, acute stress affects central GABAergic, serotonergic, and dopaminergic activity, which plays important roles in modulating stress responses and emotional behavior.⁰⁻⁷,⁹,¹² These stress-induced biological responses, if chronically or inappropriately activated, can become dysregulated and result in generalized anxiety disorder (GAD).

Patient with GAD experience chronic anxiety about events and activities, which lead to physiologic symptoms characterized by restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbances, and a high-number of comorbidities such as depression and other medical problems (hypoglycemia, cardiomyopathy).¹³,¹⁴ GAD can cause marked, clinically significant impairment of social and occupational functioning.

SSRI, SNRI, norepinephrine reuptake inhibitors, and serotonin receptor agonists have emerged as first-line therapies for patients with GAD (Table 4).⁵⁻¹³,¹⁴ The primary advantage of these agents is their favorable ADR profile with long-term use. Benzodiazepines are also effective in the treatment of GAD, but their long-term use, especially in older adults is troublesome, and they are not effective in resolving unipolar depression (Table 2).

When providing oral healthcare to patients with GAD, the goals are to develop and implement timely preventive and therapeutic strategies. The anxiety, worry, or physical symptoms can cause clinically significant distress or impairment in the patient's ability to perform optimal oral self-care, to participate in oral healthcare-related decision-making, to cooperate in their treatment, and they may perceive the dental setting as threatening.

Major Mood Disorders
Major mood disorders (MMD) are defined by the presence of depressive and/or manic or
### Table 1. Major neurotransmitters in the CNS.\(^{4-11}\)

<table>
<thead>
<tr>
<th>Neurotransmitter System</th>
<th>Receptor Types</th>
<th>Functional Class</th>
<th>Major Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glutamate</strong></td>
<td>Ionotropic AMPA, Kainate, NMDA</td>
<td>Excitatory (major)</td>
<td>Memory, learning</td>
</tr>
<tr>
<td></td>
<td>Metabotropic mGlu (_1) and mGlu (_5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mGlu (_2,4) and mGlu (_6,8)</td>
<td>Inhibitory</td>
<td></td>
</tr>
<tr>
<td><strong>GABA</strong></td>
<td>Ionotropic GABA (_A), Metabotropic GABA (_B)</td>
<td>Inhibitory (major)</td>
<td>Sleep, muscle tone, source of well-being</td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td>Metabotropic D(_1) and D(_5)</td>
<td>Excitatory</td>
<td>Enables intended movement, attention, learning, emotional regulation, memory, motivation (reward system), executive functions</td>
</tr>
<tr>
<td></td>
<td>D(_2,3,4)</td>
<td>Inhibitory</td>
<td></td>
</tr>
<tr>
<td><strong>Norepinephrine</strong></td>
<td>Metabotropic α(_1), β(_1), β(_2), and β(_3)</td>
<td>Excitatory</td>
<td>Vigilance, alertness, responsiveness to unexpected stimuli, source of well-being, sleep-wakefulness, learning, memory, attention, consciousness, regulates temperature and pituitary function, reduced digestion, increased heartbeat</td>
</tr>
<tr>
<td></td>
<td>α(_2)</td>
<td>Inhibitory</td>
<td></td>
</tr>
<tr>
<td><strong>Serotonin</strong></td>
<td>Ionotropic 5-HT(_3)</td>
<td>Excitatory</td>
<td>Mood, arousal, modulates eating (appetite), pain perception, behavior, regulates body temperature, sexual behavior</td>
</tr>
<tr>
<td></td>
<td>Metabotropic 5-HT(_1)</td>
<td>Inhibitory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-HT(_2) and 5-HT(_4,7)</td>
<td>Excitatory</td>
<td></td>
</tr>
<tr>
<td><strong>Acetylcholine</strong></td>
<td>Ionotropic Nicotinic N(_N)</td>
<td>Excitatory</td>
<td>Alertness, sleep-wakefulness, skeletal muscle contraction, memory formation, learning and general intellectual functioning, sensory responses</td>
</tr>
<tr>
<td></td>
<td>Metabotropic Muscarinic M(_1) and M(_2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscarinic M(_4)</td>
<td>Inhibitory</td>
<td></td>
</tr>
</tbody>
</table>
**Table 2. Drugs in the Top 300 Affecting GABAergic and Glutamatergic Neurotransmission.**

<table>
<thead>
<tr>
<th>Mechanisms of action*</th>
<th>Drugs*</th>
<th>Indications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine (\text{GABA}_A)-receptor modulators</td>
<td>Lorazepam, Diazepam, Temazepam, Clonazepam</td>
<td>Anxiety disorders, Seizures disorders, Insomnia, Alcohol withdrawal, Sedation, Muscle spasm</td>
</tr>
<tr>
<td>Non-benzodiazepine (\text{GABA}_A)-receptor modulator</td>
<td>Eszopiclone</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Non-benzodiazepine (\text{GABA}_B)-receptor agonism</td>
<td>Baclofen</td>
<td>Spasticity associated with spinal cord injury and motor neuron diseases (e.g., multiple sclerosis)</td>
</tr>
<tr>
<td>Non-benzodiazepine (\text{GABA}_B)-receptor modulator</td>
<td>Zolpidem</td>
<td>Hypnosis</td>
</tr>
<tr>
<td>Glutamatergic NMDA-receptor antagonism</td>
<td>Memantine</td>
<td>Alzheimer's disease</td>
</tr>
</tbody>
</table>

*FDA-approved information on specific agents is available at *DailyMed* - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.*

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Table 3. Drugs in the Top 300 Affecting Dopaminergic and Central Cholinergic Neurotransmission.²

<table>
<thead>
<tr>
<th>Mechanisms of action*</th>
<th>Drugs*</th>
<th>Indications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine precursor</td>
<td>Levodopa</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Provides substrate for increased dopamine synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine D₂-receptor agonism</td>
<td>Pramipexole Ropinirole</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Partial agonism at D₂ and 5-HT₁A receptors; Antagonism at 5-HT₂A receptors</td>
<td>Aripiprazole</td>
<td>Schizophrenia Major depressive disorder Autism-associated irritability</td>
</tr>
<tr>
<td>Dopamine D₂-receptor antagonism</td>
<td>Haloperidol</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Atypical antipsychotic agents</td>
<td>Risperidone Olanzapine Ziprasidone Quetiapine Lurasidone</td>
<td>Schizophrenia Depression Bipolar disorder Autism (risperidone)</td>
</tr>
<tr>
<td>Dopamine D₂- and serotonin 5-HT₂-receptor antagonism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarinic receptor antagonism</td>
<td>Benztropine</td>
<td>Parkinson's disease Extrapyramidal disease</td>
</tr>
<tr>
<td>Reduces cholinergic tone by modifying the actions of striatal cholinergic interneurons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitor of acetylcholine degradation</td>
<td>Donepezil</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>Inhibits acetylcholinesterase by binding to its active site</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FDA-approved information on specific agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.³
### Table 4. Drugs in the Top 300 Affecting Serotonergic and Central Adrenergic Neurotransmission.

<table>
<thead>
<tr>
<th>Mechanisms of action*</th>
<th>Drugs*</th>
<th>Indications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage inhibitors</td>
<td>Displace 5-HT, NE, and DA from storage vesicles in presynaptic nerve terminals</td>
<td>Amphetamine, Methylphenidate, Lisdexamfetamine dimesylate, Dextroamphetamine hydrochloride, Amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Inhibits the uptake of 5-HT and NE from the synaptic cleft by blocking 5-HT and NE transporters enhancing postsynaptic responses</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRI)</td>
<td>Selectively inhibit the reuptake of 5-HT from the synaptic cleft by blocking 5-HT transporters enhancing postsynaptic responses</td>
<td>Citalopram, Escitalopram, Fluoxetine, Sertraline, Paroxetine, Vilazodone</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRI)</td>
<td>Inhibit the reuptake of 5-HT and NE from the synaptic cleft by blocking 5-HT and NE transporters enhancing postsynaptic responses</td>
<td>Venlafaxine, Duloxetine, Desvenlafaxine, Milnacipran</td>
</tr>
<tr>
<td>Norepinephrine reuptake inhibitors (NRI)</td>
<td>Inhibit the reuptake of NE from the synaptic cleft by blocking NE transporters enhancing postsynaptic responses</td>
<td>Doxepin</td>
</tr>
</tbody>
</table>
Table 4. continued.

<table>
<thead>
<tr>
<th>Mechanisms of action*</th>
<th>Drugs*</th>
<th>Indications*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical antidepressant</strong></td>
<td>Weak inhibitor of 5-HT and NE uptake</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>Blocks 5-HT_{2A} and 5-HT_{2C} receptors and α₂-adrenergic autoreceptors decreasing 5-HT and increasing NE neurotransmission</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td></td>
<td>Postsynaptic 5-HT receptor antagonism</td>
<td>Trazodone</td>
</tr>
<tr>
<td><strong>Serotonin receptor agonism</strong></td>
<td>Selective 5-HT-receptor agonism</td>
<td>Buspirone</td>
</tr>
<tr>
<td></td>
<td>Partial agonism at 5-HT_{1} receptors and inhibition of 5-HT transporters</td>
<td>Vilazodone</td>
</tr>
<tr>
<td></td>
<td>Causes vasoconstriction mediated by 5-HT_{1} receptors expressed in the cerebral vasculature</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td><strong>Serotonin receptor antagonism</strong></td>
<td>Blocks 5-HT receptors with variable selectivity</td>
<td>Ondansetron</td>
</tr>
<tr>
<td><strong>PIP2-dependent signaling blockade</strong></td>
<td>Inhibits central adrenergic, muscarinic, and serotoninergic neurotransmission</td>
<td>Lithium</td>
</tr>
</tbody>
</table>

*FDA-approved information on specific agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.³
Table 5. Drugs that Affect Electrical Neurotransmission in the CNS.

<table>
<thead>
<tr>
<th>Mechanisms of action*</th>
<th>Drugs*</th>
<th>Indications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium channel inhibitors</td>
<td>Phenytoin</td>
<td>Tonic-clonic seizures, Focal seizures, Status epilepticus</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tonic-clonic seizures, Focal seizures, Bipolar disorder, Trigeminal neuralgia</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Focal seizures</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Tonic-clonic seizures, Focal seizures, Atypical absence seizures, Bipolar disorders</td>
<td></td>
</tr>
<tr>
<td>Calcium channel inhibitors</td>
<td>Pregabalin</td>
<td>Focal seizures, Postherpetic neuralgia</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Focal seizures, Peripheral diabetic neuropathy, Fibromyalgia, Postherpetic neuralgia, Neuropathic pain (spinal injury)</td>
<td></td>
</tr>
<tr>
<td>Divalproex</td>
<td>Complex partial seizures, Complex absence seizures, Manic episodes associated with bipolar disorders, Migraine (prophylaxis)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine GABA&lt;sub&gt;A&lt;/sub&gt;-receptor modulators</td>
<td>Clonazepam, Diazepam, Lorazepam</td>
<td>Status epilepticus, Tonic-clonic seizures, Focal seizures, Absence seizures, Skeletal muscle spasm</td>
</tr>
<tr>
<td>Other antiepileptic drugs</td>
<td>Topiramate</td>
<td>Tonic-clonic seizures, Focal seizures, Migraine (prophylaxis)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Tonic-clinic seizures, Focal seizures, Myoclonic seizures</td>
<td></td>
</tr>
</tbody>
</table>

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Table 6. Other Centrally Acting Muscle Relaxants.

<table>
<thead>
<tr>
<th>Mechanisms of action</th>
<th>Drugs</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems</td>
<td>Cyclobenzaprine hydrochloride</td>
<td>Skeletal muscle spasm of local origin</td>
</tr>
<tr>
<td>Central alpha2-adrenergic receptor agonism</td>
<td>Tizadine</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Alters interneuronal activity in the descending reticular formation and the spinal cord</td>
<td>Carisoprodol</td>
<td>Acute, painful musculoskeletal conditions in adults</td>
</tr>
<tr>
<td>Produces CNS depression by an unknown mechanism</td>
<td>Metaxalone</td>
<td>Acute, painful musculoskeletal conditions in adults</td>
</tr>
<tr>
<td>Non-benzodiazepine GABAe-receptor agonism</td>
<td>Baclofen</td>
<td>Spasticity associated with motor neuron diseases (e.g., multiple sclerosis) and spinal cord injury</td>
</tr>
</tbody>
</table>

*FDA-approved information on specific agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.

Table 7. Anorectics.

<table>
<thead>
<tr>
<th>Mechanisms of action</th>
<th>Drugs</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displaces 5-HT, DA, and NE from storage vesicles in presynaptic nerve terminals</td>
<td>Phentermine</td>
<td>To suppresses appetite as short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity in the presence of other risk factors (e.g., controlled hypertension, diabetes, and hyperlipidemia).</td>
</tr>
<tr>
<td>Male and female hormone modulator</td>
<td>Cyanocobalamin</td>
<td>To temporarily decrease appetite and increase energy while maintaining a low calorie diet for weight reduction</td>
</tr>
</tbody>
</table>

*FDA-approved information on specific agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.
hypomanic episodes.\textsuperscript{15-17} Patients with recurrent depressive episodes without a history of mania or hypomania are said to have major depressive disorder (MDD). Patients who have experienced at least one manic or hypomanic episode, with or without an additional history of depressive episodes, are said to have bipolar disorder (BD).

The etiology of MDD and BD are not well understood at a molecular level and no reliable biomarkers have been identified. The disorders likely reflect complex disturbances in neural circuit activity rather than a simple chemical imbalance. However, the monoamine hypothesis, based largely on the mechanisms of action of known antidepressants, proposes that decreased serotonin and/or norepinephrine levels cause MDD.\textsuperscript{7,9,15-17}

MDD is characterized by fatigue or loss of energy, anxiety or psychomotor agitation, loss of ability to concentrate, markedly diminished interest in activities, pessimism (intense sadness and despair), low self-esteem, insomnia, increased or decreased appetite, and recurrent thoughts of death or suicidal ideation.\textsuperscript{15-17} MDD can cause marked, clinically significant impairment in self-care and social and occupational functioning.

BD is characterized by a period of depression followed by a distinct period of abnormally elevated or euphoric mood. Symptoms include inflated self-esteem or grandiosity; decreased need for sleep; increased, rapid, and loud speech; distractibility; increased goal-directed activity; disorganized and racing thoughts; and inability to concentrate. BD can cause marked, clinically significant impairment of social and occupational functioning.\textsuperscript{15-17}

Commonly used therapeutic agents for the medical management of MDD include the administration of SSRI, serotonin receptor agonists, SNRI, norepinephrine reuptake inhibitors, tricyclic antidepressants, and atypical antidepressant (Table 4).\textsuperscript{2,7,9,15-17} The treatment of BD includes mood stabilizers such as lithium (Table 4), atypical antipsychotic agents (Table 3), and certain anticonvulsants (Table 5).\textsuperscript{2,7,9,15-17}

When providing oral healthcare to patients with MDD or BD, the goals are to develop and implement timely preventive and therapeutic strategies. Symptoms can cause clinically significant distress or impairment in the patient’s ability to perform optimal oral self-care, to participate in oral healthcare-related decision-making, to cooperate in his/her treatment, and may perceive the dental setting as threatening.

**Schizophrenia**

Schizophrenia is a thought disorder characterized by episodes psychosis, i.e., impairment of reality testing. Patients manifest disorders of perception, thinking, speech, emotion, and/or physical activity. The model that is most often cited to explain the pathogenesis of schizophrenia is the dopamine hypothesis, which states that the abnormal motor and mood states are caused by excess (or dysregulated) central dopaminergic neurotransmission.\textsuperscript{7,9}

Schizophrenia is characterized by symptoms such as delusions, hallucinations, disorganized speech, and catatonic behavior; and reduction or loss of normal functions such as affective flattening (decreased emotional expression), alogia (decrease in fluency of speech), and avolition (decrease in goal-oriented behavior).\textsuperscript{18,19} Schizophrenia can cause marked, clinically significant impairment of social and occupational functioning, and reduced self-care.

Over the past decades dopamine D\textsubscript{2}-receptor antagonist (Table 3) and atypical antipsychotic agents (Table 3) have emerged as first-line therapies for schizophrenia.\textsuperscript{2,18,19} The term “atypical antipsychotic” refers to newer antipsychotic drugs that confer less risk of extrapyramidal ADEs than traditional, first generation “neuroleptics.” Nonadherence, which often leads to relapse of symptoms, is a significant problem with schizophrenia.

When providing oral healthcare to patients with schizophrenia, the goals are to develop and implement timely preventive and therapeutic strategies. Confirm adherence, relapse can cause clinically significant distress or impairment in the patient’s ability to perform optimal oral self-care, to participate in oral healthcare-related decision-making, to cooperate in his/her treatment, and may perceive the dental setting as threatening.
Seizure Disorders
Neuronal stability within the complex circuits of the CNS exists in a balance between excitatory and inhibitory influences. In general, excitatory glutamatergic activity is responsible for the initiation and spread of seizure activity and inhibitory GABAergic activity is responsible for its suppression. Thus, dysfunction in glutamatergic and/or GABAergic neurotransmission presents the chemical basis for seizures.

Seizure symptoms vary according to the anatomical location of seizure activity and may include prominent motor symptoms, loss of consciousness, paroxysmal alterations in sensory functions, and changes in higher order functions (e.g., emotion, memory, language, insight). Focal seizures result from abnormal activity within a finite area of the brain. Primary generalized seizures reflect abnormal activity from a central area.

Focal seizure without altered awareness, typically results from abnormal activity in the motor, sensory, or visual cortex resulting in involuntary/repetitive movement, paresthesia, and flashing lights, respectively. Focal seizure with altered awareness typically results from abnormal activity within the temporal lobe of the cortex characterized by an aura, involuntary/repetitive movements (lip smacking, hand wringing), and impaired memory.

Primary generalized seizures emanate from central brain regions and spread rapidly to both hemispheres of the cortex and include absence seizure (brief loss of consciousness, blank stare, occasional motor symptoms such as eye blinking or lip smacking, but without an aura); myoclonic seizure (brief individual or generalized muscle contractions); and tonic-clonic seizure (muscle contractions followed by shaking movement of the body).

Drugs of choice for the long-term treatment of seizures vary (Table 5). For partial or focal seizures high-voltage-activated calcium channel inhibitors may be prescribed. Sodium channel inhibitors and benzodiazepine GABAA-receptor modulators are effective for the treatment of both focal as well as tonic-clonic seizures. Patients with complex partial or absence seizures are prescribed low-threshold T-type calcium channel inhibitors.

When providing oral healthcare to patients with seizure disorders, the goals are to develop and implement timely preventive and therapeutic strategies. Confirm adherence to medication regimen. Perioperatively monitor to confirm ongoing alertness and other symptoms appropriate for the anticipated seizure disorder (predicated on the medical/drug history of the patient) and be prepared to respond to acute seizure-related events.

Alzheimer’s Disease
Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by accumulation of cerebral amyloid plaques, loss of cholinergic neurons in the basal nucleus of Meynert, and excessive glutamatergic activity. AD progresses through three stages over a period of fifteen or more years. Decline in memory, time disorientation, lack of spontaneity, errors in judgement, and decline in personal appearance and hygiene characterize stage one.

During the second stage, there is a more rapid decline in intellectual capacity. Patients may show an inability to recognize self in a mirror (mirror sign, loss of self). They may find it difficult to carry out purposeful movements such as eating or walking, and lose the ability for self-care. Patients lose ability to understand speech, to perform calculations, to recognize familiar objects, and experience partial or total loss of speech (alogia).

The third or terminal stage leaves the patient apathetic, disoriented, and unable to walk. Significant body wasting, seizures, anxiety, aggressive behavior, hallucinations, and delusional episodes are common. Other complications include malnutrition, aspiration pneumonia, pressure necrosis of the skin, and oral/odontogenic problems. Death usually results from infection secondary to a weakened immune system.

Patients have reduced submandibular salivary flow rates. Reduced antibacterial, lubricating, and buffering capacity of saliva places patients at increased risk for caries and periodontal
diseases; dysfunctional speech, chewing, and swallowing; and ageusia or dysgeusia. Donepezil, an acetylcholinesterase inhibitor (Table 3), is the only centrally acting cholinergic inhibitor approved for use in all stages of Alzheimer’s disease. Combination therapy with donepezil and memantine, a glutamatergic NMDA-receptor antagonist (Table 2), is approved for treating moderate-to-severe disease. Atypical antipsychotic agents (Table 3) can improve some behavioral manifestations of Alzheimer’s disease.

When providing oral healthcare to patients with AD, the goals are to develop and implement timely preventive and therapeutic strategies. In stage one, patients are able to participate in oral healthcare-related decision-making and are able to cooperate in their treatment. However, in advanced stages communication is hindered, patients become uncooperative, and may perceive the dental setting as unfamiliar or threatening.

Parkinson’s Disease
Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons that arise in the substantia nigra and project to the striatum. Cardinal features of striatal dopamine deficiency, characterized by impaired ability to control skeletal muscle movement, include akinesia, bradykinesia, rigidity, tremors, and in the later stages postural instability.

Akinesia and bradykinesia manifest as poverty of spontaneous movements and slowness in initiation of movements, respectively. Rigidity is characterized by increased muscle tone in response to passive movements. Tremors, present during rest, disappear on purposeful movement. During stress or anxiety-provoking situations tremors increase and initiation of movement becomes increasingly difficult, extremely fatiguing, and ponderously inefficient.

Tongue and pharyngeal motor deficits result in difficulties with mastication and speech; inability to form an adequate bolus; hesitancy in initiating swallowing; ptyalism (lack of salivary control); and disruption of peristalsis that can result in silent aspiration and lead to bronchopneumonia, a common cause of death in patients with PD. Other findings include orthostatic hypotension, anosmia, depression, psychosis, and dementia.

Levodopa (Table 3), a dopamine precursor, is the most effective drug for the treatment of PD. Dopamine agonists (Table 3) alone are useful for the early treatment of PD and as adjunct therapy in patients taking levodopa. Anticholinergic agents (Table 3) are useful for the symptomatic control of tremor in patients younger than 60 years without cognitive impairment; however, their use is limited by bothersome anticholinergic effects.

When providing oral healthcare to patients with PD, the goals are to develop and implement timely preventive and therapeutic strategies. In the early stages, patients are able to participate in oral healthcare-related decision-making and are able to cooperate in their treatment. However, in the advanced stages communication is hindered and patients become uncooperative as they perceive the dental setting as unfamiliar or threatening.

Attention-deficit/Hyperactivity Disorder
The essential features of attention-deficit/hyperactivity disorder (ADHD) are the presence of developmentally inappropriate degrees of inattention, hyperactivity, and impulsiveness. Its etiology is not fully understood; however, several genes have been identified that may mediate susceptibility to ADHD and it is generally accepted that ADHD is the result of a chemical imbalance in the “brain reward cascade.”

ADHD appears to be associated with two neurotransmitters. Inattention and distractibility appear to be related to low levels of norepinephrine. Impulse and behavior problems appear to be related to low levels of dopamine. ADHD includes three subtypes: primarily inattention (e.g., distracted, poor organizational skills); primarily hyperactive-
impulsive behavior (e.g., fidgety, overactive, and interruptive); or a combination of the two.\textsuperscript{29,34}

Drug therapy with psychostimulants such as methylphenidate, dextroamphetamine, and mixed amphetamine salts are the most effective and safe option and are first-line therapies for ADHD (Table 4).\textsuperscript{2,7,8,29-34} Other drugs approved by the U.S. Food and Drug Administration include alpha\textsubscript{2}-receptor agonists and atomoxetine, a selective inhibitor of the pre-synaptic norepinephrine transporter.\textsuperscript{2,8,10,29-34}

When providing oral healthcare to patients with ADHD, the goals are to develop and implement timely preventive and therapeutic strategies. Children with ADHD, because of inattention, tend to have poor oral hygiene and increased incidence of caries activity. They tend to brux and are at risk of dental/oral trauma.\textsuperscript{32} They are fidgety, overactive, and interruptive and are likely to be a behavior-management challenge perioperatively.\textsuperscript{32}

Inattention and impulsivity in adults with ADHD can lead to impaired homecare, potential nicotine dependence, and increased ingestion of caffeine and soft drinks.\textsuperscript{33} These behavioral tendencies promote increased dental caries activity and contribute to increased incidence of periodontal diseases. Significant modification of office care is not required, but broken appointments and inability to carry out optimal homecare may be a challenge.\textsuperscript{34}

**Summary**

Sixty-four of the top 300 drugs dispensed by U.S. community pharmacies are prescribed for the treatment of CNS disorders. Predicated on the mechanisms of action of these drugs, prominent CNS disorders in an ambulatory patient population include generalized anxiety disorder, major mood disorders, schizophrenia, seizure disorders, Alzheimer's disease, Parkinson's disease, and attention-deficit/hyperactivity disorder.
Course Test Preview
To receive Continuing Education credit for this course, you must complete the online test. Please go to: www.dentalcare.com/en-us/professional-education/ce-courses/ce539/start-test

1. Which of the following statements related to the nervous system is correct?
   a. The nervous system, comprised of two major components, i.e., the peripheral nervous system (PNS) and the central nervous system (CNS), has three main functions: sensory input, integration of data, and motor output.
   b. The PNS is subdivided into sensory (afferent) and motor (efferent) divisions.
   c. Afferent sensory neurons conduct signals from the PNS to the CNS. Efferent motor neurons conduct signals from the CNS to the PNS.
   d. All of the above.

2. Which of the following statements related to the CNS is correct?
   a. The vegetative or lowest level of the CNS consists of the brain stem and the reticular activation system that connect the brain to the spinal cord.
   b. The mid-level of the CNS is the limbic system or the emotional center of the brain responsible for the biochemical events that constitute the stress response.
   c. The highest and most sophisticated level of the CNS is the neocortex, which is responsible for high-level functions, such as sensory perception, generation of motor commands, spatial reasoning, conscious thought, and in humans, language.
   d. All of the above.

3. Which of the following statements related to the organization of the nervous system is correct?
   a. Distant areas of the nervous system connect to one another and relay signals between the PNS and the CNS via long-tract neurons.
   b. Local circuit neurons maintain connectivity within a localized area of the CNS and modulate signal transmission.
   c. Single-source divergent neurons originate in various nuclei of the brainstem, hypothalamus, and basal forebrain and innervate broad areas of the CNS.
   d. All of the above.

4. Which of the following statements related to neurotransmitters is correct?
   a. Neurotransmitters are synthesized by cytoplasmic enzymes and are stored in neuronal vesicles.
   b. When a nerve is stimulated its resting potential changes and the action potential generated causes an influx of Ca²⁺ ions into the presynaptic nerve terminal and the content of neurotransmitter-filled vesicles exocytose into the synaptic cleft.
   c. The neurotransmitter released into the synaptic cleft binds to a neurotransmitter-gated ionotropic and/or to a metabotropic receptor on the postsynaptic axonal membrane.
   d. All of the above.

5. All of the following statements related to excitatory and inhibitory neurotransmitters are correct EXCEPT which one?
   a. Excitatory neurotransmitters induce a net inward current by opening cation-specific ion channels, e.g., Na⁺ and Ca²⁺ ion channels; or by closing K⁺ ion “leak channels.”
   b. The net influx of Na⁺ and Ca²⁺ ions and the reduced outward flow of K⁺ ions across the neuronal membrane results in axonal membrane depolarization.
   c. Inhibitory neurotransmitters induce a net outward current by opening K⁺ ion channels or Cl⁻ ion channels and induce K⁺ efflux or Cl⁻ influx, respectively.
   d. The loss of intracellular cations (i.e., K⁺ ions) and the gain of intracellular anions (i.e., Cl⁻ ions) results in neuronal membrane hypopolarization.
6. **Which of the following statement related to the termination of neurotransmission is correct?**
   a. Termination of ionotropic neurotransmission may be accomplished by degradation of the neurotransmitter by enzymes in the synaptic cleft.
   b. Termination of ionotropic neurotransmission may be accomplished by neurotransmitter uptake into the presynaptic terminal by specific transporters allowing the neurotransmitter to be recycled into synaptic vesicles for storage.
   c. Termination of signaling by a G protein-coupled neurotransmitter may involve intracellular enzymes.
   d. All of the above.

7. **Which of the following is a CNS neurotransmitter?**
   a. Acetylcholine
   b. Amino acids such as glutamate and gamma-aminobutyric acid
   c. Monoamines such as dopamine, norepinephrine, and serotonin
   d. All of the above.

8. **Which of the following is the major excitatory neurotransmitter in the CNS?**
   a. GABA
   b. Glutamate
   c. Norepinephrine
   d. Acetylcholine

9. **Which of the following statements related to GABAergic or glutamatergic drugs in the Top 300 is correct?**
   a. Benzodiazepine GABAA-receptor modulators such as lorazepam, diazepam, temazepam, and clonazepam are indicated for the treatment of anxiety, seizures, and alcohol withdrawal.
   b. Baclofen, a non-benzodiazepine GABAB-receptor agonist, is indicated for the treatment of spasticity associated with spinal cord injury and motor neuron diseases (e.g., multiple sclerosis).
   c. Memantine, a glutamatergic NMDA-receptor antagonist, is indicated for the treatment of Alzheimer’s disease.
   d. All of the above.

10. **All of the following statements related to dopaminergic or cholinergic drugs in the Top 300 are correct EXCEPT which one?**
   a. Levodopa provides substrate for increased dopamine synthesis and is indicated for the treatment of Parkinson’s disease.
   b. Haloperidol, a dopamine D2-receptor antagonist, is indicated for the treatment of Parkinson’s disease.
   c. Dopamine D2- and serotonin 5-HT2-receptor antagonist are atypical antipsychotic agents indicated for the treatment of schizophrenia, depression, and bipolar disorder.
   d. Donepezil inhibits acetylcholinesterase by binding to its active site and is indicated for the treatment of Alzheimer’s disease.
11. All of the following statements related to serotonergic or adrenergic drugs in the Top 300 are correct EXCEPT which one?
   a. Amphetamine and methylphenidate displace 5-HT, NE, and DA from storage vesicles in presynaptic nerve terminals and are indicated for the treatment of ADHD.
   b. Amitriptyline, an inhibitor 5-HT and NE the uptake from the synaptic cleft by blocking 5-HT and NE transporters enhancing postsynaptic responses, is indicated for the treatment of depression.
   c. Selective serotonin reuptake inhibitors (SSRI) are indicated for the treatment of depression and anxiety disorders.
   d. Lithium inhibits central adrenergic, muscarinic, and serotonergic neurotransmission and is indicated for the treatment of major depression disorder.

12. All of the following drugs in the Top 300 that affect electrical neurotransmission are indicated for the treatment of both focal and tonic-clonic seizures EXCEPT which one?
   a. Oxcarbazepine, a sodium channel inhibitor; and pregabalin and gabapentin, inhibitors of high-voltage-activated calcium channels.
   b. The sodium channel inhibitors such as phenytoin, carbamazepine, and lamotrigine.
   c. Benzodiazepine GABAA-receptor modulators such as clonazepam, diazepam, and lorazepam.
   d. Topiramate and levetiracetam antiepileptic drugs of unknown mechanisms.

13. Which of the following drugs is a central alpha2-adrenergic receptor agonist and is indicated for the treatment of spasticity?
   a. Cyclobenzaprine hydrochloride
   b. Tizadine
   c. Carisopradol
   d. Mataxalone

14. All of the following statements related to GAD are correct EXCEPT which one?
   a. GAD appears to be the result of dysregulated GABAergic, serotonergic, and dopaminergic neurotransmission.
   b. Patient with GAD experience chronic anxiety about events and activities, which lead to physiologic symptoms characterized by restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbances, and a high-number of comorbidities such as depression and other medical problems (hypoglycemia, cardiomyopathy).
   c. SSRI, SNRI, norepinephrine reuptake inhibitors, and serotonin receptor agonists have emerged as first-line therapies for patients with GAD.
   d. GAD does not cause clinically significant distress or impairment in the patient’s ability to perform optimal oral self-care, to participate in oral healthcare-related decision-making, to cooperate in their treatment, and tend not to perceive the dental setting as threatening.

15. All of the following statements related to major mood disorders (MMD) are correct EXCEPT which one?
   a. MMD are defined by the presence of depressive and/or manic or hypomanic episodes.
   b. The etiology of MDD and BD are not well understood: however, the monoamine hypothesis proposes that decreased serotonin and/or norepinephrine levels cause major mood disorders.
   c. The treatment of MDD includes mood stabilizers such as lithium, atypical antipsychotic agents, and certain anticonvulsants.
   d. MMD can cause clinically significant distress or impairment in the patient’s ability to perform optimal oral self-care, to participate in oral healthcare-related decision-making, to cooperate in his/her treatment, and may perceive the dental setting as threatening.
16. **All of the following statements related to schizophrenia are correct EXCEPT which one?**
   a. Schizophrenia is a thought disorder characterized by episodes psychosis, i.e., impairment of reality testing.
   b. The model that is most often cited to explain the pathogenesis of schizophrenia is the dopamine hypothesis, which states that the abnormal motor and mood states are caused by decreased central dopaminergic neurotransmission.
   c. Over the past decades dopamine D<sub>2</sub>-receptor antagonist and atypical antipsychotic agents have emerged as first-line therapies for schizophrenia.
   d. Nonadherence, which often leads to relapse of symptoms, is a significant problem with schizophrenia.

17. **All of the following statements related to seizure disorders are correct EXCEPT which one?**
   a. In general, glutamatergic activity is responsible for the initiation and spread of seizure activity and GABAergic activity is responsible for its suppression.
   b. Focal seizures emanate from central brain regions and spread rapidly to both hemispheres of the cortex.
   c. Sodium channel inhibitors and benzodiazepine GABA<sub>2</sub>-receptor modulators are effective for the treatment of both focal as well as tonic-clonic seizures.
   d. Perioperatively monitor to confirm ongoing alertness and other symptoms appropriate for the anticipated seizure disorder (predicated on the medical/drug history of the patient) and be prepared to respond to acute seizure-related events.

18. **All of the following statements related to Alzheimer's disease are correct EXCEPT which one?**
   a. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by accumulation of cerebral amyloid plaques, loss of cholinergic neurons in the basal nucleus of Meynert, and excessive glutamatergic activity.
   b. Patients with stage three AD lose ability to understand speech, to recognize familiar objects, and experience partial or total loss of speech (alogia).
   c. Donepezil, an acetylcholinesterase inhibitor is approved for use in all stages of Alzheimer's disease - combination therapy with memantine (a glutamatergic NMDA-receptor antagonist) is approved for treating moderate-to-severe disease.
   d. In advanced stages of AD, communication is hindered; patients become uncooperative, and may perceive the dental setting as unfamiliar or threatening.

19. **Which of the following statements related to Parkinson's disease is correct?**
   a. Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons that arise in the substantia nigra and project to the striatum.
   b. Cardinal features of striatal dopamine deficiency, characterized by impaired ability to control skeletal muscle movement, include akinesia, bradykinesia, rigidity, tremors, and in the later stages postural instability.
   c. Levodopa, a dopamine precursor, is the most effective drug for the treatment of PD; dopamine agonists alone are useful for the early treatment of PD and as adjunct therapy in patients taking levodopa.
   d. All of the above.
20. All of the following statements related to attention-deficit/hyperactivity disorder (ADHD) are correct EXCEPT which one?
   a. The essential features of attention-deficit/hyperactivity disorder (ADHD) are the presence of developmentally inappropriate degrees of inattention, hyperactivity, and impulsiveness.
   b. Inattention and distractibility appear to be related to low levels of norepinephrine; Impulse and behavior problems appear to be related to low levels of dopamine.
   c. Drug therapy with psychostimulants such as methylphenidate, dextroamphetamine, and mixed amphetamine salts are the most effective and safe option and are first-line therapies for ADHD.
   d. Adults with ADHD, in particular, are likely to be a behavior-management challenge perioperatively and require significant modification of office care.
References
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