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Sacramento, CA 95899
Tel: 800-232-4238 (within the U.S.)
916-783-4238 (outside the U.S.)
Fax: 916-783-6067
Email: Info@NetCE.com
Website: www.NetCE.com

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James Trent, PhD

Featured Contributing Faculty
A. José Lança, MD, PhD
Jane C. Norman, RN, MSN, CNE, PhD
Amanda Perkins, MSN, DNP
Carol Whelan, APRN

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Migraine: Diagnosis and Therapeutic Advances

Audience
This course is designed for nurses, nurse practitioners, physicians, physician assistants, and other healthcare professionals involved in the care of patients with known or suspected migraine.

Course Objective
The purpose of this course is to provide an update of research elucidating the pathophysiology of migraine, which has resulted in "mechanism-based" therapies; to review the differential diagnosis of headache disorders; and to summarize the current and evidence-based guidelines for clinical management of migraine. The course will highlight the need for a graded therapeutic response based on frequency of attacks and pattern of symptoms, and the importance of patient education and self-management techniques as a means of ensuring compliance and improving outcomes.

Learning Objectives
Upon completion of this course, you should be able to:

1. Discuss the prevalence of migraine in relation to age, gender, and such factors as socioeconomic status, education, and comorbidities.
2. Provide an updated overview of the progress made in the understanding of migraine pathophysiology.
3. Review the clinical profiles and diagnostic criteria of migraine with or without aura, and summarize disease staging.
4. Provide an update overview of the differential diagnosis of migraines focusing on medical and dental conditions, such as temporomandibular disorders, sinusitis, and orofacial pain.
5. Discuss the preventive and acute treatment of migraine.

Faculty
A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and received a Young Investigator Award by the American Brain & Behavior Research Foundation. (A complete biography appears at the end of this course.)

Faculty Disclosure
Contributing faculty, A. José Lança, MD, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Jane C. Norman, RN, MSN, CNE, PhD

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INTRODUCTION

Migraine is the leading condition of recurrent cephalalgias of moderate or severe intensity. It is the most common type of headache in patients who seek medical treatment. According to the 2016 Global Burden of Disease study, over 1 billion persons experience a migraine headache each year [20]. Migraine is among the top five most disabling medical conditions worldwide and the burden is greatest in women between 15 and 45 years of age [20; 191].

Migraine has been identified as one of the most common neurologic disorders, and in the United States, its prevalence in the general population is approximately 15% [190]. In children, the prevalence ranges from 1% to 4% and does not present a gender bias. However, after menarche, its prevalence in women (20.5%) is more than two times greater than the prevalence in men [2; 3].

Medical advances have provided insightful evidence regarding the role of the trigeminal system, cortical spreading depression, ion-channel pathology, and signaling molecules (such as nitric oxide, adenosine, and calcitonin gene-related peptide [CGRP]) in the pathophysiology of migraine. Together, they have led to the "mechanism-based" development of new drugs that show promising clinical efficacy coupled with a lower occurrence of adverse effects. The improved risk/benefit profile of a newer generation of antimigraine medications will be discussed in this course.

The differential diagnosis and management of other cephalalgias relevant to medical and dental practice, such as cranial neuralgias, trigeminal pathology, temporomandibular joint dysfunction, and oral pathologies, are seldom addressed in discussions of migraine. However, this course will extensively review the differential diagnosis between migraine and the most common medical conditions with similar presentation (e.g., cluster and tension headache).

PREVALENCE, INCIDENCE, AND SOCIAL BURDEN OF MIGRAINE

How common are primary headaches?

Cephalalgias have a lifetime prevalence of more than 90% and an estimated prevalence of 50% in the adult population worldwide [2; 3]. Primary headaches are the fourth most common cause for patients to seek emergency care in the United States [4; 5]. Secondary headaches, although less frequent, have well-defined etiologies, including infections (e.g., sinusitis, meningitis), cerebrovascular disorders (e.g., ischemia, thrombus, hemorrhage), or neoplasias, and are diagnosed based on history, examination, laboratory tests, and imaging studies (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI]) [6; 7].

According to the International Classification of Headache Disorders, published by the International Headache Society, there are four main types of primary headaches: tension-type headache, cluster headache/trigeminal autonomic cephalalgias (TACs), migraine, and a group that includes miscellaneous types of primary headaches not included in the previous three groups [6; 8]. Tension-type headache is the most common, with a prevalence of 30% to 78% [2; 6; 8; 9]. Typically, tension-type headache is bilateral with mild-to-moderate intensity and non-pulsating quality. It is neither associated with nausea nor aggravated by routine physical activity [6; 8; 9].

Cluster headache and TACs are severe and uncommon headaches with a prevalence of 0.07% to 0.4% and occur more commonly in men than in women [10]. These headaches are intermittent, short-lasting, and excruciatingly painful unilateral headaches. The quality of the pain is sharp or stabbing but not pulsating, which typically differentiates them from migraines. The pain peaks within 10 to 15 minutes and persists for an average of one hour. During cluster headache, patients do not seek rest (quite unlike during migraine headache), but are noticeably agitated and restless and present with parasympathetic autonomic dysfunction (e.g., conjunctival injection, lacrimation) [6; 8; 9].

The miscellaneous group of primary headaches is made up of a variety of conditions, including thunderclap headache and exertional headache. These conditions can mimic potentially serious secondary headaches and require thorough clinical evaluation supported by appropriate laboratory tests and imaging procedures. Thunderclap headache occurs suddenly, reaches maximum intensity within one minute, and lasts 1 to 24 hours or even several days. Typically, patients describe the pain of a thunderclap headache as an "explosion in the head" or "being hit with a bat" [11]. Thunderclap headache mimics the pain of a ruptured cerebral aneurysm. Considering that up to 25% of patients with thunderclap headache have subarachnoid hemorrhage (SAH) and that the mortality rate from SAH is approximately 50%, these patients require emergency evaluation, including detailed physical examination and CT scan. Imaging tests are used in the differential diagnosis with other potentially life-threatening conditions, such as intracerebral hemorrhage, cerebral venous thrombosis, hypertensive emergency, and ischemic stroke, in addition to SAH. Lumbar puncture is recommended in patients with thunderclap headache and non-diagnostic CT scan. The risk/benefit of CT or MRI angiography should be taken into account in patients with normal brain CT and cerebrospinal fluid (CSF) analysis, considering that the risk of SAH and death is extremely low in this group [12; 13]. Clinically, it is recommended that the diagnosis of thunderclap headache should apply only when no specific etiology is identified despite comprehensive diagnostic evaluation [8; 11; 12].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American College of Radiology, trigeminal autonomic cephalgia are diagnosed clinically, but head MRI may be appropriate, because secondary causes need to be excluded. Head magnetic resonance angiography and computed tomography angiography are not usually indicated initially.

(https://acsearch.acr.org/docs/69482/Narrative. Last accessed June 21, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

Exertional headache is triggered by physical exercise and is a pulsating headache that lasts from minutes to two days. These patients require comprehensive neurologic evaluation and imaging studies to help eliminate possible underlying secondary causes, including SAH and arterial dissection [6; 8; 9; 14].

As noted, migraine is the leading condition of recurrent cephalalgias of moderate-to-severe intensity. Pain usually builds up over a 1- to 2-hour period and lasts 4 to 72 hours. These headaches present at least two of the following characteristics:

- Typically pulsating or throbbing
- Unilateral and localized in the frontotem-poral and ocular area, although the pain may be felt anywhere in the head or neck
- Aggravated by routine activity

In addition, migraine is usually accompanied by photophobia and/or phonophobia and nausea and/or vomiting [6; 8; 9].

In Western countries, including the United States, migraine has been identified as one of the most common neurologic disorders. The age-adjusted prevalence of migraine and severe headache in the United States has remained stable for more than two decades. According to a 2020 review of national health surveillance data, the prevalence of migraine is 15.9% in adults, and highest among those 18 to 44 years of age (18.7%) [228]. The biologic sex ratio is also stable, with 21% of women and 10.7% of men affected. The prevalence of migraine is highest in American Indian/Alaska Natives (22.1%) compared with White, Black, or Hispanic Americans (15.6% to 16.3%), and lowest in Asians (9.1%). In childhood, migraine is less common (1% to 4%) and equally prevalent among boys and girls [18; 19]. The prevalence increases in adolescence (12%), affecting prepubertal boys and postmenarche girls [1]. The lifetime prevalence of migraine increases from age 12 to 40 years then declines thereafter in both sexes [17].

The individual, familial, and social impact of migraine is significant. In the United States, approximately 23% of households have at least one member who suffers from migraine [17; 20; 191]. More than half of migraineurs report that severe headaches cause substantial impairment in daily activities and require bed rest, while one-third of migraine sufferers missed at least one day of work or school in the previous three months because of migraine and work or school productivity was reduced by at least 50% [17]. An estimated 4 million emergency department visits each year are for migraine/severe headache, and among female patients 15 to 64 years of age, migraine is the third most common reason for emergency department visits [228].

The burden of migraine falls disproportionately on persons of lower socioeconomic status. Among respondents with migraine who participated in governmental surveys conducted between 2009 and 2018, 38% were unemployed, 42% subsisted at or near the poverty level, 34% had received a high school education or below, and 18% were uninsured [228]. Socioeconomic factors could influence prevalence and burden of migraine by exerting a negative impact on incidence and severity, nutritional status, and access to care and effective therapies.

Migraine accounts for nearly 4.2% of years lived with disability, and the Global Burden of Disease study has ranked it among the top five most disabling medical conditions [5; 17; 20; 21; 191]. Specifically, chronic migraine represents close to 50% of all cases of chronic headache and has a lifetime prevalence of 1% to 2%. The incidence is higher in women, those of two or more races, and those who are obese and/or have a diagnosis of diabetes [22; 23; 190]. Longitudinal studies of chronic migraine show the devastating effects of the condition, with most patients in the United States reporting increased disability after a two-year follow-up [24; 25].

CLASSIFICATION OF MIGRAINES

The International Classification of Headache Disorders categorizes migraines as acute or chronic [6; 8]. Acute or episodic migraine with aura is characterized by "transient focal neurologic symptoms that usually precede or sometimes accompany the headache" [8]. Some patients have premonitory symptoms occurring hours or days before the headache as well as a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue, and neck stiffness and/or pain [8]. Twenty-five percent of patients with migraine with aura experience visual disturbances, including flashing lights (i.e., phosphenes), hemianopsia, and scotomas, that precede the onset of the cephalalgia and last no longer than 60 minutes [9]. In 30%

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of patients with migraine with aura, sensory symptoms, such as perioral numbness or tingling, are present. Although less common, hemiparesis, speech and/or language impairment (e.g., dysarthrias), and/or brainstem symptoms (e.g., vertigo, ataxia) may also occur [8; 9].

Acute migraine without aura is defined as a recurrent headache disorder manifesting in attacks lasting 4 to 72 hours with unilateral location, pulsating quality, moderate or severe intensity, aggravation with routine physical activity, and association with nausea and/or photophobia and phonophobia, in the absence of aura. Migraine without aura is seen in less than 10% of women during their menstrual cycle, but tends to last longer and be accompanied by more severe nausea than cases occurring outside of menstruation [6; 8].

The criteria of chronic migraine were updated and included in the revised ICHD-2R, and later confirmed in the ICHD-3 [8; 26]. Chronic migraine is defined as a tension-type headache and/or migraine headache occurring 15 or more days per month for more than three months and having the features of migraine headache on at least eight days per month [8; 26]. Pain medication overuse is the most common reversible cause of headaches resembling chronic migraine [8; 27]. Previously, the ICHD-2R criteria noted that the diagnosis of chronic migraine should not apply to patients with medication overuse; however, the updated ICHD-3 includes medication overuse as the most common cause of symptoms suggestive of chronic migraine and indicates that chronic migraine often reverts to an episodic migraine after drug withdrawal in approximately 50% of patients [8].

PATHOPHYSIOLOGY OF MIGRAINE

Traditionally, migraine was classified as a typical neurovascular disorder with unilateral extracranial vasodilation of the frontal branch of the superficial temporal artery ipsilateral to the headache [28]. The vasogenic theory is consistent with the headache-inducing properties of vasodilating drugs (e.g., nitroglycerine) and the therapeutic properties of vasoconstrictors (e.g., ergotamine). This localized vasodilation was considered to be the rebound of an initial vasoconstriction and transient hypovascularization in discrete brain regions. However, a number of imaging studies have revealed a discrepancy between the temporal profile of vascular dysregulation and migraine pain. This discrepancy is further supported by the fact that vasodilating neuropeptides, such as vasoactive intestinal peptide, do not induce migraine pain [29; 30].

Alternatively, the neurogenic theory views migraine as the combination of neuronal hyperactivity with a local process of neurogenic inflammation triggered by an increase in pro-inflammatory mediators such as CGRP, neurokinin, and substance P [29; 31]. In addition, low levels of the endogenous opioid enkephalin found during migraine correlate to a decrease in pain threshold and are responsible for the reported regional allodynia of the head and upper trunk [32; 33].

The diversity of clinical manifestations observed by patients with migraine is an indication no single theoretical model is likely to account for the complex pathophysiology of the disease. Rather, migraine is the product of multiple mechanisms affecting broad areas of the central nervous system. Over the past decade, research findings have provided insightful evidence regarding the role of cortical spreading depression, trigeminal nerve activity, signaling molecules (e.g., serotonin, CGRP, nitric oxide), and genetic alteration of ion channels and transporters in the pathophysiology of the disease [29; 32; 34; 35]. It is now known that the pathogenesis of migraine involves the trigeminal nerve and its axonal projections to the intracranial vasculature (the trigeminovascular system) [229]. Neuronal afferent fibers innervate the meninges and its vessels and also project to areas within the brain. Activation of the trigeminovascular system, which releases vasoactive substances and inflammatory mediators, is followed by further sensitization and then relay of nociceptive signals to cortical areas that subserve perception of pain [229]. Progress in understanding these components of pathogenesis has enabled development of mechanism-based, targeted therapies with increased clinical efficacy and fewer adverse effects [36].

CORTICAL SPREADING DEPRESSION AND TRIGEMINAL NEUROPATHIES

Cortical spreading depression is an intense wave of neuronal and glial excitation (i.e., depolarization) progressing in the cerebral cortex at a rate of 2–3 mm per minute. This wave of depolarization is followed by transient suppression of spontaneous neuronal activity (hyperpolarization) and changes in vascular diameter and blood flow caused partly by introduction of inflammatory molecules and CGRP to the dura [37; 229]. Clinically, the net effect is an aura followed by migraine headache. Cortical spreading depression is the neurophysiologic event typically associated with migraine with aura and the activation of *N*-methyl-D-aspartate (NMDA) glutamate receptors. The direct intercellular transfer of ions via gap junctions and the release of inflammatory mediators are required for cortical spreading depression to occur [32; 38; 39]. However, the precise role of cortical spreading depression in migraine without aura remains elusive. Animal models have shown that induction of cortical spreading depression causes meningeal vasodilation, a mechanism that requires participation of the trigeminal nerve [40]. The clinical relevance of cortical spreading depression in migraine has also been supported by imaging techniques, namely positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [41; 42; 43; 44].

The trigeminal nerve (V) is a mixed cranial nerve that originates in the trigeminal nucleus located in the brain stem. Together with the trigeminal ganglion, motor output, and sensory input, it is known as the trigeminocervical complex. Its motor fibers innervate the masticatory muscles, whereas its three sensory branches—ophthalmic (V1), maxillary (V2), and mandibular (V3)—play a key role in the nociceptive perception of the front of the face, head, dura mater, regional meningeal vasculature, cheek, cornea, lower face, jaw, and anterior two-thirds of the tongue. The ophthalmic branch (V1) plays a key role in the nociception of orofacial pain, cephalalgias, and neurovascular pathology of migraine [32; 45; 46]. Sensory stimuli originating in the dural vessels activate the nociceptive trigeminal fibers, which initiate the ascending pathway to the brainstem, hypothalamus, thalamus, and finally the cerebral cortex [34; 47].

It should be noted that the innervation of adjacent areas by trigeminal branches (i.e., V1/V2 and V2/V3) presents a certain degree of overlap and accounts for the occasional lack of definition of precise localization of pain that makes the differential diagnosis between sinusitis, odontalgia, and migraine challenging in some patients [48; 49; 50; 51; 198]. Guidelines for clinical evaluation and differential diagnosis will be discussed later in this course.

SIGNALING MOLECULES AND GENETIC MUTATIONS

Which mechanisms are related to the pathophysiology of migraine?

Signaling molecules are the neurochemical messengers used by neurons and glial cells to transfer information among each other [52]. Glial cells play a role beyond myelination and extracellular ionic homeostasis, as they also release proinflammatory mediators that regulate neuronal activity, vascular tone, and intercellular concentrations of ions [39; 52; 53].

Gap junctions between glial cells and neurons regulate ion transfer and neuronal depolarization in cortical spreading depression. Conflicting results of clinical trials have been noted with regard to using a gap junction blocker (e.g., tonabersat) for migraine prophylaxis. In one trial, tonabersat was shown to be effective, while another showed efficacy only in migraine without aura; another trial showed no proven efficacy [213]. Additional research and clinical studies are required to determine the efficacy of gap junction blockers for the treatment of migraine [196; 197; 213].

Voltage-gated calcium and sodium channels regulate neuronal excitability and intracellular signaling pathways [52]. Mutations in the genes encoding for these channels cause them to malfunction, leading to a variety of conditions known as channelopathies. Augmented channel function and neuronal hyperexcitability is associated with clinical conditions such as epilepsy and migraine, whereas decreased function is associated with hypoexcitability and paralysis [54; 55; 56]. Accordingly, channel blockers such as valproate and topiramate used in the management of epilepsy are also effective in migraine prevention [36; 56; 57].

Additional mechanisms, including an increase in synthesis and release of signaling molecules such as neurotransmitters (e.g., serotonin), neuropeptides (e.g., CGRP), vasodilators (e.g., nitric oxide), and pro-inflammatory mediators (e.g., histamine), play a key role in the pathogenesis of migraine. The association between serotonin (5-hydroxytryptamine or 5-HT) and vascular changes is well-established. Increases in synthesis and concentrations of 5-HT in the brain, as well as elevated urinary levels of the 5-HT metabolite 5-hydroxyindolacetic acid (5-HIAA), are observed during migraine attacks [36; 58; 59]. The multiple vascular effects of 5-HT observed in different organs depend on the subtype of the receptors involved. The effectiveness of ergotamine and its derivatives in the treatment of acute migraine results from their vasoconstrictive properties, which are mediated by their binding to the 5-HT_1 receptors abundant in meningeal blood vessels [60; 61]. These drugs are agonists at the 5-HT_1 autoreceptors and inhibit presynaptic release of serotonin, causing vasoconstriction. Triptans are selective agonists at the 5-$HT_{1B/1D}$ receptor subtypes. This action triggers vasoconstriction of the cranial circulation, making these medications highly effective in the treatment of acute migraine and further supporting the role of the serotonergic system, and the 5-$HT_{1B/1D}$ receptor in particular, in migraine pathophysiology [36; 58; 59]. 5-$HT_{1B/1D}$ receptors are also present in high levels in cardiac vessels, thus explaining the potential for adverse cardiac effects (e.g., vasoconstriction of the coronary arteries) with ergotamine derivatives and triptans [60; 61]. Although the therapeutic properties of triptans will be discussed in detail later in this course, it is relevant to point out that they result from the combination of three different mechanisms of action: vasoconstriction of meningeal vessels by direct effect on vascular smooth cells; inhibition of the release of vasoactive and proinflammatory peptides by trigeminal neurons; and inhibition of nociceptive transmission in the brainstem [60; 62].

High levels of the excitatory neurotransmitter glutamate are present in the CSF of patients with migraine, and genetic studies support a crucial role played by a hyperactive glutamatergic system in migraine [63]. Furthermore, antagonists of the glutamate NMDA receptor (e.g., memantine) are effective in the prevention of migraine [54; 55].

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The role of dopamine in the pathophysiology of migraine stems is supported by two main points: the role of the dopaminergic system in nausea, vomiting, and blood pressure changes that occur during a migraine attack, and the therapeutic effectiveness of dopamine antagonists (e.g., metoclopramide, prochlorperazine, chlorpromazine) in the treatment of migraine [201; 202]. However, these are not antimigraine drugs of choice, and their clinical use remains limited to the management of nausea and vomiting. They are parenterally administered in emergency settings in addition to triptans [46; 64].

The activation of nociceptive fibers of the trigeminal ophthalmic (V1) and maxillary (V2) branches elicits the release of neuropeptides such as CGRP and substance P [29; 37; 65; 66]. These peptides trigger mast cell degranulation and the release of histamine and nitric oxide, thus promoting meningeal vasodilation and plasma extravasation. Direct stimulation of the trigeminal ganglion activates the ascending nociceptive pathway, leading to sensitization and decreased pain threshold [29; 32; 35; 37; 65; 67].

CGRP is a potent vasodilatory neuropeptide that increases blood flow in the meningeal arteries [66]. The fundamental role played by CGRP in migraine is supported by four main lines of evidence. First, CGRP blood levels are elevated during acute migraine pain. Second, infusion of CGRP in patients with migraine causes a migraine-like headache. Third, selective CGRP antagonists lower CGRP levels and are effective in the acute treatment of migraine. And finally, in a double-blind clinical trial a CGRP antagonist (telcagepant) had the same efficacy in migraine resolution as a 5-$HT_{1B/1D}$ agonist (zolmitriptan) [66; 68; 69]. After success in several clinical trials, three novel CGRP antagonists were approved by the FDA in 2018 for migraine prophylaxis [176; 214; 225; 226].

The association between nitric oxide and migraine is supported by animal studies and clinical evidence that administration of nitric oxide donors (e.g., sodium nitroprusside, nitroglycerine) triggers headaches in patients with migraine, whereas nitric oxide synthase inhibitors reverse the condition and are effective in treating acute migraine [70]. However, non-selective nitric oxide synthase inhibitors cause hypertension and potentially other serious adverse effects, such as coronary vasoconstriction, precluding their clinical usefulness. Research is being actively conducted to develop nitric oxide synthase inhibitors selective to the regional vessels implicated in migraine [61; 70; 210].

Histamine mediates neuroinflammation, causes vasodilation, and triggers headaches with characteristics similar to the ones observed with nitric oxide increases. These effects are reversed by administration of antihistamines that block the H1 receptor (e.g., diphenhydramine, fexofenadine) [61].

In women, low levels of estrogen are correlated with an increase in migraine attacks in the perimenstrual and perimenopausal stages; high estrogen levels and pregnancy are associated with a reduction in the occurrence of migraine attacks [71]. However, the relationship between estrogen levels and migraine is complex and much debated. Research and updated CDC reports indicate that oral contraceptives may be used by women with migraine without aura, but the cardiovascular risks outweigh the benefits of oral contraceptives for women with migraine with aura [211; 212]. Considering the increased risk of cardiovascular diseases in women with migraine (particularly migraine with aura) and the increased risk of stroke in women who take combination oral contraceptives, the risk should be carefully evaluated before oral contraceptives or hormone replacement are considered [72; 73; 74].

Genetic mutations that encode ion channels and pumps have been identified as the cause of familial hemiplegic migraine (FHM), a rare cause of migraine with aura, suggesting that disturbances in ion homeostasis in the brain are responsible for this migraine type [75]. FHM is the first migraine syndrome to be linked to a specific genetic polymorphism in specific loci in chromosomes 1 and 19 that encode for voltage-gated calcium and sodium/potassium channels. Mutations in calcium channels have been identified in FHM type 1 and mutations in the sodium/potassium channels in FHM type 2 [54; 56; 76]. These findings provide the mechanistic explanation for the therapeutic efficacy of channel blockers such as valproate and topiramate in the prevention of migraine [46; 57; 77].

Although the role played by genetic mutations in non-familial forms of migraine is unclear, half of patients with migraine have a first-degree relative also suffering from migraine, and in monozygotic twins, there is 50% heritability with a multifactorial basis [78; 79; 80]. Genetic variants related to the excitatory neurotransmitter glutamate and its receptors have also been identified in non-familial migraine [63]. This evidence further supports the therapeutic value of memantine—a glutamate NMDA receptor antagonist—in the treatment of migraine [81; 82].

The dopaminergic system has also been implicated in the etiology of migraine, and although results regarding variability of dopamine receptor genes are not conclusive, evidence clearly demonstrates the association between variability of the dopamine hydroxylase and the dopamine transporter genes and the pathogenesis of migraine with aura [83]. These results provide support for the role of antidopaminergic medications in the treatment of migraine with aura [84; 85].

MIGRAINE DIAGNOSIS

ACUTE MIGRAINE WITH AND WITHOUT AURA

What are the components of POUND, a mnemonic for the diagnosis of acute migraine?

Useful evidence-based clinical guidelines for the diagnosis of migraine have been developed and are summarized in the mnemonic POUND: pulsatile headache; one-day duration (4 to 72 hours); unilateral location; nausea or vomiting; and disabling intensity [87; 88].

Acute or episodic migraine with aura occurs in 25% to 30% of migraines. Aura is a combination of focal neurologic symptoms that precede or accompany an attack, progress for 5 to 20 minutes and last less than 60 minutes. Auras are the clinical manifestations of focal cortical spreading depression originated in the occipital cortex and moving at a rate of 2–3 mm/minute [32; 38; 39]. Visual auras such as scotomas ("blind spots" in the visual field), phosphenes (scintillations or flashing lights), and teichopsia (zigzag lines) are the most common and frequently affect half the visual field [15; 64]. Neurologic auras such as dysarthria, paresis, and paresthesia require thorough clinical evaluation if they last for more than 60 minutes, are accompanied by paralysis or syncope, or occur for the first time in patients 50 years of age or older or in women after initiation of oral contraception [15; 89]. In women, migraine with aura is associated with a twofold increased risk for cardiovascular events such as myocardial infarction and stroke [90].

Typically, the headache is unilateral, although bilateral occurrence is commonly reported. Up to 50% of patients with unilateral pain report that either side can be affected in any particular migraine episode [10; 206]. It begins as a dull ache that, within minutes or hours, progressively develops into an intense throbbing pain that worsens with each arterial pulse. The pain is often disabling and interferes with professional, social, and familial commitments [10; 17]. The temporal profile of acute or episodic migraine attack includes an initial premonitory phase, a headache phase either with or without aura, and a resolution or recovery phase.

In acute or episodic migraine without aura, up to 80% of patients have premonitory symptoms or prodromes, such as fatigue, irritability, difficulty concentrating, neck stiffness, cold hands, frequent urination, and/or change in appetite, that precede the headache by up to 48 hours. Some patients recognize their prodromes, allowing them to follow an early management approach and effectively abort or minimize subsequent headache [8; 15].

In some patients, migraine can be initiated by variety of triggers, such as monosodium glutamate (MSG), excess caffeine, and foods rich in nitrites, sulphates, tyramine, and/or a vasoactive amine present in aged cheese, red wine, and chocolate. Decompression (e.g., high altitudes and scuba diving), dehydration, and fluctuating estrogen levels (e.g., menarche, menstrual period, perimenopause) have also been identified as potential triggers of migraine [64; 86]. Knowledge of a patient's triggers can be helpful in preventing a migraine attack.

Gastrointestinal symptoms of nausea and vomiting are reported by 90% and 30% of patients, respectively [64; 91]. A variety of other autonomic symptoms accompanying acute migraine attacks include constipation, diarrhea, abdominal cramps, nasal stuffiness, facial pallor, and diaphoresis. Neurologic symptoms of sensory hypersensitivity are commonly reported by patients during migraine attacks and are manifested as photophobia, phonophobia, or hyperosmia, and patients tend to seek a dark, quiet location to rest. A variety of psychologic symptoms (e.g., anxiety, depression, drowsiness, irritability, restlessness) are also present in patterns that vary among patients but usually have a predictable pattern in each patient [15; 64; 91].

Potential complications of migraine include [8]:

- Status migrainosus: Persistent (>72 hours), debilitating migraine with or without aura, often caused by medication overuse
- Persistent aura without infarction: Aura symptoms persisting for one week or more without evidence of infarction on neuroimaging, often bilateral and lasting for months or years
- Migrainous infarction: One or more migraine aura symptom associated with an ischemic brain lesion in the appropriate territory demonstrated by neuroimaging, with onset during course of a typical migraine with aura
- Migraine aura-triggered seizure: A seizure triggered by an attack of migraine with aura

As the cephalalgia resolves, many patients experience a sense of fatigue or exhaustion, irritability, impaired concentration and memory, mood changes, and neck stiffness. This postdrome phase can last from a few hours to up to two days after termination of the headache [8; 15; 64; 91; 92].

Additional criteria that are useful to assist in making the correct diagnosis of migraine include:

- Absence of daily headache
- Stable pattern
- History of similar events
- Family history of migraine
- Normal neurologic examination

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- Improvement with rest and/or sleep
- Association with menses

Absence of aura and lack of identification of a selective trigger should not eliminate the diagnosis of migraine [6; 8; 26; 64].

Clinical examination of the patient should pay close attention to the presence of alarm signs that play a crucial role in the differential diagnosis between migraine and potentially lethal conditions such as stroke, SAH, and ruptured aneurism. These signs include [15; 64]:

- Acute headache with focal neurologic signs or papillary edema
- Acute headache in a patient 50 years of age or older
- Acute onset of a headache described as "the first of this kind" and "the worst ever"
- Intensifying pain of a subacute headache
- Headache associated with systemic illness (e.g., fever, stiff neck, nausea, vomiting, skin rash)
- Acute headache in patients with cancer or human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS)

Several imaging studies, including PET and fMRI, have provided insight regarding the involvement of specific brain structures, such as the visual motion processing network, in the pathophysiology of migraine with and without aura [93; 203]. Blood oxygen level-dependent MRI studies of the visual cortex have shown that both visual aura and cortical spreading depression correspond to an initial stage of noticeable hyperemia that lasts for three to five minutes, which is followed by one to two hours of oligemia (mild hypoperfusion) [29]. Diffusion tensor MRI showed an increase in thickness of the visual cortex in areas involved in cortical spreading depression and visual aura as well as changes in the superior colliculus and lateral geniculate nucleus, areas also implicated in visual processing [94; 95; 203]. Morphologic changes in brainstem regions involved in pain modulation (periaqueductal gray) and serotonin-producing neurons (dorsolateral pons) have also been reported [96]. MRI findings of periventricular focal white matter hypertense lesions are four times more frequent in migraine patients than in non-migraine age- and sex-matched controls [97]. However, most patients with migraine with aura do not consistently present with these imaging alterations [37]. These findings should be evaluated on an individual basis, considering the history and pattern of the headache and differential diagnosis of early stages of multiple sclerosis or vascular diseases [97].

Imaging studies have shown that brainstem hyperactivity ipsilaterally correlates to acute migraine, suggesting that lateralization of the pain relates to unilateral brainstem dysfunction and altered transmission in the trigeminal nucleus caudalis. Hyperactivity in the thalamus is associated with allodynia, and activity in cortical regions normally associated with pain processing is observed with imaging during acute migraine [93; 204]. These studies are particularly important because they demonstrate that structural and functional changes occur during acute migraine and that changes in vascular function do not represent the primary cause of migraine attacks, further validating the role of cortical spreading depression and the neural etiology of migraine [204].

SIGNS AND SYMPTOMS THAT SUGGEST A SECONDARY CAUSE OF HEADACHE AND REQUIRE FURTHER CLINICAL AND IMAGING EVALUATIONS

Abnormal neurologic signs
New onset of headache
Abrupt onset
Progressive symptoms
Headache with exertion
Change with head position
Change with Valsalva maneuver (e.g., cough, sneeze, strain)
Symptoms consistent with a trigeminal autonomic cephalalgia diagnosis

Source: [7] *Table 1*

According to clinical guidelines from the American Academy of Neurology and the U.S. Headache Consortium, neither imaging procedures nor clinical laboratory tests specific for migraine are available. As such, these modalities are not usually warranted for patients with migraine and normal neurologic examination and no recent changes in headache characteristics. Less than 0.2% of patients in this category show clinically significant intracranial lesions on neuroimaging [6; 7; 93; 168; 199; 200]. The presence of abnormal neurologic examination or changes in headache patterns, such as intensity and temporal profile, are considered "red flags" and prompt MRI imaging is appropriate for these patients (***Table 1***) [7].

The diagnosis of migraine is based solely on a constellation of signs and symptoms, and a comprehensive medical and neurologic examination is required to exclude secondary headache [15]. Competence of the clinician and effective communication with the patient play a crucial role in the diagnosis of migraine. It has been estimated that 50% of migraine patients remain undiagnosed or misdiagnosed, and only a small number (8% to 10%) of individuals with migraine take migraine-specific medications such as triptans or ergotamines [98; 99; 100].

Of particular clinical relevance is mounting evidence of an increased comorbidity of migraine and neurologic (e.g., transient ischemic attacks, ischemic stroke, epilepsy), psychiatric (e.g., anxiety, depression, bipolar disorder), cardiovascular (e.g., Raynaud phenomenon, angina, myocardial infarction), and metabolic (e.g., hypercholesterolemia, insulin resistance, obesity) disorders [64; 90; 101; 102; 103; 104; 105; 106]. When compared with the rest of the population, patients with migraine with aura have a doubled risk of developing an ischemic stroke [107]. Migraine with aura in women using oral contraceptives has been identified as a risk factor for cardiovascular comorbidity [8]. Particularly relevant are the seven-fold higher odds of stroke in women with migraine with aura who smoke and take oral contraceptives compared with women with probable migraine with visual aura who do not smoke or use oral contraceptives [108].

CHRONIC MIGRAINE

Chronic migraine is defined as headaches that occur on 15 or more days per month for more than three months, which have the features of migraine headache on at least eight days per month [8]. The criterion that a patient must have at least 15 days of headache monthly is not intended to be restrictive, but rather a guideline that patients with a high number of monthly headaches should be included in this group and receive appropriate therapy [26; 27].

Chronic migraine has a prevalence of 1% to 2%, and it represents approximately half of all cases of chronic primary headache. It is more frequently observed in women of European heritage, in patients who are obese, and during the fourth decade of life [22; 24; 109].

In chronic migraine, it is impossible to distinguish the individual episodes, and the characteristics of the headache often change frequently, even within the same day. It is also difficult to keep patients medication-free in order to observe the natural history of the headache. The most common cause of symptoms suggestive of chronic migraine is medication overuse, and in at least 50% of these patients, the condition is reversed after discontinuation of medications. Other patients, however, do not improve after drug discontinuation and their condition should not be diagnosed as medication-overuse headache [8; 27]. Patient education regarding the judicious use of medications should begin before rather than after medication-overuse headache is established [15].

In addition to the findings of imaging studies related in the previous section, dysfunction of the descending inhibitory pathways is also observed in chronic migraine, resulting in hypofunction of the descending pain modulatory circuitry [110]. Chronic migraine should respond favorably to pharmacologic treatment with ergots or triptans [27].

LONG-TERM ASSESSMENT OF MIGRAINE PATTERN AND PATIENT STAGING

The pattern of migraine presented by a patient changes over the lifetime, and its assessment determines the combination of clinical management with patient education, pharmacologic treatment, and behavioral interventions [15]. This evaluation takes into account frequency, intensity, and impact of migraine on the patient's life [15]. Based on the findings, patients may be categorized in one of four stages and treated accordingly.

In stage one, patients have one or fewer migraine attacks per month or two or fewer headache days per month and normal function between episodes. Early administration of over-the-counter medication (e.g., ibuprofen, naproxen, or a combination of acetaminophen, aspirin, and caffeine) and sleep are usually adequate to manage the condition. The patient is fully functional within a few hours and rarely presents for consultation. If severe pain is experienced, patients may seek medical treatment, and in these cases, either triptans or nonsteroidal anti-inflammatory drugs (NSAIDs) are usually effective to stop a migraine attack [15].

Patients in stage two present with one to three attacks monthly, with less than five headache days per month. Each event is limited in time, but occasional absenteeism from work or family or social functions may occur. Treatment with triptans, either alone or in combination with NSAIDs (e.g., sumatriptan, naproxen), is usually effective to stop a migraine attack [15]. Patient education should be aimed at limiting the use of analgesics to prevent medication-overuse headache, emphasizing that the use of analgesics should be limited to the early management of individual acute migraines and the need to limit drug administration to no more than twice per week [15].

In stage three, patients present with frequent attacks (four to eight per month with less than 12 headache days per month). Assessment should include the use of acute medications (NSAIDs and triptans) and determination of possible medication overuse. It is important to set strict limits on medication use or opt for discontinuation, with preventive therapy initiated concurrently. The choice among preventive medications should take into account the existence of comorbidities, such as beta-blockers in patients with hypertension and tricyclic antidepressants in patients with depression. However, it is important to remember that the appropriate dosage for prevention of migraine might be below the therapeutic effective for the comorbid condition [15].

Patients in stage four have more than eight attacks per month and more than 15 days of headache per month. These patients should be treated by headache specialists on interdisciplinary teams focused on pain management. Medication overuse should be evaluated in each patient and appropriately managed. The medication should be

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THE MIGRAINE DISABILITY ASSESSMENT (MIDAS) QUESTIONNAIRE FOR MIGRAINE PATIENTS

INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... ____ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches?
   (Do not include days you counted in question 1 where you missed work or school.) ..... ____ days
3. On how many days in the last 3 months did you not do household work because of your headaches?..... ____ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches?
   (Do not include days you counted in question 3 where you did not do household work.) ..... ____ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?..... ____ days

   A. On how many days in the last 3 months did you have a headache?
      (If a headache lasted more than one day, count each day.) ..... ____ days

   B. On a scale of 0–10, on average how painful were these headaches?
      (Where 0 = no pain at all, and 10 = pain as bad as it can be.) ..... ____

Migraine Disability Score
(Questions 1–5 are used to calculate the MIDAS score.)
Grade I—Minimal or Infrequent Disability: 0–5
Grade II—Mild or Infrequent Disability: 6–10
Grade III—Moderate Disability: 11–20
Grade IV—Severe Disability: >20

Source: Reprinted with permission from Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) questionnaire to assess headache-related disability. Neurology. 2001;56(6 Suppl 1):S20-S28. *Figure 1*

discontinued, and if necessary, a bridging therapy—such as naratriptan (1 mg twice daily for five days) or naproxen (440 mg twice daily for five days)—can be initiated to prevent or manage rebound headaches from the medication withdrawal. Preventive pharmacotherapy should preferably be initiated after discontinuation of previous medication(s). Management of patients with complex migraine often requires referral and interprofessional collaboration [111].

After migraine is properly diagnosed, the severity of the disease and its impact on quality of life and ability to function should be assessed using the Migraine Disability Assessment (MIDAS) questionnaire, a simple and reliable tool (***Figure 1***) [112; 113].

DIFFERENTIAL DIAGNOSIS

Differentiating migraine from other primary or secondary headaches requires a thorough medical history and physical examination and an understanding of the typical characteristics of primary headaches. The initial differential diagnosis of migraine considers three main areas: other primary headaches, secondary headaches, and orofacial pain. Some red-flag signs and symptoms—including focal neurologic signs, papilledema, neck stiffness, an immunocompromised state, sudden onset of the worst headache in the patient's life, personality changes, headache after trauma, and headache that worsens with exercise—suggest serious underlying pathology and require neuroimaging and/or laboratory testing to evaluate the cause of headache.

Other Primary Headaches

Tension-Type Headache

Tension-type headache is the most common primary headache. The pain is dull and non-pulsating, with a mild-to-moderate intensity and a bilateral or a "hatband" distribution. Typically, tension-type headache is not associated with aura, nausea, or vomiting. Mild photo- or phonophobia may infrequently be reported. Palpation of the cervical or pericranial muscles may identify tender spots [6; 10; 64].

NSAIDs are effective drugs of choice in the treatment of tension-type headache. Ibuprofen (400 mg) and naproxen sodium (550 mg) provide better analgesia than acetaminophen (1,000 mg) and have fewer adverse effects than aspirin (650 mg). However, the choice should take into account cost and individual patient preference. Amitriptyline (10–25 mg at bedtime) is the most effective in the prophylaxis of tension-type headaches [10].

Cluster Headache/Trigeminal Autonomic Cephalalgias

Cluster headache and TACs are severe and uncommon headaches with a shorter duration (15 to 180 minutes) than migraine and occur up to eight times per day [8; 10]. Cluster headache is more common in men than in women (at a ratio of 3:1) with age of onset between 20 to 40 years of age [8]. It often occurs at night and wakes patients from their sleep. Typically, cluster headache presents as a unilateral headache located behind the eye and radiating to the territory of the ipsilateral trigeminal nerve. It occurs in clusters followed by periods of complete remission that can last for weeks to months. Aura and gastrointestinal symptoms are not observed, but ipsilateral lacrimation, conjunctival injection, rhinorrhea, and blocked nasal passage are typically present [10; 114]. Relevant to the differential diagnosis, patients experiencing a cluster headache do not seek rest during an attack but are noticeably agitated, restless, pacing, rocking, and even aggressive. This is in sharp contrast to patients with migraine, who seek relief by resting in a dark, quiet place and prefer to remain motionless during attacks [6; 8; 9; 46; 114]. The standard treatment for cluster headache/TAC is high-flow oxygen (100% O_2 at 7–10 L/min for 15 to 30 minutes).

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, oxygen inhalation is a highly effective treatment for cluster headaches when delivered at the beginning of an attack with a non-rebreathing facial mask (7–15 L/min). Most patients will obtain relief within 15 minutes.

(https://www.icsi.org/wp-content/uploads/2019/01/HeadacheRR.pdf. Last accessed June 21, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

In addition to supplemental oxygen, sumatriptan and zolmitriptan are effective in the acute treatment of episodic cluster headache. Verapamil (240 mg/day) has been the first-line prophylactic therapy and can be used to treat chronic cluster headache; however, the CGRP antagonist erenumab-aooe received FDA-approval in 2018 for cluster headache prophylaxis [176; 214]. Further clinical studies are required to compare the effectiveness of these agents. Lithium (800–900 mg/day) is also effective, although it requires closer monitoring for adverse effects (e.g., hypothyroidism). More invasive treatments, including nerve stimulation and surgery, may be helpful in refractory cases [10; 46; 64; 114; 115; 216].

Thunderclap Headache

Thunderclap headache occurs suddenly, reaches peak intensity in less than one minute, and lasts for at least five minutes and up to 24 hours. Patients often describe thunderclap headache as the "worst headache of their lives." These headaches are often associated with life-threatening vascular intracranial disorders such as SAH, intracerebral hemorrhage, cerebral venous sinus thrombosis, ischemic stroke, arterial dissection, and hypertensive encephalopathy [10; 116; 117]. Primary thunderclap headache should be a diagnosis of last resort, reached only when all organic causes have been demonstrably excluded [8].

Differentiating among thunderclap headache, migraine, and serious secondary headaches requires a comprehensive examination and initial CT scan and CSF analysis, possibly followed by an MRI if these are negative or inconclusive. Primary thunderclap headache responds poorly to analgesics, and the best management is provided by nimodipine (a dihydropyridine calcium channel antagonist) or gabapentin [46; 116].

Secondary Headaches

Clinical history and patient examination also play a critical role in differentiating migraine from potentially life-threatening secondary headaches resulting from SAH, cerebral parenchymal hemorrhage, cerebral vein thrombosis, cavernous sinus thrombosis, increased intracranial pressure, meningitis/encephalitis, hypertensive emergency, brain metastases, and HIV/AIDS [46; 118; 199]. A change in severity, frequency, or characteristics of the headache, the presence of a new progressive headache that persists for days, or headache developing after head trauma or associated with neck stiffness or fever is suggestive of secondary origin. Headache is also reported by 50% of patients diagnosed with either primary or metastatic brain tumor, with characteristics typical of migraine in 9% of patients and of tension-type headache in 77%; in one study, "classic" early morning brain tumor headache occurred in only 17% of patients [119].

Differential diagnosis of secondary headache requires a detailed history and thorough examination. If the situation is unclear, an initial CT scan of the head without contrast and CSF analysis are required, possibly followed by an MRI [46; 118; 199].

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Orofacial Pain

The multifaceted etiology of oral, facial, and head pain is the result not only of various pain mechanisms but also of the complex anatomy of the head and orofacial region. Its diagnosis and management often require a multidisciplinary approach and collaboration [120; 121; 122].

Approximately 20% of the population experiences orofacial pain more than once every six months [123]. Odontogenic pathology is the most common cause of orofacial pain, followed by nonodontogenic pain (e.g. temporomandibular disorders, neuropathies) and burning mouth syndrome [124; 125]. Primary headaches, such as migraine, cluster headache, and tension-type headache, can also present as pain with orofacial location. The most prevalent etiology of nonodontogenic orofacial pain is musculoskeletal pathology (e.g., temporomandibular disorders), followed by episodic or chronic neuropathies (e.g., post-traumatic, trigeminal, post-herpetic) and oral cancer [121; 126]. Sinusitis may also cause orofacial pain and headache, and a careful assessment of the patient is required to establish a differential diagnosis [8; 50; 124; 127].

Odontogenic Pain

Odontogenic pain is caused by odontogenic pathology, such as injury or inflammation/infection of the dental pulp or periodontal tissues, and accounts for more than 50% of all orofacial pain [128]. Clinical and radiographic examination should be corroborated by at least one other test aimed at differentiating between odontogenic and nonodontogenic pain, including percussion, palpation, biting, or thermal. If radiographic and clinical examination are both negative, then two of these other tests must be positive in order to correctly establish the diagnosis and location of the pain [128].

Dentin hypersensitivity presents as a transient sharp pain in response to thermal, chemical, or tactile stimulation. Dental caries present as painful response to any stimulation and can be easily confirmed by clinical and radiographic examination.

Pulpitis is an inflammation of the dental pulp caused either by caries or fracture. Reversible pulpitis is a mild inflammation and presents as localized, sharp, and intermittent pain elicited by thermal changes, particularly cold drinks. Irreversible pulpitis results from chronic inflammation and infection associated with pulpar necrosis, which can be either associated with throbbing pain with no response to thermal stimuli or with poorly localized, dull, and persistent pain [128; 129]. A localized periapical abscess is a common complication of pulpitis, and symptoms include tenderness on tapping and lymphadenopathy. This condition requires dental referral for drainage and subsequent reconstruction or extraction; antibiotics are usually not recommended. If the infection has spread to adjacent teeth or surrounding tissues, causing cellulitis, or if the clinical situation does not allow for immediate dental surgical treatment, appropriate antimicrobial therapy with broad-spectrum antibiotics, specifically amoxicillin with clavulanate, should be initiated before referral. Clindamycin is a recommended alternative, particularly in patients with an allergy to penicillins [128; 129; 130]. It is important to remember that antibiotics are not substitutes to curative dental treatment. In fact, very seldom are antibiotics an appropriate substitute for removal of the source of the infection (i.e., extraction, endodontic treatment, incision and drainage, periodontal scaling and root planing) [130].

Periodontalgia resulting from gingivitis or periodontal abscess is not as deep-seated, intense, and throbbing as endodontic pain. This pain is associated with gingival inflammation, localized bleeding, and tooth mobility and is usually more generalized than endodontic pain. Antibiotic therapy is an option, and referral to periodontal treatment is required [128].

Nonodontogenic Tooth Pain

Nonodontogenic tooth pain is defined as pain that presents as tooth pain but without dental pathology. Although it often coexists with true tooth pathology, its true nature is revealed when the dental pain is treated. It can present as a deep, dull ache with occasional lancinating pain in the ear, temple, or face. The most prevalent etiology of nonodontogenic tooth pain is muscular. These presentations include myospasm, myalgia, and myofascial pain syndrome, with pain elicited by the stimulation of trigger points in the muscles involved. For example, stimulation of the anterior digastric muscle trigger points can cause referred pain in the lower incisors, whereas stimulation of the anterior or posterior temporal muscle trigger points causes pain in the maxillary anterior or posterior teeth, respectively [131]. Local injection of neuromuscular blocker botulinum toxin (e.g., Botox, Dysport, Xeomin) is effective treatment.

Atypical odontalgia, also known as neuropathic tooth pain, neurovascular odontalgia, oral neuropathic pain, or atypical facial pain, is a nonodontogenic pain of neuropathic origin. Classically, atypical odontalgia presents as throbbing, persistent pain in the teeth or alveolar process occurring over a prolonged period of time without any pathologic, clinical, or radiologic findings [132]. Onset can coincide with dental treatment, including denervation or dental extraction, a condition known as phantom tooth pain [133]. Most patients are women in their mid-40s, and they are often misdiagnosed and submitted to repeated endodontic therapy and dental extractions that fail to relieve their pain [134]. Diagnosis and management are challenging, but tricyclic antidepressants such as amitriptyline or imipramine are the treatment of choice. Gabapentin, baclofen, topical anesthetics, and opioids are possible alternatives [135].

Temporomandibular Disorders

What triggers temporomandibular disorder pain?

Temporomandibular disorders have a lifetime prevalence of 75% and account for approximately 5% of orofacial pain that requires therapeutic management [124; 125]. These disorders are associated with usually unilateral pain with temporal, periorbital, or frontal location. The pain is persistent and dull, with well-localized trigger points in the muscle, fascia, or tendons. Temporomandibular pain of myogenous origin includes jaw and facial pain arising from masticatory muscles, whereas pain of arthrogenous origin is associated with joint noise, incoordination of the disk-condyle relationship either with or without locking, and limited range of motion.

Typically, temporomandibular pain is triggered or aggravated by clinical examination with palpation, passive movement, and active movement (e.g., yawning, chewing, talking) and intensified when muscle is contracted against fixed resistance [124; 136; 137]. The role of temporomandibular disorder as a cause of chronic headaches and facial pain is often overlooked, and patients may be misdiagnosed as suffering from daily migraines or chronic sinusitis or rhinitis [124; 127].

Imaging with MRI is indicated to study soft tissues and assess disk position. In the past, panoramic and tomographic studies were considered the most appropriate to evaluate bone, although cone-beam CT is now the first choice [124]. Referral to an expert in temporomandibular pain is advised to establish the treatment plan, which will be determined by the degree of impairment and complexity of the disorder. Interventions range from patient education (e.g., avoid chewy foods and chewing gum) and physical therapy (e.g., apply heat or ice, perform jaw-stretching exercises) to pharmacotherapy with NSAIDs, muscle relaxants, botulinum toxin, sedatives, corticosteroids (e.g., methylprednisolone, triamcinolone), or topical analgesics (e.g., capsaicin, lidocaine in transdermal patch). Advanced and complex cases require surgery (e.g., arthrocentesis, arthrotomy, joint replacement) [121; 124].

Sinusitis and Rhinosinusitis

Sinusitis and rhinosinusitis are potential causes of facial pain and headache. The floor of the maxillary sinus is in close proximity to the roots of the maxillary teeth, specifically the second premolar and the first premolar. It might extend as far anteriorly as the canine and posteriorly as far as the third molar [207]. Up to 11% of patients with maxillary sinusitis report toothache, and the involved maxillary teeth may be tender to percussion and hypersensitive to cold stimuli, with tenderness, edema, and erythema of the oral mucosa adjacent to the compromised sinus. Periapical radiographs may also illustrate widening of the periodontal ligament. Together, this constellation of signs and symptoms requires a thorough history and examination [207; 208; 209].

The frontal, ethmoid, and sphenoid sinuses are each contiguous with the intracranial vault, and congestion or inflammation in any of these sinuses frequently leads to headache, the character and location of which is determined by the specific sinus involved. The floor of the frontal sinus forms a portion of the roof of the orbit. Frontal sinusitis causes pain (headache) above the eye in the frontal region of the skull, accompanied by local tenderness and occasionally slight edema of the eyelid. This headache often occurs mid-morning and is aggravated by bending forward. The ethmoid air cells are variable in number and occupy the boney area between the nasal cavity and the medial wall of the orbit. Headache associated with anterior ethmoid sinusitis is referred to the parietal area of the head, while posterior ethmoiditis causes headache in the mastoid or occipital regions. The sphenoid sinus is located behind the orbit, and the roof of this sinus forms the pituitary fossa at the base of the brain. Sphenoid sinusitis produces a deep, boring retro-orbital pain and coronal headache that can become severe and unremitting.

The cardinal clinical features of sinusitis are nasal congestion/obstruction, purulent nasal discharge, and pain (regional facial pain and/or headache). Commonly, the discomfort of sinus congestion becomes worse when the patient bends over or lies down. Sinusitis may be unilateral or bilateral and more than one anatomic sinus is often affected (e.g., fronto-maxillary or fronto-ethmoid sinusitis). Regional pain may be accompanied by the sensation of periorbital and frontal pressure, and there may be localized tenderness, mild erythema, or edema adjacent to the involved sinus. Fever is not a prominent feature and is more common in children than in adults. Complaints of increased post-nasal drainage and cough, particularly at night, are common. The diagnosis can usually be made by careful clinical assessment combined with sinus transillumination and, perhaps, plain radiographs of the face ("sinus views"). Head neuroimaging is reserved for persistent, recurrent, or complicated cases.

Sinusitis usually develops as a complication of viral upper respiratory infection or nasal allergy; however, persistent or progressive symptoms are often the result of secondary bacterial infection. The treatment regimen is designed to promote drainage, relieve pain, and treat bacterial infection. A systemic and/or topical decongestant (e.g., phenylephrine, oxymetazoline) should be administered, perhaps combined with nasal corticosteroid (e.g., fluticasone, mometasone) for patients if nasal allergy is prominent. Amoxacillin, either alone or in combination with clavulanate, is the antibiotic of choice for most cases [138; 139].

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Patients suffering from daily migraines may be misdiagnosed with chronic sinusitis or rhinitis and repeatedly and unsuccessfully treated with broad-spectrum antibiotics [124; 127]. A systematic review found that if thorough otolaryngologic and neurologic examinations are performed, the majority of patients presenting with sinus headache in the absence of significant acute inflammatory findings are diagnosed with migraine. The researchers recommend that the appropriate treatment for these patients is migraine-specific medication [140].

Giant Cell Arteritis

Giant cell arteritis should be considered as part of the differential diagnosis of orofacial pain in patients 50 years of age and older [141]. Arteritis of the temporal artery presents as sudden, severe, and pulsating temporal pain that worsens with cold temperatures. Patients also often display tenderness to palpation, jaw claudication with limited range of motion, and allodynia of the scalp. It is commonly associated with signs of systemic inflammation (e.g., fever, fatigue, malaise, anorexia, sweating). The constellation of signs associated with the throbbing temporal pain in giant cell arteritis allows for a reliable differential diagnosis with migraine. Imaging tests may appear normal, but laboratory tests will show elevated erythrocyte sedimentation rate (ESR) and C-reactive protein. Giant cell arteritis is considered a medical emergency because partial or total obstruction of the blood vessel may result in transient ischemic attacks, stroke, or permanent loss of vision. Prompt treatment with prednisone (starting at 10–20 mg and increasing up to 60 mg/day), either alone or in conjunction with aspirin (81 mg/day), is very effective in most cases. ESR values can be used to monitor progression and response to therapy [142; 143; 144].

Burning Mouth Syndrome

Burning mouth syndrome, also referred to as glossodynia, is a condition of unclear (possibly neuropathic) etiology, and diagnosis is established when other known causes (e.g., xerostomia, candidiasis, diabetes mellitus, food sensitivity, deficiencies in vitamin B12 or iron) have been excluded. As the diagnosis is made by exclusion of other known conditions, a detailed medical history and pain history are required [145]. The International Headache Society defines burning mouth syndrome as "a burning sensation for which no dental or medical cause can be found" [6]. It is most commonly observed in postmenopausal women and is usually confined to the tongue. It may be associated with xerostomia and loss of taste (ageusia) [146; 147]. Burning mouth syndrome may develop as an adverse effect of angiotensin-converting enzyme inhibitors, with the condition subsiding after drug discontinuation [145]. If pharmacotherapy is required, clonazepam and gabapentin are the most commonly prescribed drugs for this condition [147].

MIGRAINE TREATMENT

NONPHARMACOLOGIC APPROACHES

Nonpharmacologic alternatives to migraine treatment include a variety of lifestyle changes and complementary and alternative therapies. Lifestyle changes play an important role in the prevention of acute as well as chronic migraine [15; 27]. These changes include a structured lifestyle, healthy diet, consistent hydration, regular exercise, regular sleep patterns, quitting smoking, avoidance of specific headache triggers (e.g., excess caffeine, alcohol, chocolate), and avoidance and management of stress. Increased general fitness and moderate physical activity, such as 30-minute walks three to five times per week, are recommended, although high-intensity exercise and irregular patterns of exercise may trigger headache [148].

Complementary and alternative therapies, such as relaxation techniques, biofeedback, cognitive-behavioral therapy, massage, acupuncture, botulinum toxin, coenzyme Q10, vitamin B12 or B2 supplementation, and herbal medications such as feverfew (*Tanacetum parthenium*) and butterbur (*Petasites hybridus*), have also been evaluated in migraine prophylaxis, with varying levels of success [149; 150; 151; 152; 153]. Patient education is another important tool in migraine management, and useful information for migraineurs is available online (***Resources***).

CLINICAL MANAGEMENT OF ACUTE MIGRAINE ATTACKS

The management of acute migraine attacks includes pharmacologic and nonpharmacologic approaches. The patient will usually first cope with symptoms by lying down in a dark and quiet location. However, medication is often necessary. The appropriate drug choice takes into account the severity of the attack and previous individual response to specific medications. An estimated 50% to 70% of mild and moderate migraine attacks can be managed with oral medications; severe events require parenteral treatment. As a general rule, medications used to alleviate the pain of a migraine attack should be taken early after onset, when the headache is still mild.

The U.S. Headache Consortium has identified several goals for the treatment of acute attacks [154; 217]:

- Treat the attacks rapidly and consistently and eliminate recurrence of the attack
- Restore the patient's ability to function
- Minimize the use of backup and rescue medications
- Optimize self-care and reduce subsequent use of resources
- Institute cost-effective approaches for overall management
- Minimize or avoid adverse events

A comparison of the effectiveness of various abortive medications is limited due to the paucity of clinical trials directly comparing different drug classes. However, five general guidelines have been developed [154; 217]:

- Educate patients with migraine about their condition and its treatment and encourage them to participate in their own management.
- Use migraine-specific agents in patients with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine.
- Select a non-oral route of administration for patients whose migraines are characterized by nausea or vomiting early in the course of an attack.
- Consider use of a self-administered rescue medication for patients with severe migraines that fail to respond well to other treatments.
- Guard against medication-overuse headache.

Face-to-face education with a healthcare professional has been found to increase medication efficacy by 11% compared with written patient instructions without altering the placebo response [15].

Lifestyle modifications, including identification and avoidance of possible triggers and adherence to a structured sleep schedule, are an effective and often neglected tool in the prevention and management of migraine [148; 155]. The role of exercise is supported by a three-month randomized, controlled trial that showed exercising for 40 minutes three times per week provided benefits comparable to relaxation according to a recorded program or daily topiramate use titrated to the individual's highest tolerable dose (maximum: 200 mg/day) [156].

Pharmacotherapy

The primary endpoint in the acute treatment of migraine is to optimize the number of patients who are pain-free at two hours after administration of medication, and prompt initiation of treatment as soon as possible after first symptoms provides the maximum benefit [84; 87; 157; 158; 159]. Medications used in the treatment of acute migraine attacks are either non-specific analgesics, such as NSAIDs, acetaminophen, and opioids, or migraine-specific drugs, such as agonists at the serotonin receptor 5-$HT_{1B/1D}$ (ergots and triptans) and dopamine antagonists.

It should be noted that opioids are not recommended in the treatment of acute migraine, except when administered intravenously in the emergency department [160]. Opioid treatment is associated with a high recurrence rate of migraine headache and an inherent potential for misuse, abuse, and dependence. It is recommended that opioids may only be considered for short-term use in cases of intractable, severe migraines or end-of-life care [161].

Clinical practice guidelines developed by the Institute for Clinical Systems Improvement recommend a stepwise escalation of medical management of migraine headaches. Treatment of severe migraine headache in emergency settings should start with triptans and NSAIDs, progressing to dihydroergotamine and ultimately neuroleptics. Opioids and dexamethasone may be added as adjuncts in refractory cases [162; 217].

Non-Specific Medications

The heterogeneous group of non-specific migraine medications consists of a variety of drugs that do not target the 5-$HT_{1B/1D}$ serotonin receptor. This includes anti-inflammatory medications and/or analgesics (e.g., NSAIDs, opioids, corticosteroids), antidopaminergics, (e.g., metoclopramide, chlorpromazine, haloperidol), antihistamines (e.g., diphenhydramine, dimenhydrinate, hydroxyzine), steroids (e.g., dexamethasone, prednisone), anticonvulsants (e.g., valproate), anesthetics (e.g., lidocaine, bupivacaine, nitrous oxide, propofol), and magnesium sulphate.

NSAIDs inhibit the neuroinflammatory cascade that leads to release of vasoactive mediators that cause vasodilation. They also inhibit the release of prostaglandins that activate nociceptive neurons in the trigeminal nucleus [158]. More than 50% of patients use non-prescription NSAIDs effectively to treat acute migraine, and those who present with complaint of migraine have usually tried these medications unsuccessfully [4; 87; 163]. NSAIDs evaluated for the treatment of acute migraine include a combination of acetaminophen, aspirin, and caffeine (Excedrin Migraine, two tablets every six hours, for a maximum of 48 hours), ibuprofen (Advil, Motrin, generic, 400 mg every three to four hours), and naproxen (Aleve, generic, 200–550 mg twice per day). When administered early in a migraine attack, NSAIDs are effective, and they are approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild-to-moderate attacks [4; 46; 87; 163]. Ketorolac (30 mg IV or 60 mg IM) has also been shown to be effective and is recommended for acute treatment in emergency settings [85; 164; 165; 218].

As discussed, opioids (e.g., morphine, fentanyl, buprenorphine, meperidine, nalbuphine, tramadol) are not currently recommended in the treatment of acute migraine, except when administered intravenously in the emergency department, when necessary for end-of-life care, and when effective analgesia was not achieved and patients are not able to tolerate specific medications due to pre-existing comorbidity (e.g., cardiovascular disease) [85; 160; 161; 164; 166]. In these cases, intractable migraine pain may be managed with an opioid (not meperidine) or dexamethasone. However, if at all possible, clinicians should avoid opioids. The brief pain-relief window, induction of inflammatory neurochemical release, and vasodilatation are counterproductive to treatment issues and migraine pathophysiology. Meperidine is not recommended because its neurotoxic metabolite (normeperidine) may promote seizures [162].

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Antidopaminergic drugs may be categorized as either antiemetics (e.g., metoclopramide) or neuroleptics (e.g., chlorpromazine, haloperidol, droperidol). Several antiemetics, including metoclopramide, are effective in the management of nausea in acute migraine. Metoclopramide blocks D_2 dopamine and 5-HT_3 serotonin receptors in the chemoreceptor trigger zone and accelerates gastric emptying. Its antidopaminergic properties also offer additional antimigraine effects [87]. Metoclopramide (Reglan) 10–20 mg IV is used in emergency settings, and its efficacy is supported by an exhaustive review of the literature published in 2015 [164; 218]. Granisetron (Granisol), a selective 5-HT_3 antagonist, has also been used in the emergency settings, although studies are limited and show a greater risk of adverse effects [84; 164]. One study showed that granisetron is more beneficial than metoclopramide, because it also controls migraine-related emesis [219]. However, more studies are required to determine if the benefits outweigh the risks of granisetron.

The butyrophenones haloperidol (Haldol, generic, 5 mg in 500 mL IV solution) and droperidol (Inapsine, generic, 0.1–2.5 mg IV) are effective in 80% and 54% of the patients, respectively [84]. Common side effects include sedation and akathisia, and these effects have resulted in almost 20% of patients being unwilling to be treated with haloperidol again [167]. The neurologic side effects of butyrophenones and their cardiovascular risks (e.g., QT prolongation, arrhythmias) outweigh their benefits, and their use in the treatment of acute migraine is generally not recommended [164; 218].

The phenothiazine neuroleptics, prochlorperazine (10 mg IV) and chlorpromazine (12.5–25 mg IV), have been found to provide pain relief to up to 90% and 70% of patients, respectively [84; 164]. Side effects are less common with prochlorperazine than with chlorpromazine, but both agents are recommended in the treatment of acute migraine in emergency settings [84; 164].

Antihistamine drugs (e.g., diphenhydramine, hydroxyzine) have been evaluated in combination with other medications for the treatment of acute migraine attack, with variable outcomes [84]. One trial showed benefits with diphenhydramine 12.5 mg IV plus prochlorperazine 10 mg IV, when compared with sumatriptan 6 mg subcutaneous [169]. However, another trial found that there was no improvement to migraine when diphenhydramine 50 mg IV was added in conjunction with metoclopramide 10 mg IV [220]. More high-quality data are required to determine the efficacy of diphenhydramine administered in combination with other drugs for the treatment of migraine.

The anticonvulsant valproate (900–1,200 mg IV) has been evaluated for intractable migraine attack in emergency settings, with a reduction in pain within 50 to 60 minutes in 75% of patients [170]. However, its use as acute therapy is not recommended due to a lack of clear evidence of a favorable risk-benefit profile [164].

In patients with severe acute migraine resistant to treatment, anesthetics may be considered. Topical 4% lidocaine (0.5 mL) may be administered either by the physician or the patient into the nostril of the affected side over 30 seconds, with patient in the supine position [84; 87; 171]. Intravenous lidocaine and propofol are not recommended, as serious side effects outweigh possible benefits [164].

Steroids—specifically dexamethasone (IV 6–24 mg) or prednisone (40 mg/day)—are used as adjuncts to the standard emergent treatment of migraine [172]. These agents act to suppress inflammation underlying migraine. In one study, combined dexamethasone (6 mg IV) plus metoclopramide (5–10 mg IV) provided migraine pain relief at 30 minutes in approximately 80% of patients, an outcome similar to dihydroergotamine (0.75–1 mg IV) plus metoclopramide (5–10 mg IV) [172]. Steroids should be used cautiously in diabetic patients. Repeated administration increases the risk of osteoporosis and well-known endocrine disorders [87; 158].

Magnesium has also been used in the treatment of acute migraine, and interestingly, up to 50% of patients have lowered levels of magnesium in the plasma during an acute migraine attack [157; 173]. Magnesium has an effect on a variety of neurotransmitters and receptors underlying acute migraine, including serotonin receptors, NMDA receptors, nitric oxide, and substance P [157; 173]. Research has shown that magnesium sulphate (1 g IV) is effective in 80% of patients 15 minutes postinfusion in emergency settings [157; 174]. The most common adverse effect is facial flushing. Considering that only a few small clinical trials have evaluated the efficacy of magnesium, the established guidelines do not recommend its use in the treatment of acute migraine [164; 166].

Migraine-Specific Medications

Moderate and severe acute migraines are more effectively treated with migraine-specific medications, particularly ergots and triptans. Interestingly, these medications do not have analgesic properties; rather their clinical effectiveness results from their targeting of the pathophysiologic mechanism underlying migraine. Migraine-specific medications are agonists at the serotonin 5-$HT_{1B/1D}$ autoreceptor, preventing release of serotonin from the presynaptic terminals and causing vasoconstriction of the meningeal blood vessels. These drugs also target the serotonin autoreceptors on terminals of the trigeminal nerve, which results in the inhibition of the release of proinflammatory vasoactive peptides and inhibition of nociceptive transmission in the brainstem [60; 62; 98; 175].

The ergot alkaloids ergotamine and dihydroergotamine are non-selective agonists at the 5-HT_1 serotonin receptor, with a lower affinity for alpha-adrenergic and dopaminergic receptors. On the other hand, triptans are considered to be highly selective agonists at the 5-$HT_{1B/1D}$ serotonin receptor subtype, with lower affinity for binding to other serotonin receptors.

Ergotamine is available in oral formulation (Ergomar) or in combination with caffeine for either oral (Cafergot) or rectal (Migergot) administration. Dihydroergotamine is available for nasal administration (Migranal, generic) or for IV and subcutaneous injection (DHE, generic). The use of ergots has declined since the introduction of triptans, although clinical studies have demonstrated that both drug groups have a similar efficacy in the treatment of acute migraine [161]. Adverse effects of ergots include nausea and vomiting, tingling of the extremities, muscle cramps, and chest discomfort [161]. As discussed, 5-$HT_{1B/1D}$ receptors are also expressed in high levels in the coronary arteries, resulting in the increased potential for adverse cardiac effects (i.e., coronary vasoconstriction) associated with ergotamine derivatives and triptans [161]. Ergots are contraindicated in patients with heart conditions or hypertension, and any chest or cardiac symptoms should be appropriately evaluated [60; 61; 161; 176]. Dihydroergotamine is oxytocic and should not be used during pregnancy or breastfeeding [175; 176]. Dihydroergotamine causes fewer adverse effects than ergotamine, but the use of any ergot alkaloids should be avoided within 24 hours of administration of triptans and serotonergic agonists, due to risk of severe vasoconstriction, and within two weeks of discontinuing monoamine oxidase (MAO) inhibitors. Ergots are contraindicated with potent inhibitors of CYP3A4, such as azole antifungals, macrolide antibiotics, and protease inhibitors [157; 176].

Triptans are considered the first-line therapy for the acute treatment of migraine in patients resistant to NSAIDs. As noted, triptans have a higher selectivity than ergots for the 5-$HT_{1B/1D}$ receptors and very low or no affinity for adrenergic or dopaminergic receptors. Their clinical efficacy results from their vasoconstrictive properties, which are mediated by their binding to the 5-HT_1 receptors abundant in meningeal blood vessels [60; 61; 175]. As of 2021, seven triptans are available in the United States: naratriptan (Amerge), rizatriptan (Maxalt), eletriptan (Relpax), sumatriptan (Imitrex), zolmitriptan (Zomig), almotriptan (Axert), and frovatriptan (Frova). The pharmacodynamic properties and efficacy of all triptans are similar, and their clinical variability relates to the route of administration and individual patient response [157; 161; 176]. Failure or intolerance to one triptan warrants the trial of an alternative agent [157; 161]. It is advisable to switch from one oral triptan to another if three migraine attacks have been treated without success [229]. In one study, sumatriptan 50 mg was similar to ibuprofen 400 mg and to effervescent aspirin 1,000 mg in reducing moderate-to-severe migraine pain, although sumatriptan was superior to the other medications at two hours after administration [177]. A combination of sumatriptan 85 mg and naproxen 500 mg (Trexima) has been shown to provide better pain relief than either drug alone [87]. However, prediction of a patient's response to a particular medication is difficult, and complete pain relief within two hours is only achieved in 45% to 77% of patients taking triptans [87; 178].

Potential side effects of triptans include paresthesias, dizziness, flushing, chest pain, nausea, vomiting, local bleeding, bruising at the site of the injection, and nasal discomfort and dysgeusia for intranasally administered drugs [157; 161; 176]. Triptans are contraindicated in patients with a history of myocardial infarction, cerebrovascular accident, Prinzmetal angina, uncontrolled hypertension, and patients treated with MAO inhibitors. Patients being treated with selective serotonin reuptake inhibitors should avoid triptans due to the increased risk of life-threatening serotonin syndrome [87; 98]. In 2014, analysis of the 16-year Sumatriptan, Naratriptan, and Treximet Pregnancy Registry found that the risk of major birth defects following in utero exposure to these drugs during the first trimester was not increased when compared with studies of birth defects among migraineurs with and without other medication exposure during pregnancy [179]. However, the authors caution that these findings should not be extrapolated to other medications in the triptan class, and triptans are usually avoided during pregnancy [179]. Additionally, a 2017 study supported the position that triptans have no effect on pregnancy outcome, although it was noted that sumatriptan is the best-studied triptan and, therefore, likely the safest choice [220].

In 2019, lasmiditan, a ditan, was approved for the treatment of migraine [176]. Lasmiditan is similar to a triptan but is a high-affinity, highly selective 5-HT_{1F} receptor agonist. The selective targeting of the 5-HT_{1F} receptor is hypothesized to decrease stimulation of the trigeminal system and treat migraine pain without causing vasoconstriction. In a phase 3 study, patients reporting being free of headache after two hours with lasmiditan 200 mg (32.2%) or 100 mg (28.2%) compared with placebo (15.3%). Patients who received lasmiditan were also significantly more likely to report alleviation of their most bothersome symptom compared with placebo [235]. Adverse events were mostly mild or moderate in intensity.

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PREVENTIVE TREATMENT

In some patients, the frequency, severity, and unresponsiveness of migraine attacks to abortive medications require the initiation of preventive therapy. In patients with repeated acute attacks, the overuse of medications—opioids and barbiturates in particular—may lead to migraine chronification [8; 180].

Preventive pharmacotherapy is used in conjunction with effective nonpharmacologic approaches as part of a comprehensive plan including avoidance of migraine triggers, implementation of lifestyle changes, stress management techniques, and a reduction in the use of analgesics or acute migraine medications [181]. Patients with migraine should be considered for preventive treatment in any of the following situations [182; 183; 230]:

- Use abortive medications at least two times per week with limited effectiveness
- Frequent attacks (i.e., four or more per month)
- Attacks significantly interfere with daily routines despite abortive treatment
- Have adverse effects with abortive treatment
- Have migraine attacks with serious and unusual symptoms
- Have an established pattern of medication overuse

Preventive medications improve patients' quality of life and health outcomes and reduce disability and healthcare costs [184; 185]. The decision to opt for preventive pharmacotherapy should be discussed with the patient and should take into consideration the variability in patient response and the possibility of significant side effects [185].

Novel Preventive Treatment of Migraine

In 2018, the first medications in a novel class of drugs received FDA-approval for the prevention of migraine [176; 214; 225; 226]. As previously noted, CGRP is a potent vasodilatory neuropeptide that increases blood flow in the meningeal arteries [66]. It has long been postulated that one cause of episodic migraine is a combination of neuronal hyperactivity and a local process of neurogenic inflammation triggered by an increase in pro-inflammatory mediators such as CGRP, neurokinin, and substance P [29; 31]. Following the development of a monoclonal antibody that blocks the activity of the CGRP peptide, a significant reduction in days with migraine was shown in clinical trials with CGRP antagonists [214; 221; 222; 223].

The first of three clinical trials prior to FDA-approval showed that six months of treatment with erenumab-aaoe resulted in one to two fewer monthly migraine days on average than those on placebo among 955 patients. A second study of 577 patients with episodic migraine showed one fewer migraine day over the course of three months. A third study of 677 patients with chronic migraine showed 2.5 fewer monthly migraine days after three months of treatment [214; 221]. Erenumab-aaoe is recommended for those who do not respond to conventional treatment.

Erenumab-aaoe is initially administered at a dose of 70 mg once-monthly by subcutaneous self-injection, but this can be increased to a maximum of 140 mg once-monthly in divided doses [176]. There are no contraindications to erenumab-aaoe, and known side effects are limited to injection site reactions (less than 6%) and constipation (3%) [176]. Pregnancy and breastfeeding considerations are unknown; however, adverse events were not seen in animal reproduction studies [176].

The results of multiple phase II and phase III clinical trials resulted in additional CGRP antagonists receiving FDA approval in 2018, 2019, and 2020 [222; 227]. Like erenumad, fremanezumab-vfrm, galcanezumab, ubregepant, and eptinezumab-jjmr are administered subcutaneously for prevention of migraine in adults [225; 226]. Fremanezumab-vfrm is administered either as a 225-mg monthly dose or 675 mg every three months [225]. The initial dose of galcanezumab is 240 mg, followed by 120-mg monthly doses [226]. Ubregepant is taken orally at a dose of 50–100 mg (maximum in 24 hours: 200 mg) [227]. The initial dose of eptinezumab-jjmr is 100 mg every three months, but it may be titrated up to a maximum of 300 mg every three months.

Conventional Preventive Treatment of Migraine

Which medication has the highest level of effectiveness in the preventive treatment of migraine?

The precise mechanism of action of drugs used for the conventional prophylactic treatment of migraine is unclear. It has been postulated that these medications prevent the underlying processes that set a migraine attack into motion and raise the threshold for migraine headache.

Initially, treatment should begin with the lowest possible dose, and a trial of at least two medications at the appropriate dosage is typically required before effectiveness can be assessed. If required, the dose should be slowly titrated up until benefits or unacceptable adverse reactions are observed. When possible, long-acting formulations should be used in order improve patient compliance. In addition, selecting medication that may also treat co-existing conditions, such as hypertension or depression, can improve adherence to the treatment plan [186]. One challenging scenario is presented by migraineurs who become less responsive (i.e., tolerant) to preventive migraine medications. This greatly impacts quality of life, and the establishment of an effective treatment plan for these patients requires an understanding of the mechanisms underlying tolerance to migraine therapy [181].

MEDICATIONS USED FOR THE PREVENTION OF EPISODIC MIGRAINE	
Drug Class	**Medications and Dose Ranges**
Level A: Established as effective, should be offered to patients requiring migraine prophylaxis	
Anticonvulsants	Divalproex and sodium valproate[a] (400–1,000 mg/day) Topiramate[a] (25–200 mg/day)
Antihypertensives, beta blockers	Propranolol[a] (120–240 mg/day) Timolol[a] (10–15 mg twice daily) Metoprolol (47.5–200 mg/day)
Other	Butterbur (*Petasites hybridus*) (50–75 mg twice daily)
Level B: Probably effective, should be considered for patients requiring migraine prophylaxis	
Tricyclic antidepressants	Amitriptyline (25–150 mg/day)
Serotonin/norepinephrine reuptake inhibitors	Extended-release venlafaxine (150 mg /day)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Fenoprofen (200–600 mg three times daily) Ibuprofen (200 mg twice daily) Ketoprofen (50 mg three times daily) Naproxen (500–1,100 mg/day) Naproxen sodium (550 mg twice daily)
Antihypertensive, beta blockers	Atenolol (100 mg/day)
Other	Feverfew (*Tanacetum parthenium*) (50–300 mg twice daily or 2.08–18.75 mg three times daily for MIG-99) Magnesium (600 mg/day trimagnesium dicitrate) Riboflavin (400 mg/day) Histamine (1–10 ng subcutaneously, twice per week)
Level C: Possibly effective, may be considered for patients requiring migraine prophylaxis	
Antihypertensive, angiotensin II receptor blockers (ARBs)	Candesartan (16 mg/day)
Antihypertensive, angiotensin-converting enzyme (ACE) inhibitors	Lisinopril (10–20 mg/day)
Anticonvulsants	Carbamazepine (600 mg/day)
Antihypertensive, alpha-2 agonists	Clonidine (0.75–0.15 mg/day; patch formulations also studied) Guanfacine (0.5–1 mg/day)
Antihypertensive, beta blocker partial agonists	Pindolol 10 (mg/day)
Antihypertensive, selective beta-1 blockers	Nebivolol (5 mg/day)
NSAIDs	Flurbiprofen (200 mg/day) Mefenamic acid (500 mg three times daily)
Antihistamine, H1 antagonists	Cyproheptadine (4 mg/day)
Other	Coenzyme Q10 (100 mg three times daily)
[a]Approved by the FDA for prophylactic treatment of migraine.	
Source: [186; 205]	*Table 2*

Although preventive treatments do not completely prevent the occurrence of migraines, they do reduce the frequency by at least 50% [185; 187]. Evidence-based guidelines regarding drug effectiveness for the prevention of episodic migraine have haven prepared by the American Headache Society and the American Academy of Neurology (AHS/AAN) (***Table 2***) [74; 186; 230]. These guidelines categorize the available prophylactic medications according to the level of available evidence. The following oral treatments have established efficacy and should be offered for prevention of migraine: antiepileptic drugs (e.g., divalproex sodium, valproate sodium, topiramate), beta-blockers (e.g., metoprolol, propranolol, timolol), and frovatriptan (for short-term preventive treatment of menstrual migraine). An exception

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to the use of valproate sodium and topiramate is that, due to risk of birth defects, it should not be prescribed to women of childbearing potential who are not using a reliable method of contraception [230]. Evidence indicates the following treatment options are probably effective and should be considered for prevention: antidepressants (e.g., amitriptyline, venlafaxine), beta-blockers (e.g., atenolol, nadolol), and angiotensin receptor blockers (e.g., cardisartan) (230).

Caution is required when NSAIDs are used for preventive therapy, as their use is associated with induction of medication-overuse headache and chronification of migraine [185]. Although the Canadian Headache Society guideline for migraine prophylaxis recommends the use of the anticonvulsant gabapentin, this is not supported by a 2014 Cochrane review or a 2016 review of literature, which confirmed the effectiveness of topiramate, divalproex, and sodium valproate, but concluded that the evidence was insufficient to support the use of gabapentin [152; 188; 224]. Extended-release topiramate is contraindicated in patients with metabolic acidosis taking metformin, during pregnancy, in women of childbearing age not using contraception, and in patients with recent alcohol use (within six hours prior or six hours following administration). Divalproex and sodium valproate are contraindicated in patients with impaired liver function, urea cycle disorders, and pregnant women (for the prevention of migrane) [176].

For the prevention of menstrual migraines, the AHS/AAN recommend frovatriptan (2.5 mg twice daily perimenstrually, following a loading dose), naratriptan (1 mg twice daily perimenstrually for five days), or zolmitriptan (2.5 mg two or three times per day perimenstrually). It should be noted, however, that the FDA did not feel evidence for triptans, including frovatriptan, was sufficient to approve these medications for prevention of migraine [74; 186; 215]. The AHS recommends an NSAID (such as naproxen 550 mg) twice-daily for five to seven days surrounding the menstrual window, estrogen supplementation of 1 mg per day during menstruation, and magnesium supplementation 15 days from the start of menses until menses begins [215].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement asserts that migraines occurring in association with menses and not responsive to standard cyclic prophylaxis may respond to hormonal prophylaxis with use of estradiol patches, creams, or estrogen-containing contraceptives.

(https://www.icsi.org/wp-content/uploads/2019/01/HeadacheRR.pdf. Last accessed June 21, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

TREATMENT OF REFRACTORY CHRONIC MIGRAINE

Up to 10% of migraine sufferers become less responsive to preventive migraine medications. A variety of mechanisms have been implicated in tolerance, including pharmacokinetic (e.g., metabolic, drug-drug interactions), pharmacodynamic (e.g., receptor down-regulation), behavioral (e.g., unconscious adaptations), drug-induced disease progression (e.g., medication overuse, opioid abuse), and natural variability of migraine factors [189]. For these patients, a review of therapy compliance, drug quality and delivery, and environmental aggravating factors is the effective first step. Drug dosages should be adjusted or patients may be switched to an alternative medication. An effort should be made to identify and manage environmental and lifestyle triggers (e.g., sleep patterns, smoking, excess caffeine). Patients may benefit from a drug holiday of two to three months to obtain accurate baseline information and compare treatment effects.

DEVELOPMENT OF NEW THERAPIES FOR MIGRAINE

Research has provided a better understanding of the pathophysiology of migraine, and effective translational medicine is beginning to lead to the availability of new drugs.

As previously noted, gap junction channels appear to be involved in several ways in the pathophysiology of migraine, although limited research has been conducted on gap junction blockers in the prevention or treatment of migraine and results have been conflicting. Clinical studies have shown that efficacy for the gap junction blocker tonabersat remains unclear [192; 193; 213].

Occipital nerve stimulation has been found to be effective in the treatment of medication-resistant chronic migraine. The European Headache Federation recommends the use of this modality after all alternative drug and behavioral therapies have failed [194].

In 2013, the FDA approved a device using transcranial magnetic stimulation (TMS) technology for use when a patient with migraine feels a headache or migraine coming on or when the pain begins. This device is held to the back of head with both hands and a button is quickly pressed and released, sending a magnetic pulse to stimulate the brain's occipital cortex. This is the only device that has received FDA approval to treat migraine with aura [195].

In 2014, the FDA approved the first transcutaneous electrical nerve stimulation (TENS) device as an alternative to medication for migraine prevention [195]. This approach consists of a small, portable, battery-powered, prescription device that resembles a plastic headband worn across the forehead. The patient positions the device in the center of the forehead, just above the eyes, using a self-adhesive electrode.

The device applies an electric current to stimulate branches of the trigeminal nerve [195]. The TENS device is specifically authorized to be used prior to the onset of headache in patients with a history of chronic migraine.

MIGRAINE IN CHILDREN AND ADOLESCENTS

Migraine in children and adolescents is relatively common and potentially disabling. It may be more prevalent than data from national health surveys indicate. A systematic review of population-based studies found that the prevalence of migraine is 9.7% in female children and adolescents and 6% in male children and adolescents [231]. Adolescents with migraine are reported to have high levels of disability, low health-related quality of life, and tend to have inferior academic performance as compared to their peers [232]. A Canadian health survey, conducted over multiple time periods and involving 61,000 subjects between 12 and 19 years of age, found a strong and consistent association between migraine and anxiety/mood disorders and perceived mental health in adolescents [232]. The authors recommended screening for symptoms of anxiety and depression in children and adolescents presenting with migraines. According to a review of pediatric clinical studies, the most effective pediatric/adolescent management strategy includes the combination of timely pharmacologic interventions (NSAIDs and/or triptans) for acute attacks combined with education in self-management techniques and biopsychosocial approaches such as biofeedback, relaxation therapy, and cognitive-behavioral therapy [233].

In 2019, the AAN and the AHS published practice guidelines for treatment of acute migraine in children and adolescents [234]. Ibuprofen oral solution (10 mg/kg) is the initial treatment option recommended to reduce pain and is more likely to be effective when administered early, within one hour of headache onset. The efficacy of triptans is less well established, and triptans are less commonly prescribed in children than in adults. Four triptans have been approved by the FDA for treatment of migraine in adolescents (12 to 17 years of age): sumatriptan/naproxen, almotriptan, rizatriptan, and zolmitriptan. When response to a triptan is less than satisfactory, ibuprofen or naproxen in combination should be offered to improve migraine relief. It is important to counsel patients and families on the cumulative duration limits of NSAID and triptan use to avoid adverse effects and overuse headache. AAN/AHS guidelines recommend that ibuprofen or acetaminophen use be limited to no more than 14 days per month, and triptan use limited to no more than 9 days per month [232]. Ergots and naproxen for acute migraine have not been studied in children [234].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient history is such a vital aspect of the assessment of migraine, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures is being provided, the use of an interpreter should be considered.

CONCLUSION

Migraine is a complex and multifaceted condition that requires an appropriate evaluation, detailed medical history, and neurologic examination. Other primary and secondary causes of headache should be considered in the clinical evaluation in order to ensure the correct diagnosis. After the diagnosis of migraine is established, an individualized management strategy should be crafted using the combination of nonpharmacologic, pharmacologic, and patient education interventions. Optimization of therapy for either abortive or prophylactic management of acute or chronic migraine is required, and interprofessional collaboration between primary care providers and specialists is necessary to effectively treat patients with challenging migraines.

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RESOURCES

American Academy of Neurology
https://www.aan.com

American Migraine Foundation
https://americanmigrainefoundation.org

National Institute of Neurological Disorders and Stroke (NINDS)
https://www.ninds.nih.gov

American Headache Society
https://americanheadachesociety.org

European Headache Federation
https://ehf-org.org

The Migraine Research Foundation
https://migraineresearchfoundation.org

FACULTY BIOGRAPHY

A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and received a Young Investigator Award by the American Brain & Behavior Research Foundation.

Dr. Lança participated in international courses and conferences on neurosciences. He has contributed to a better understanding of the mechanisms underlying the ontogenetic development of the brain opiatergic system. As a research scientist at the Addiction Research Foundation (ARF) in Toronto, he initiated research on the functional role played by dopaminergic cell transplants on alcohol consumption, leading to the publication of the first research reports on cell transplantation and modulation of an addictive behavior. Subsequently, he also investigated the role played by other neurotransmitter systems in the limbic system and mechanisms of reward, co-expression of classical neurotransmitters and neuropeptides and potential role in neuropsychiatric disorders.

He is an Assistant Professor in the Department of Pharmacology and Toxicology at the Faculty of Medicine and at the Faculty of Dentistry at the University of Toronto, where he lectures and directs several undergraduate and postgraduate pharmacology and clinical pharmacology courses. He was the Program Director for Undergraduate Studies in the Department of Pharmacology and Toxicology of the University of Toronto. He has developed clinical pharmacology courses for the Medical Radiation Sciences and Chiropody Programs of The Michener Institute for Health Sciences at the University of Toronto.

Dr. Lança's commitment to medical education started while a medical student, teaching in the Department of Histology and Embryology, where he became cross-appointed after graduation. In Toronto, he has contributed extensively to curriculum development and teaching of pharmacology to undergraduate, graduate, and medical students.

He has authored research and continuing education in peer-reviewed publications and is the author of six chapters in pharmacology textbooks. Dr. Lança has conducted research in various areas including neuropharmacology, pharmacology of alcoholism and drug addiction, and herbal medications.

He has developed and taught courses and seminars in continuing medical education and continuing dental education. His commitment to continuing education emphasizes an interdisciplinary approach to clinical pharmacology.

Customer Information/Evaluation insert located between pages 88–89.

Psychopharmacology

Audience
This course is designed for nurses and pharmacy professions involved in the care of patients with mental health conditions.

Course Objective
In the management of patients with mental health disorders, pharmacotherapy remains a vital part of optimal treatment. This course will review the approaches to incorporating pharmacotherapy into the management of the most common mental health disorders in the United States. A variety of potential adverse effects and considerations will also be included.

Learning Objectives
Upon completion of this course, you should be able to:

1. Outline the history of pharmacology in psychiatry.
2. Describe the action and use of typical antipsychotics.
3. Compare and contrast the various atypical antipsychotics.
4. Evaluate class-wide adverse effects of antipsychotics.
5. Identify available antidepressant medication and their use in the treatment of major depression.
6. Discuss potential adverse effects and warnings associated with antidepressants.
7. Describe medications used in the management of bipolar disorder.
8. Assess the role of antidepressants in the management of anxiety disorders.
9. Discuss the use of benzodiazepines for the treatment of anxiety.
10. Review available pharmacotherapy to incorporate into the treatment of substance use disorders.

Faculty
Carol Whelan, APRN, has been working in nursing education since 2000. She received her Master's degree in psychiatric/mental health nursing from St. Joseph College in West Hartford, Connecticut, and completed post-graduate nurse practitioner training at Yale University. Ms. Whelan is an Associate Clinical Professor and Lecturer at Yale University and works as an APRN at the Department of Veterans' Affairs in Connecticut, where she also serves as the Vice President of Medical Staff. She has authored many articles, textbook chapters, and books.

Faculty Disclosure
Contributing faculty, Carol Whelan, APRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Jane C. Norman, RN, MSN, CNE, PhD

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Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

Psychiatry and the medications prescribed for psychiatric issues are intertwined with culture and society that it is impossible to discuss its history without also talking about the societal context and cultural beliefs that surround it. No orthopedic surgeon has ever had to convince a patient that a broken leg was not caused by demons and that the therapy prescribed is medically needed. The same cannot be said for psychiatry. Even in the 21st century, clinicians who deal with the complex medications used to treat psychiatric illness encounter patients who feel shame, guilt, and doubt associated with their diagnoses and the medications used to manage them.

The root of this skepticism can be traced to the French philosopher René Descartes in the 1500s and the famous Cartesian motto "I think therefore I am." According to this widely embraced philosophy, one exists because s/he thinks, not because the heart beats, the muscles work, or the lungs breathe. From this perspective, one is because their brain is healthy.

Given this belief that a disordered mental state calls one's very existence into question, it is no wonder patients are reluctant to seek help, ashamed to report their symptoms, and afraid that they may lose their job or custody of their children—there is an underlying belief that their existence will be questioned if something is wrong with their thoughts, emotions, and the inner core of their being. This is the world psychiatric medication are being prescribed in. But how did we get here?

A BRIEF HISTORY OF PSYCHIATRY AND PSYCHOPHARMACOLOGY

In the United States, the first attempt at humane treatment of psychiatric disorders was by the Quakers, who in 1752 used the Pennsylvania Hospital in Philadelphia to house patients in its basement; however, the environment in the hospital was damaging to patients, some of whom were shackled to walls [1]. Other early institutions for people deemed "mentally disturbed" were opened in the late 1700s in New York. In 1824, the Eastern Lunatic Asylum (now Eastern State Hospital) opened in Lexington, Kentucky. By 1890, every state had at least one publicly supported mental hospital, with populations that were rapidly expanding; by the 1950s, these institutions housed more than 500,000 patients [1]. One of the earliest practitioners of what could be called psychiatry was Dr. Benjamin Rush, who has been called the father of American psychiatry and who wrote the first American textbook on mental diseases (*Medical Inquiries and Observations upon Diseases of the Mind*) in 1812.

EARLY CUSTODIAL CARE AND THE ADVENT OF INSTITUTIONS

The Association of Medical Superintendents of American Institutions for the Insane was founded in 1844; in 1921, the name changed to the American Psychiatric Association (APA) [2]. In the 1800s, there was no real psychopharmacology or even a true appreciation of the biologic nature of mental illness. However, it is important to acknowledge Rush's decision to refer to "diseases of the mind," rather than more judgmental terminology common to the time, such as spiritual disease or weakness. In fact, Rush hypothesized that psychiatric disorders were caused by irritation of the blood vessels in the brain. This led to treatments such as bleeding and purging and to what could be called the first attempt at the development of a psychoactive medication—the use of mercury as a treatment for mental illness. While it is easy to dismiss such early attempts, this theory of a vascular cause of psychiatric symptoms is consistent with some current knowledge of vascular dementia, and while the theories seem ill-informed today, it is important to note that other popular theories of psychiatric etiology of the time attributed mental illness to demons, witchcraft, or moral turpitude.

During this early period, institutional care of the mentally ill was often a means to persecute women and others whom society wished to confine, which led to what some call the "coercive era" of psychiatric care. One of the most important of these cases was that of Elizabeth Packard in 1860. Elizabeth Packard was married to a clergyman who forcibly placed her in an Illinois asylum. In 1860, Illinois law allowed for involuntary hospitalization of a spouse (generally a wife) by request without any evidence. Ms. Packard was eventually able to obtain release from the hospital, but due to her husband's continuing campaign, she was forced to petition the court and was released in 1863 with a habeas corpus hearing. After gaining her freedom, Ms. Packard began a campaign for the protection of women's rights. As a result of her efforts and the efforts of others at the time, laws were passed requiring a jury trial prior to involuntary hospitalization. It is notable that the Association of Medical Superintendents of American Institutions for the Insane (now the APA) opposed these laws at the time. The damage done by these forcible hospitalizations was huge, and the association of psychiatry with coercion persist to this day. These beliefs influence both the public's acceptance of psychopharmacology as a valid and effective treatment and the acceptance of psychiatric diagnoses as true medical diagnoses, as opposed to an excuse to prescribe medications or force hospitalization.

Another leader in the development of humane custodial care of the psychiatric patients was Dorothea Dix, who, in addition to her other accomplishments, is credited with opening more than 30 state mental hospitals throughout the United States. Dix advocated for humane institutions, particularly for the poor and unhoused, and reformation of mental health treatment.

The landmark court case O'Connor v. Donaldson ruled that the government cannot confine an individual who is not dangerous and is capable of living outside the institution. This ruling was based on the case of Kenneth Donaldson, who in his youth had undergone a course of brief psychiatric care, but had recovered, married, and moved from Florida to Pennsylvania. In 1956, he travelled to Florida to visit his parents, where he made a remark (possibly a joke) that he believed someone in Pennsylvania may have been trying to poison his food. In response, his father hired a lawyer, and at a hearing (where he had no legal representation), Donaldson was civilly committed. He was then placed in a housing unit with dangerous and violent criminals. He received no treatment and, as a Christian Scientist, refused all medications and did not agree that he was experiencing mental illness, which was against the typical routine of admitting illness, accepting treatment, and being released. Donaldson spent more than 15 years in this asylum, despite friends petitioning the administrator for his release and guaranteeing that they would care for him. He eventually won his release by petitioning the courts directly and then proceeded to file suit against the administrator (O'Connor) who had blocked his release, on the constitutional ground of illegal confinement denying him his right to liberty.

The court found that mental illness alone cannot justify custodial confinement against the will of the individual. Further cases (e.g., Lake v. Cameron) introduced the concept of care in the least restrictive setting, and in 1999, the Supreme Court ruled in Olmstead v. L.C. that mental illness is a disability covered under the Americans with Disabilities Act.

At the same time that the courts were acknowledging the rights of persons with mental illness, pharmacologists were making breakthroughs; therapeutic use of chlorpromazine (Thorazine) had been discovered, and the world of psychiatry would never be the same.

THE BIRTH OF MODERN PSYCHIATRY AND PSYCHOPHARMACOLOGY

The history of psychopharmacology is intertwined with the history of neurology and psychiatry. During the 19th century, psychiatry and neurology were chiefly concerned with the treatment of psychosis and deviant behaviors. The treatment of less severe conditions (e.g., depression, neurosis) was considered outside the province of psychiatry or neurology.

At the beginning of the 20th century, Sigmund Freud published his famous theories on the unconscious roots of what he termed psychoneurosis [3]. He was especially interested in conversion disorders, whereby patients displayed paralysis or other somatic symptoms that could not be explained in a medical context. Freud developed psychoanalysis (talk therapy) and thus began the outpatient treatment of patients with psychiatric concerns.

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By the mid-20th century, psychoanalysis became overwhelmingly popular and was employed not only in the treatment of patients with anxiety or neurosis but also in the treatment of patients with more severe psychiatric disorders, such as psychosis, for which talk therapy had little to offer. Some postulate that the development of psychoanalysis stunted the development of psychopharmacology by promoting the notion that talk therapy could effectively treat all mental health issues.

One of the first treatments of psychosis—electroconvulsive therapy or ECT—was developed in the 1930s. Its development arose from the observation that patients with both psychosis and epilepsy seemed to experience improvements in psychotic symptoms following a seizure. While this apparent improvement may have actually been a postictal phase of the seizure disorder, it spurred a search for ways to induce seizures in patients with severe psychiatric disorders. Initial attempts used high doses of stimulant drugs to produce seizures, and the term convulsive therapy was coined. Due to drawbacks evident with the use of stimulant drugs, Italian neurologist Ugo Cerletti experimented with inducing seizures using electrical shocks delivered to the head [4].

Despite its roots in somewhat dubious observations of the effects of electric shocks on livestock, ECT remains in use today as a valid psychiatric treatment. In fact, it was one of the only truly effective psychiatric treatments in the 1930s and 1940s. It was also arguably one of the first treatments to address mental illness as a biologic disorder. Some consider the advent of convulsive therapy as the true beginning of psychopharmacology, as it relied on alteration of brain chemistry to produce improvements in patients.

Building on these advances, psychopharmacology exploded in the 1950s with the development of chlorpromazine, early antidepressants, and early mood stabilizers.

THE DEVELOPMENT OF PSYCHOPHARMACOLOGY

Most experts date the birth of modern psychopharmacology to the synthesis of which drug?

The term psychopharmacology traces its roots to 1920, appearing first in the title of a paper by David Macht describing the use of quinine and antipyretics in tests on neuromuscular coordination. However, most experts date the true birth of psychopharmacology to 1951, when chlorpromazine was first synthesized [5].

Chlorpromazine was developed in the lab of Rhône-Poulenc (an early French pharmaceutical company) for use in general anesthesia to induce calmness. It was not long before French surgeons saw the potential for the use of chlorpromazine in the treatment of psychiatric illness. The first paper on chlorpromazine (titled "A new stabilizer") was published in February 1952 in La Presse Medicale [5].

The first documented clinical psychiatric use of chlorpromazine was on January 19, 1952, when 50 mg intravenous chlorpromazine was given to a patient, 24 years of age, with severe agitation, psychosis, and possibly mania. The effects were noted as calming but also were transient in nature. After 20 days of treatment with a cumulative total of 900 mg of chlorpromazine along with concomitant barbiturates and ECT, the patient was able to be discharged home [5]. By 1957, chlorpromazine had become internationally recognized, and the American Public Health Association presented Albert Lasker Awards for Medical Research to several scientists and physicians associated with the development of chlorpromazine and introduction of the drug into clinical practice.

Perhaps the greatest contribution of chlorpromazine was not in its clinical effects but rather in its ability to distinguish the biologic basis of schizophrenia. During the course of the 1950s, studies of chlorpromazine use led to an understanding of synaptic transmission and development of the theory that synaptic transmission was not a merely electrical event but rather a chemically mediated event. By the end of the 1950s, six neurotransmitters had been identified in the central nervous system, including dopamine, norepinephrine, and serotonin [5].

The success of chlorpromazine led to the development of more antipsychotics, including thioridazine (Mellaril), haloperidol (Haldol, Decanoate), trifluoperazine (Stelazine), and fluphenazine (Prolixin). However, all of these early antipsychotics were noted to have neurologic side effects, most notably extrapyramidal symptoms with parkinsonian features.

Some consider the 1950s to be a "golden age" of psychopharmacology. Beginning in 1958, tricyclic compounds based on the structure of imipramine were synthesized; these are referred to as second-generation (atypical) antipsychotics. One of these compounds was clozapine (Clozaril, Versacloz), an antipsychotic still in use today. Interestingly, clozapine did not initially attract much attention. Small trials showed mixed results, and unlike chlorpromazine, there was no consensus as to its effectiveness. The lack of extrapyramidal side effects led many researchers to erroneously believe that it was not a true antipsychotic, as the dopamine blockade theory of schizophrenia was still widely held.

THE ORGANIC BASIS OF MENTAL ILLNESS AND THE ADVANCEMENT OF PSYCHOPHARMACOLOGY

The development of medications to treat psychiatric illnesses has greatly informed our understanding of the biologic nature of these illnesses—most notably the link between antipsychotics and schizophrenia. This translational research also led to the understanding of neurotransmitters and further informed the development of large classes of psychoactive medications.

The dopamine receptor D2 is a common target of the antipsychotics. Assessment of medications' ability to target receptors was made possible by the introduction of the spectrophotofluorimeter in 1955. This instrument allows for analysis of chemicals in the brain, including monoamines, which allowed for the further advancement of the field of psychopharmacology [5].

With their introduction in the 1950s, monoamine oxidase inhibitors (MAOIs) became the first class of medications used to treat depression. The incorporation of these agents into clinical practice further moved psychiatry away from inpatient care in institutions toward effective outpatient care.

Another historical breakthrough in psychopharmacology was the discovery of the use of lithium for the treatment of mania. While there is some evidence of usage in the 1800s, the seminal research reintroducing lithium for the treatment of mania was published in 1949 by John Cade [6]. Despite its ready availability and widespread use worldwide, lithium was not approved by the U.S. Food and Drug Administration (FDA) until 1970; the United States was the 50th country to approve the use of lithium for the management of mania [6].

The discovery of medications effective in the treatment of affective disorders induced a shift away from the talk therapy-only approach originally developed by Freud. Further, the ability of lithium to improve symptoms of depression supported the burgeoning biologic theory of mental illness. This change in understanding of mental illness had extensive and widespread influence on the practice psychiatry. It extended beyond schizophrenia and bipolar disorder and helped transform etiologic theories of diseases such as autism from a focus on environmental influence (e.g., poor mothering in the case of autism) to a biologic understanding of psychiatric disorders prevalent today.

In the later part of the 20th century, psychopharmaceutical advancements continued at record pace. The development of benzodiazepines, lithium, barbiturates, and MAOIs led to an era of deinstitutionalization and the mainstream diagnosis and management of psychiatric disorders without a reliance on talk therapy. This seismic change was not without controversy, and proponents of talk therapy and psychoanalysis resisted the use of psychopharmacology to treat mental illness.

This philosophical conflict was clearly evident in the revision process for the APA's *Diagnostic and Statistical Manual of Mental Disorders* (DSM). In 1980, the DSM was extensively revised (creating the DSM-III), and psychoanalytic language was abandoned. In contrast to the DSM-II, the DSM-III focused on symptom-based descriptions of mental disorders for diagnostic criteria.

Psychiatry continued to evolve to accept the biologic basis of mental illness and embrace the use of pharmacologic treatment. The introduction of selective serotonin reuptake inhibitors (SSRIs), which were both well-tolerated and had better safety profiles than previous medications, revolutionized the treatment of depression. The first SSRI, fluoxetine (Prozac), was approved by the FDA in 1987. While there has been controversy regarding the possible overdiagnosing of depression or overprescribing of antidepressants, no one disputes the enormous impact fluoxetine has had on psychopharmacology [3].

At virtually the same time as the introduction of fluoxetine, a group of second-generation (atypical) antipsychotics were being approved in the United States. These medications, including risperidone (Perseris, Risperdal) and olanzapine (Zyprexa), challenged the traditional belief that only the D2 receptor/dopamine was involved in psychosis. This renewed interest in the forgotten medication clozapine and novel treatment approaches for schizophrenia.

While clozapine had been originally introduced in the 1950s and approved by the FDA in 1971, small studies had been unable to show efficacy. Use of the drug effectively ended in 1975, when the Finnish National Board of Health reported 18 individuals prescribed clozapine who developed severe blood disorders (most commonly agranulocytosis, a severe decrease or an absence of white blood cells increasing the risk of potentially fatal infection); 9 of these patients died [7]. Research since that time indicates that agranulocytosis occurs in about 1% of patients taking clozapine and neutropenia is seen in about 3% [8].

These early roadblocks to the use of clozapine were overcome, first by a system of monitoring white blood cell counts and secondly by longer studies that showed that the effect of clozapine continue to increase after four weeks of therapy, unlike chlorpromazine, which had a peak effect after two to three weeks [7]. As a result of these findings, clozapine was approved for the treatment of psychosis in the United States in 1990 [7]. The price of this drug when it was first approved, approximately $9,000 per patient per year for the medication and monitoring, was initially controversial, but it was more cost-effective than inpatient care or institutionalization [3; 7].

The risk for leukopenia remains a barrier to wider use of clozapine; however, it has become a mainstay for treatment-resistant schizophrenia and is also acknowledged to reduce the risk of suicide in patients with schizophrenia. It is also used off-label in the management of treatment-resistant bipolar disorder and dementia- or Parkinson-related psychosis or agitation. With the availability of a generic version, the price of clozapine is now less than many other newer antipsychotics. Knowledge that the risk of agranulocytosis is highest in the first three months has also led to a reduction in the frequency of long-term monitoring.

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NEW HORIZONS: PSYCHOPHARMACOLOGY AND ADDICTION MEDICINE

Substance use disorder is a significant issue in the United States, affecting more than 20 million individuals annually [9]. Historically, addiction was considered a moral failing—a symptom of criminality or weak character. A variety of non-effective treatments were used until the 1900s, ranging from cocaine-based therapy, hydrotherapy, and institutionalization. In the 1930s, 12-step and self-help models were established for alcohol dependence treatment. In 1949, disulfiram (Antabuse) became the first drug approved to treat alcoholism [10]. The drug works by increasing the concentration of acetaldehyde, a toxic byproduct that occurs when alcohol is broken down in the body. Excess amounts of this byproduct (as when alcohol is consumed along with the medication) cause unpleasant symptoms, such as nausea and flushing of the skin. The anticipation of these effects can assist with cessation and abstinence. For more than 40 years, disulfiram was the only medication approved for the treatment of alcohol use disorder [10]. Since then, two additional medications—naltrexone (ReVia, Vivitrol) and acamprosate (Campral)—have been approved. The conceptualization of addiction and substance use disorder has also evolved and is now recognized to be a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biologic, psychological, social, and spiritual manifestations [11]. As a primarily biologic illness, addiction is now recognized as a valid target for pharmacotherapy.

In the early 21st century, the United States experienced an unprecedented increase in opioid prescribing, use disorder, and fatal overdose [12]. In addition to the highly beneficial therapeutic effects, the toxic side effects and addictive potential of opioids have been known for centuries. These undesired effects have prompted a search for a potent synthetic opioid analgesic free of addictive potential and other complications. However, all synthetic opioids introduced into medical use share the same abuse liabilities of the classical opioids. The search for new opioid therapeutics has resulted in the synthesis of opioid antagonists and compounds with mixed agonist-antagonist properties, such as buprenorphine, which has expanded therapeutic options and provided the basis of expanded knowledge of opioid mechanisms [13].

Nonmedical use of prescription opioids was reported in literature as early as 1880. A report in 1928 documented that injection of opioids contributed to the development of nonmedical use and misuses of prescription opioids. Before 1930, the prevalence of nonmedical opioid injecting in the United States was low. But by the mid-1940s, more than one-half the admissions to the National Institute of Mental Health's Lexington Hospital were for the misuse of prescription opioids [14]. As of 2018, there were an estimated 2.1 million individuals with opioid use disorder in the United States [15]. In addition, more than 81,000 drug overdose deaths occurred in the United States in the 12 months ending in May 2020, the highest number of overdose deaths ever recorded in a 12-month period, and the rise was mainly attributed to synthetic opioids [16].

While methadone has long been in use in specialized clinics with strict licensing, the development of alternative treatments for opioid use disorder, including buprenorphine/naloxone (Suboxone), has revolutionized the approach to managing and treating this disorder.

ANTIPSYCHOTIC MEDICATIONS

With the development of clozapine, antipsychotic medications have been divided into typical antipsychotics (also referred to as first-generation antipsychotics) and atypical antipsychotics (also referred to as second-generation antipsychotics). In addition, a group of novel atypical antipsychotics have been developed and generally act on serotonin as well as dopamine receptors.

The choice of antipsychotic should be guided by the side effect profile, available route of administration (e.g., liquid forms, oral disintegrating tablets), and the patient's medical history, current medications, and preference. Many patients will be unwilling to switch from a drug that has been effective, even if a different drug may yield better results.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Psychiatric Association recommends that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects. This guideline statement should be implemented in the context of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia.

(https://psychiatryonline.org/doi/full/10.1176/appi.books.9780890424841.Schizophrenia02. Last accessed September 28, 2021.)

Strength of Recommendation/Level of Evidence: IA (High confidence that the evidence reflects the true effect)

TYPICAL ANTIPSYCHOTIC MEDICATIONS					
Drug	**Dose Range**	**Typical Starting Dose**	**Usual Maintenance Dose[a]**	**Route(s)**	**Indication(s)**
Chlorpromazine	25–800 mg/day	25–50 mg/day	100–400 mg daily or BID	IM, IV, PO	Schizophrenia, bipolar disorder, intractable hiccups, agitation/aggression (severe, acute) associated with psychiatric disorders
Droperidol	0.625–10 mg/day	2.5–10 mg/day	10 mg/day	IM, IV	Postoperative nausea/vomiting, acute undifferentiated agitation (off-label)
Flupentixol	IM: 5–40 mg/day Oral: 1–6 mg/day	IM: 5–20 mg/day Oral: 1 mg/day	IM: 20–40 mg every 2 to 3 weeks Oral: 3–6 mg/day in divided doses	Oral, IM (depot)	Schizophrenia
Fluphenazine	2.5–40 mg/day	2.5–10 mg every 6 to 8 hours	Oral: 5–40 mg/day IM: 12.5–25 mg every 2 to 4 weeks	PO, IM, decanoate	Psychotic disorders
Haloperidol (Haldol)	0.5–30 mg/day	Oral: 0.5–5 mg BID	5–15 mg BID	PO, IM, IV, decanoate	Bipolar disorder, hyperactive delirium, schizophrenia, Tourette-associated tics, acute/severe agitation (off-label)
Loxapine (Adasuve)	5–125 mg BID	10–25 mg BID	60–100 mg BID	PO, inhalation	Schizophrenia, acute agitation
Methotrimeprazine	6–200 mg/day	Mild: 6–25 mg/day in divided doses Severe: 50–75 mg/day in divided doses	Oral: IM: 75–100 mg/day in divided doses	PO, IM	Anxiety/tension disorders, insomnia, nausea/vomiting, pain, psychotic disorders
Molindone	5–75 mg TID	5–15 mg BID	10–25 mg TID	PO	Schizophrenia
Periciazine	5–40 mg/day	5–20 mg in the morning, followed by 10–40 mg in the evening	Titrate to lowest effective dose	PO	Psychosis
Perphenazine	2–24 mg BID	2–4 mg BID	8–24 mg BID	PO	Schizophrenia, nausea/vomiting
Pimozide	0.5–10 mg/day	1–2 mg/day in divided doses	Lowest effective dose (maximum: 10 mg)	PO	Tourette syndrome, delusional infestation (off-label)

Table 1 continues on next page.

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TYPICAL ANTIPSYCHOTIC MEDICATIONS *(Continued)*					
Drug	**Dose Range**	**Typical Starting Dose**	**Usual Maintenance Dose[a]**	**Route(s)**	**Indication(s)**
Prochlorperazine (Compro)	2.5–25 mg/day	Oral: 5–10 mg every 6 to 8 hours IM: 5–10 mg every 3 to 4 hours IV: 2.5–10 mg every 3 to 4 hours Rectal: 25 mg every 12 hours	Maximum: 40 mg/day	PO, IM, IV, rectal	Acute nausea and vomiting
Thioridazine	50–800 mg/day	50–100 mg TID	200–800 mg BID or QID	PO	Schizophrenia
Thiothixene	2–30 mg BID	2–5 mg BID	10–15 mg BID	PO	Schizophrenia
Trifluoperazine	2–40 mg/day	1–2mg BID	15–20 mg/day	PO	Schizophrenia
Zuclopenthixol	10–400 mg/day	Oral: 10–50 mg/day in divided doses IM: 50–150 mg/day	Oral: 20–40 mg/day IM: Up to a maximum 400 mg/day	PO, IM	Schizophrenia, psychoses (acute and long-term)
[a]All dosing is for adults. For pediatric uses, consult pediatric-specific literature. BID = twice daily, IM = intramuscular, IV = intravenous, PO = oral, QID = four times per day, TID = three times per day.					
Source: [17; 18; 19]					*Table 1*

TYPICAL ANTIPSYCHOTICS

Which typical antipsychotic may be administered via inhalation?

Typical antipsychotics (***Table 1***) have a primary site of action at the D2 receptor and are potent D2 receptor blockers. They also have noradrenergic, cholinergic, and histaminergic blocking action. These agents can also be described as high, intermediate, or low potency. High-potency antipsychotics are prescribed in lower doses, with the most widely prescribed of these being haloperidol (Haldol). Haloperidol is available in oral, intramuscular (IM), and long-acting IM decanoate formulations. Low-potency antipsychotics are prescribed in higher doses; the most widely used of these is chlorpromazine [17; 18].

Adverse Effects

The adverse and side effect profiles of typical antipsychotics are generally poorer than the atypical antipsychotics. The prevention, detection, and treatment of extrapyramidal symptoms, most notably tardive dyskinesia, is the main challenge when prescribing typical antipsychotics.

Neurologic Effects

Patients who are prescribed typical antipsychotics should be monitored for neurologic side effects using the standardized Abnormal Involuntary Movement Scale (AIMS) (***Figure 1***). The AIMS consists of 12 items and can usually be completed within 10 minutes. It was developed specifically to detect and record the occurrence of tardive dyskinesia in any patient taking neuroleptic medication. Tardive dyskinesia is a syndrome characterized by abnormal involuntary movements of the patient's face, mouth, trunk, or limbs, and it affects

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Patient Name _____ Date of Visit _____

Code: 0 = None 1 = Minimal 2 = Mild 3 = Moderate 4 = Severe

Movement Ratings:
- Rate highest severity observed in category I, II, III.
- Rate movements that occur upon activation one point less than those observed spontaneously.
- Circle movements as well as code number that applies.

		RATER / DATE	RATER / DATE	RATER / DATE	RATER / DATE
I FACIAL & ORAL MOVEMENTS	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g. puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw Biting, clenching, chewing, mouth opening , lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
II EXTREMITY MOVEMENTS	**5. Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
III TRUNK MOVEMENTS	**7. Neck, shoulders and hips** Rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
IV GLOBAL JUDGEMENT	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patients report: No Awareness = 0 Aware, no distress = 1 Aware, mild distress = 2 Aware, moderate distress = 3 Aware, severe distress = 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
V DENTAL STATUS	**11. Current problems with teeth and/or dentures**	YES NO	YES NO	YES NO	YES NO
	12. Are dentures usually worn	YES NO	YES NO	YES NO	YES NO
	13. Endentia?	YES NO	YES NO	YES NO	YES NO
	14. Do movements disappear with sleep?	YES NO	YES NO	YES NO	YES NO

Source: [20] *Figure 1*

20% to 30% of patients who have been treated for months or years with neuroleptic medications. Patients who are older, are heavy smokers, or have diabetes are at increased risk of developing tardive dyskinesia. For most patients, this side effect develops three months after the initiation of neuroleptic therapy; in elderly patients, however, tardive dyskinesia can develop after as little as one month [20].

Regular use of the AIMS allows the severity of symptoms to be followed over time. Initial AIMS testing should be done prior to the initiation of treatment and every three to six months during therapy. Either before or after completing the examination procedure, the patient should be observed unobtrusively at rest (e.g., in the waiting area). The chair used in the examination should be firm and without arms.

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The patient should remove his or her shoes and socks and any gum, candy, or food from his/her mouth prior to the examination. In addition to the examination and observation, the patient should be asked about:

- Dental/oral health (e.g., use of dentures, problems with teeth)
- Unintended movements in the extremities, mouth, or face and whether these movements are a bother or interfere with activities

Patients should be instructed to sit in a chair with their feet flat on the ground; a general observation of the patient's body may be made at this point. Patients should also be asked to drape their arms over their legs, with their hands hanging over their knees. Several additional tasks should be done, including:

- Opening the mouth to observe whether the tongue is moving or at rest
- Sticking out the tongue out to observe for any abnormal movements
- Tapping the thumb with each finger as rapidly as possible to observe the flexibility of fingers as well as any other body movements that occur while the patient is concentrating on this manual task
- Flexing and extending the arms and wrists one at a time to monitor for rigidity and cogwheeling
- Walking around the room to observe for any parkinsonian-type movements

All findings during the examination should be recorded. It is important to note that repetitive, regular, rhythmic tremors are not recorded on the AIMS, as the tool is specific to tardive dyskinesia. However, these tremors may in fact be an adverse effect of neuroleptic treatment. If present, these movements should be monitored and considered when making treatment and pharmacotherapy decisions.

Metabolic Effects

Meta-analyses have shown that all antipsychotics are associated with an increased risk for weight gain, with the greatest gain seen with atypical agents (clozapine and olanzapine) and the least with typical agents (haloperidol). Numerous studies have concluded that H1 receptor antagonism action is most correlated with weight gain, although other receptor sites (including 5HT receptors) were also significantly associated with weight gain [21].

A reasonable approach to monitoring metabolic side effects involves measuring vital signs and weight prior to prescribing an antipsychotic agent and at every follow-up visit. Baseline blood work including a lipid profile, hemoglobin A1C, and a basic metabolic panel is also advised. Variances from baseline values and the presence or absence of weight gain can help guide the frequency of monitoring. However, obtaining laboratory studies at least yearly should be considered.

Cardiovascular Effects

Monitoring for QTc prolongation should be a consideration for all patients prescribed an antipsychotic. Obtaining a baseline electrocardiogram (EKG) prior to prescribing is good practice. Values greater than 500 msec should prompt referral to cardiology and a consideration to avoid medications that can prolong the QTc interval. Values of 450–500 msec require close follow-up EKG monitoring both after initiation of treatment and during any dosage adjustments.

ATYPICAL ANTIPSYCHOTICS

Antipsychotics remain a consistently popular option for the management of psychosis and schizophrenia. Since the reintroduction of clozapine in the 1990s, there has been a steady increase in the proportion of atypical antipsychotics prescribed compared with typical antipsychotics. By 2014, atypical antipsychotics accounted for almost 80% of total antipsychotics prescribed [22]. This has been partially attributed to treatment failure with typical antipsychotics (e.g., up to 30% of patients with schizophrenia fail to respond to typical antipsychotics), a desire to avoid extrapyramidal symptoms, and expansion of FDA-approved indications for atypical agents [17]. It should be noted that some of the lesser-used low-potency typical antipsychotics may also avoid extrapyramidal effects.

As of 2021, there were 14 atypical antipsychotics approved for use in the United States (***Table 2***). Like the typical agents, these drugs are used primarily for the treatment of psychoses, although several are adjunctive treatments for major depressive disorder. Novel antipsychotics with various mechanisms of actions continue to be studied and approved; clinicians should consult the latest prescribing literature when selecting a medication for their patient.

When choosing an atypical antipsychotic, it is important that the clinician fully understand the mechanism of action of the drug being considered, as they have a wide variety of actions. There are also significant pharmacokinetic differences.

Aripiprozole

Aripiprozole is a partial dopamine agonist (not a blocker). Some research indicates that this medication may have a lower risk of tardive dyskinesia and metabolic syndrome. The initial effects of the oral preparation may be observed within days of treatment of bipolar disorder or acute mania and within one to two weeks in those with major depressive disorder or schizophrenia [19]. In all patients, continued improvement in efficacy is noted over the next several weeks. For bipolar/acute mania, maximal efficacy is seen in one to two weeks [19]. However, those with schizophrenia may see improvements for 4 to 6 weeks, and those with major depressive disorder may see maximal effects after 6 to 12 weeks [19].

ATYPICAL ANTIPSYCHOTIC MEDICATIONS					
Drug	**Dose Range**	**Typical Starting Dose**	**Usual Maintenance Dose[a]**	**Route(s)**	**Indication(s)**
Aripirazole (Abilify)	2–30 mg/day	2.5–5 mg/day	10–20 mg/day	PO, decanoate	Bipolar disorder, treatment-resistant depression (adjunctive), schizophrenia
Asenapine (Saphris, Secuado)	5–10 mg BID	5 mg BID	10 mg BID	SL, transdermal patch	Bipolar disorder, schizophrenia
Brexipiprazole (Rexulti)	2–4 mg/day	1 mg/day	4 mg/day (with titration)	PO	Schizophrenia, treatment-resistant depression (adjunctive)
Cariprazine (Vraylar)	1.5–6 mg/day	1.5–6 mg/day	3–6 mg/day (with titration)	PO	Bipolar disorder, schizophrenia
Clozapine (Clozaril, Versacloz)	25–800 mg/day	25–800 mg/day	250–400 mg hourly or BID (Strict titration guidelines, must be in REMS)	PO (including oral disintegrating tablet)	Schizophrenia, suicidal behavior in schizophrenia or schizoaffective disorder
Iloperidone (Fanapt)	1–12 mg/day	1–2 mg BID	12 mg/day (lower doses in patients with hepatic dysfunction)	PO	Schizophrenia
Lumateperone (Caplyta)	42 mg/day	42 mg/day	42 mg/day	PO	Schizophrenia
Lurasidone (Latuda)	20–80 mg/day	20 mg/day	80 mg/day	PO	Bipolar major depression, schizophrenia
Olanzapine (Zyprexa)	2.5–20 mg/day	2.5–5 mg/day	15–20 mg/day	PO, IM, IV	Bipolar disorder, agitation/aggression associated with psychiatric disorders, schizophrenia
Paliperidone (Invega)	3–12 mg/day	3 mg/day	6 mg/day	PO, IM decanoate	Schizophrenia, schizoaffective disorder
Pimavanserin (Nuplazid)	34 mg/day	34 mg/day	34 mg/day	PO	Parkinson-associated psychosis
Quetiapine (Seroquel)	25–800 mg/day	50 mg/day	200–400 mg/day	PO, extended-release	Bipolar disorder, schizophrenia
Risperidone (Perseris, Risperdal)	0.5–6 mg/day	1–2 mg/day	4 mg/day	PO, IM decanoate	Bipolar disorder, schizophrenia
Ziprasidone (Geodon)	20–80 mg/day	40 mg BID	80 mg BID	PO, short-acting IM	Bipolar disorder (adjunctive), schizophrenia

[a]All dosing is for adults. For pediatric uses, consult pediatric-specific literature.
BID = twice daily, IM = intramuscular, IV = intravenous, PO = oral, QID = four times per day, REMS = Risk Evaluation and Mitigation Strategy, SL = sublingual.

Source: [17; 18; 19] *Table 2*

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Aripiprozole is metabolized hepatically and is primarily excreted in the feces (55%) and urine (25%). Peak plasma levels are noted in three to five hours following oral tablet administration, though high-fat meals can delay this time by hours. Following multiple IM doses of the extended-release formulation, peak plasma levels are noted in four days after deltoid administration or after five to seven days following gluteal administration [19].

The only absolute contraindication to the use of aripiprozole is hypersensitivity (including anaphylaxis) to the drug or any components of the formulation. The drug is associated with orthostatic hypotension and should be used with caution in patients predisposed to this effect or who are unable to tolerate transient hypotensive episodes [19]. Other possible adverse effects include increased serum glucose, weight gain, constipation, tremor, nausea/vomiting, agitation, anxiety, sedation/drowsiness, extrapyramidal reactions, headache, and insomnia [19].

Asenapine

What is the only atypical antipsychotic available in a sublingual formulation?

Asenapine is a dibenzo-oxepino pyrrole atypical antipsychotic with mixed serotonin-dopamine antagonist activity. It is unique as the only atypical antipsychotic available in a subligual formulation. When administered sublingually for the management of agitation, the onset of effects is seen within 15 minutes. In bipolar disorder/acute mania, initial effects are present within days, with continued improvements over one to two weeks [19]. In patients being treated for schizophrenia, the initial effects are observed within one to two weeks, and maximal effects are noted in four to six weeks.

Asenapine is metabolized by the liver and excreted primarily in the urine and feces [19]. Peak plasma levels are attained within 0.5 to 1.5 hours for the sublingual formulation and within 12 to 24 hours for the transdermal patch.

Severe hepatic impairment (Child-Pugh class C) and hypersensitivity are considered absolute contraindications to asenapine. Possible adverse effects include drowsiness/fatigue, insomnia, extrapyramidal reactions, headache, weight gain, increased serum triglycerides and serum glucose, and oral hypoesthesia [19].

Brexiprazole

Brexiprazole exhibits partial agonist activity for 5-HT1A and D2 receptors and antagonist activity for 5-HT2A receptors. As a partial dopamine agonist, it is associated with a decreased risk for extrapyramidal reactions (including tardive dyskinesia) and metabolic syndrome. The onset of action for the oral formulation is typically within 1 to 2 weeks, with increased efficacy over the following weeks (4 to 6 weeks in those with schizophrenia and 6 to 12 weeks in those with major depressive disorder) [19].

Brexiprazole undergoes hepatic metabolism, primarily by CYP3A4 and CYP2D6. It is excreted in the feces and urine. Brexiprazole reaches peak plasma levels within four hours [19].

The only absolute contraindication to the use of brexiprazole is hypersensitivity reactions. However, it should be used with caution in patients with renal impairment. The most common adverse effects of brexiprazole are increased serum triglycerides (typically <500 mg/dL), weight gain, and akathisia (inability to remain still) [19].

Cariprazine

Cariprazine acts as a partial dopamine (D2) and serotonin (5-HT1A) agonist, with antagonist activity at serotonin 5-HT2A receptors. Onset of initial effects varies from days (with bipolar disorder/acute mania) to up to two weeks (with schizophrenia) [19]. As with the other atypical antipsychotics, effects increase over time to peak efficacy experienced in up to 12 weeks.

Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to active metabolites [19]. It is excreted through several routes, but most prominently through the urine. Peak plasma levels occur within three to six hours. Due to the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks.

There are no absolute contraindications to the use of cariprazine aside from hypersensitivity. Common adverse effects include extrapyramidal reactions, parkinsonian-like syndrome, akathisia, headache, nausea, and insomnia [19].

Clozapine

Clozapine has demonstrated efficacy in reducing the risk of suicide in patients with schizophrenia and known efficacy in treatment-resistant schizophrenia. It is believed to act through antagonism of the D2 and serotonin type 2A (5-HT2A) receptors [19]. The onset of action for the oral formulation is observed from within days up to two weeks, with increased effects for the subsequent weeks. For patients with treatment-resistant schizophrenia, longer trials of 8 to 12 weeks are recommended [19].

Metabolism of clozapine is extensively hepatic, with urinary and fecal excretion. Time to peak plasma levels is 2.2 to 2.5 hours, depending on the route of administration [19].

Serious hypersensitivity to clozapine or any component of the formulation is considered an absolute contraindication to its use [19]. Though not included in the U.S. labeling, Canadian labels include myeloproliferative disorders, impaired bone marrow function, active hepatic disease, severe renal impairment, paralytic ileus, uncontrolled epilepsy, severe nervous system dysfunction, and severe cardiovascular disease as additional contraindications. Common adverse effects are hypertension, hypotension, tachycardia, increased serum

glucose levels, dyslipidemia, weight gain, constipation, decreased gastrointestinal motility, dyspepsia, nausea/vomiting, sialorrhea, dizziness, drowsiness/sedation, insomnia, vertigo, and fever [19].

The Clozapine REMS Program

Clozapine is associated with severe neutropenia (absolute neutrophil count [ANC] less than 500/mcL). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a centralized point of access for prescribers and pharmacies to certify before prescribing or dispensing clozapine and to enroll and manage patients on clozapine treatment [23]. The monitoring requirements are established for the general population (most patients being prescribed clozapine) and for patients with benign ethnic neutropenia (BEN). BEN is a condition observed in certain ethnic groups whose average ANCs are lower than "standard" laboratory ranges for neutrophils. It is most commonly observed in individuals of African descent (approximate prevalence of 25% to 50%), some Middle Eastern ethnic groups, and in other non-White ethnic groups with darker skin; it is also more common in men [23]. At initiation of therapy, ANC monitoring should be conducted weekly for six months. If ANC levels remain ≥1,500/mcL in the general population or ≥1,000/mcL in patients with BEN, monitoring frequency may be reduced to every two weeks from 6 to 12 months, then monthly after 12 months. If neutropenia develops, monitoring may be more frequent, from three times weekly to daily depending on the severity of the neutropenia [23]. Prescribers are required to submit patients' ANC levels to the Clozapine REMS Program for every prescription of clozapine according to the patient's monitoring frequency.

Iloperidone

Iloperidone exhibits mixed dopamine (D2)/serotonin (5-HT2) antagonist activity. The agent's low affinity for histamine H1 receptors may decrease the risk for weight gain and somnolence, and its affinity for norepinephrine α1/α2C may improve cognitive function but increase the risk for orthostasis. With oral administration, the onset of antipsychotic action may be observed within one to two weeks of treatment, with four to six weeks to peak effect [19].

Hepatic metabolism of iloperidone results in creation of the active metabolites P88 and P95. These metabolites are excreted primarily in the urine and, less extensively, in the feces. Peak plasma levels are achieved in two to four hours [19].

Contraindications are limited to hypersensitivity reactions. The most common adverse effects are tachycardia, dizziness, drowsiness, increased serum prolactin, and weight gain [19].

Lurasidone

Lurasidone has documented mixed serotonin-dopamine antagonist activity, with high affinity for D2, 5-HT2A, and 5-HT7 receptors. Improvements in psychosis or bipolar disorder/depressive episode are noted within one to two weeks of treatment, although efficacy will improve for up to six weeks [19]. The medication should be given with food to improve absorption.

Hepatic metabolism is achieved primarily via CYP3A4 and results in two main active metabolites and two main nonactive metabolites [19]. Excretion is mainly in feces. Peak serum concentration occurs within one to three hours, with steady state concentrations achieved within seven days.

Lurasidone is contraindicated with hypersensitivity reactions or concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil) and inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine) [19]. It should be used with caution and at the lowest possible dose in patients with hepatic impairment. Other common adverse effects include dyslipidemia, increased serum glucose, nausea, extrapyramidal reaction, drowsiness, akathisia, parkinsonian-like syndrome, and insomnia.

Olanzapine

Olanzapine displays potent antagonism of serotonin, dopamine, histamine, and alpha1-adrenergic receptors [19]. Its antipsychotic action is believed to be related to its effect on dopamine and serotonin. For acute agitation, effects are seen within 15 minutes with IM injection or within 5 to 10 minutes with IV administration. When administered orally for the management of bipolar disorder/acute mania or schizophrenia, initial effects are seen within days to two weeks; improvements may be noted for up to six weeks [19]. This agent is available in a long-acting injection formulation, and details about managing patients prescribed this route will be discussed in detail later in this course.

Olanzapine is metabolized via direct glucuronidation and cytochrome P450-mediated oxidation; 40% is removed via first-pass metabolism [19]. It is excreted in the urine (57%) and feces (30%). Maximum plasma concentrations after IM administration are five times higher than maximum plasma concentrations produced by an oral dose [19]. Clearance is increased in cigarette smokers and decreased in female patients. Following short-acting injection, peak plasma concentrations occur in 15 to 45 minutes; with extended-release injection, peak levels are noted in about one week. Following oral administration, peak serum concentrations are noted within six hours [19].

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While there are no published contraindications to olanzapine, hypersensitivity is a likely barrier to use. This drug is associated with dose-related increases in prolactin levels, with associated menstrual-, sexual-, and breast-related effects [19]. Adverse reactions seen most commonly include dyslipidemia, increased serum glucose, weight gain, increased appetite, xerostomia, decreased serum bilirubin, akathisia, dizziness, drowsiness/fatigue, extrapyramidal reactions, headache, insomnia, parkinsonism, and asthenia [19].

Quetiapine

As with the other atypical antipsychotics, the antipsychotic effects of quetiapine are believed to be the result of its antagonism of dopamine (D2) and serotonin (5-HT2) receptors [19]. It also has antagonistic action against 5-HT1A, D1, histamine (H1), and adrenergic alpha1- and alpha2-receptors, some of which may result in adverse effects. After oral administration, initial effects are seen within days (for bipolar disorder/acute mania or bipolar disorder/depressive episode) or up to two weeks (for schizophrenia). Continued improvement in symptoms should be expected for 1 to 12 weeks [19]. If the extended-release formulation is used in the management of generalized anxiety disorder, the initial effects are observed within four to seven days, with continued improvement for eight weeks.

Quetiapine metabolism is primarily hepatic, with mainly urinary elimination. The time to peak plasma level is 1.5 hours for the immediate-release version and 6 hours for the extended-release formulation [19].

There are no absolute contraindications to the use of quetiapine, aside from hypersensitivity. Drowsiness is a common effect and may be severe enough to result in impairment, inability to safely carry out activities of daily living (increased fall risk), and nonadherence [19]. Other common adverse effects include hypertension, orthostatic hypotension (particularly among elderly patients), tachycardia, dyslipidemias, weight gain, increased appetite, xerostomia, agitation, dizziness, extrapyramidal reaction, headache, and withdrawal syndrome.

Risperidone

Risperidone's high 5-HT2 and dopamine-D2 receptor antagonist activity is responsible for its antipsychotic action. However, alpha1, alpha2 adrenergic, and histaminergic receptors are also antagonized with high affinity. Onset of action is within days to 2 weeks, though peak effect may be experienced after up to 12 weeks [19]. An orally disintegrating tablet may be used to manage acute agitation, with 70 minutes mean time to calm.

Risperidone undergoes extensive hepatic metabolism to create the active metabolite 9-hydroxyrisperidone [19]. It is primarily excreted in the urine. Time to peak plasma level is about 1 hour with oral administration (but it is 3 to 17 hours for the active metabolite). When administered subcutaneously, the first peak is in 4 to 6 hours; the second peak is in 10 to 14 days.

Hypersensitivity to risperidone, paliperidone, or any component is an absolute contraindication. Following each subcutaneous injection, a lump may develop and persist for several weeks. This is a self-limiting effect, and the injection site should not be rubbed or massaged [19]. Other common adverse effects include hyperprolactinemia, weight gain, constipation, nausea/vomiting, upper abdominal pain, akathisia, anxiety, dizziness, drowsiness/fatigue, extrapyramidal reaction, headache, insomnia, parkinsonism, and tremor.

LONG-ACTING INJECTABLE ANTIPSYCHOTICS

A subset of antipsychotics (both typical and atypical) are available as long-acting injectable forms (***Table* 3**). When prescribing a long-acting injectable antipsychotic, clinicians first initiate treatment with the oral form for a long enough period to demonstrate tolerance. The oral formulation should be continued until the long-acting therapy has been established. Both fluphenazine and haloperidol use sesame oil in their suspension, which may cause allergic reactions in patients sensitive to sesame.

There are no randomized controlled trials showing superiority of decanoate injections over other formulations; however, some small studies have shown at least similar efficacy of long-acting injected and oral haloperidol [24]. Plasma serum concentrations with steady-state decanoate yield lower plasma drug concentrations than with oral administration. This suggests that decanoate forms are at least as effective as oral agents and that lower doses may be effectively used with this formulation [24].

The efficacy of long-acting injectable antipsychotics other than haloperidol is not clear [25]. Studies have found varying results for different antipsychotics, both in terms of efficacy and side effect profile [24; 25]. The ultimate decision to select a long-acting injectable antipsychotic is complicated and typically driven by a need to improve compliance.

CLASS-WIDE ADVERSE EFFECTS AND WARNINGS

There are a variety of adverse effects and special population warnings that apply across the class of antipsychotic medications. These should be taken into account when selecting an agent, structuring the treatment plan, and conducting follow-up assessments.

LONG-ACTING INJECTABLE ANTIPSYCHOTICS				
Drug	**Usual Dosing**	**Onset**	**Oral Overlap**	**Comments**
Fluphenazine decanoate	25 mg every 3 weeks	24 hours	24 hours	—
Haloperidol decanoate	50–200 mg every 4 weeks	One week	7 to 14 days	—
Paliperidone palmitate	117–156 mg monthly OR 273–819 mg every 3 months OR 1,092–1,560 mg every 6 months	—	None	Dosage will depend on the dose established prior to switching to the long-acting formulation. Maintenance dose started 3 weeks after dose 2.
Risperidone (Risperdal Consta)	12.5–25 mg every 14 days	7 days	3 weeks	—
Olanzapine (Zyprexa Relprevv)	300 mg every 4 weeks	7 days	None	Post-injection syndrome limits usage.
Aripiprazole	300–400 mg every 30 days	7 days	7 days	High cost may limit access.

Source: [19] *Table 3*

Dementia-Related Psychosis

In general, the management of behavioral and psychological symptoms of dementia (most prominently psychosis and agitation/aggression) relies on the off-label use of atypical antipsychotics, along with any effective behavioral interventions. Unfortunately, these drugs are often less than clinically effective, with many patients displaying no or only partial response [26]. Furthermore, elderly patients with dementia are much more likely to experience the adverse effects of antipsychotics. The FDA has included a boxed warning on the labels of all atypical antipsychotics regarding the increased mortality risk when these medications are used in elderly patients [26]. The APA recommends that non-emergency antipsychotic medication should "only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient" [27].

Suicidality in Children, Adolescents, and Young Adults

Some antipsychotics are approved or used for the treatment of depressive episodes in bipolar disorder or as adjunctive treatment for. In this capacity, they are considered antidepressants, and antidepressants have been shown to increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (≤24 years of age) in the first months of treatment [28]. As such, a boxed warning has been added to the labeling information for these agents regarding this increased risk. This risk will be discussed in more detail later in this course.

Neuroleptic Malignant Syndrome

In patients taking antipsychotic medications, when might symptoms of neuroleptic malignant syndrome appear?

Neuroleptic malignant syndrome is a life-threatening idiosyncratic reaction to antipsychotic medications (including newer atypical agents, although it is more common with typical antipsychotics). It is a rare condition (occurring in approximately 0.01% to 0.02% of patients receiving antipsychotics), but it is unpredictable and potentially fatal, making it a significant concern [29]. Higher doses, higher potency, and long-acting formulations increase the risk of neuroleptic malignant syndrome.

Onset of symptoms is generally apparent within two weeks of treatment initiation. Clinical presentation consists of rigidity/stiffness, high fever, sweating, confusion, unstable blood pressure, and agitation. Signs and symptoms usually progress to a peak after three days. Prompt recognition is necessary to avoid significant morbidity and mortality, and treatment is immediate cessation of the antipsychotic medication and implementation of supportive measures (e.g., hydration, cooling) [30]. In more severe cases, administration of bromocriptine mesylate or dantrolene sodium may be indicated.

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Elevated Prolactin Levels

An often-overlooked side effect of antipsychotics is elevated prolactin levels, which can present in men as gynecomastia or in women as galactorrhea and absence of menses. Elevated prolactin levels should be monitored and may necessitate changing agents.

Movement Disorders

As noted, extrapyramidal reactions can occur with antipsychotic therapy and can be a significant barrier to the effective use of these agents. There have also been anecdotal reports of dyskinesia seen with virtually all classes of medications, but the majority of patients with tardive dyskinesia have had exposure to antipsychotics. Studies estimate that up to 30% of patients on long-term antipsychotic therapy will develop various movement disorders [17; 31]. The risk is also elevated in elderly patients.

The pathophysiology of tardive dyskinesia is believed to be related to abnormal functioning of the extrapyramidal tracks in the nervous system. Tardive literally means "late occurring," and although there are case reports of patients having symptoms after a single dose of a neuroleptic medication, the primary defining factor of tardive dyskinesia is that it is a later-occurring syndrome, as opposed to dystonia and akathisia, which usually develop in the early phases of treatment.

Tardive dyskinesia is also characterized by involuntary, uncontrollable movements. This differentiates it from dystonia, which is characterized by stiffness and decreased movement and can often be identified during AIMS testing by flexing the patient's wrists and elbows and observing for resistance. Akathisia is the perception of wanting to move and difficulty staying still; it often manifests as a constant need to pace or walk. In AIMS testing, akathisia can be identified in patients who have difficulty sitting without tapping feet, moving their legs, or otherwise having difficulties sitting still. Tardive dystonia typically presents with a fixed posturing of the face and neck, often a sideways tilt of the head, that the patient is unable to voluntarily correct. The most classic presentation of this is torticollis.

Proper diagnosis of movement disorders is essential, as treatment should be tailored to the specific disorder. Work-up of movement disorders should include consultation with appropriate specialists. This is especially important in the treatment of elderly patients for which the onset of parkinsonian movements may in fact be the hallmark of primary Parkinson disease as opposed to secondary parkinsonian side effects. Further assessment should be guided by neurologic consultation and may involve imaging.

After the specific movement disorder has been identified, treatment will focus on the goals of decreasing the movement disorder and the need to avoid destabilizing the patient's psychotic disorders.

Treatment of Tardive Dyskinesias

Treatment of tardive dyskinesia can be difficult and an impediment to the clinical stabilization of the patient. The primary consideration for patients receiving typical antipsychotics should be dose reduction or switching medications. Patients should be warned that tardive dyskinesia symptoms may initially worsen transiently as medication dosages are lowered (i.e., withdrawal-emergent dyskinesias). If a new medication will be used, clozapine should be considered first, as it has the lowest risk of tardive dyskinesia. However, it is vital to ensure that control of psychosis is maintained, particularly in patients at risk for self-harm or violence.

In 2017, the FDA approved the first medications for the treatment of tardive dyskinesia: velbenazine (Ingrezza) and deutetrabenazine (Austedo). The initial dose of velbenazine is 40 mg once daily. This is increased to 80 mg once daily after one week [19]. Continuation of a daily dose of 40 mg or 60 mg may be considered based on response and tolerability. Improvement is seen in 2 to 6 weeks, with the result stabilizing between 16 to 32 weeks. Deutetrabenazine is started at a dosage of 6 mg twice daily. This is increased as needed and tolerated in increments of 6 mg/day up to a maximum of 48 mg/day [19].

Although there is little evidence supporting this use, anticholinergics are often used to prevent extrapyramidal side effects caused by antipsychotics. Some clinicians will co-prescribe these drugs in an effort to prevent the development of extrapyramidal reactions. However, studies have shown that the numerous side effects associated with anticholinergics (e.g., cognitive impairment, urinary disturbances, vision changes, constipation) may preclude their use [31; 32]. Elderly patients are particularly vulnerable to these effects, and male patients older than 40 years of age are especially susceptible to acute urinary retention. The Canadian Psychiatric Association recommends that clinicians consider discontinuation of anticholinergic medications for the treatment of tardive dyskinesia, keeping in mind that there is very little evidence to support this course of action and that drug-induced parkinsonism may worsen [33]. If anticholinergics are used, they should be prescribed at the lowest possible dose, patients should receive education on the potential risks and benefits, and informed consent should be obtained.

RISK MITIGATION STRATEGIES FOR PATIENTS PRESCRIBED ANTIPSYCHOTICS	
Risk Mitigation Strategy	**Frequency of Assessment[a]**
AIMS testing	Every three months and after each dosage change
Electrocardiogram	One month after initiation, then yearly if QTc is less than 450 msec Recheck after any major dosage change
Weight	At each visit
Vital signs	At each visit
Laboratory studies[b]	With stable baseline values, consider monitoring every six months Recheck with any significant weight gain or symptoms
[a]All testing/assessment should occur prior to the initiation of therapy (to establish a baseline) and immediately after initiation. [b]Laboratory studies should include hemoglobin A1C, basic metabolic panel, complete blood count, and prolactin level.	
Source: Compiled by Author	*Table 4*

RISK MITIGATION STRATEGIES

As discussed, risk mitigation strategies should be initiated when prescribing any antipsychotics. Although only clozapine has a formal REMS program, there are steps that should be taken with any antipsychotic prescription to minimize the potential for adverse effects and manage associated risks (***Table 4***).

Patients prescribed antipsychotics should receive education on the effects of the drugs, possible risks and benefits, and any recommended monitoring. However, this can be difficult if the patient has active psychosis or delusional paranoia. In these cases, caregivers and/or surrogate decision makers should be sought. All discussions should be fully documented. Patient education is an ongoing process (not a single event), and efficacy and adverse effects should be discussed regularly with patients as well as steps taken to treat or ameliorate adverse effects.

While ***Table 4*** presents an example of risk mitigation strategies for all antipsychotics, the actual strategies used should be specific to the patient and agent(s); abnormalities should generate a consult to appropriate medical team members. Aside from prevention and early detection of adverse effects, risk mitigation strategies should include a treatment plan for any possible adverse reactions. As discussed, there are several class-wide potential adverse effects, and these known risks should be reviewed and planned for.

CASE STUDY

Patient A is 34 years of age with a history of schizoaffective bipolar disorder, first diagnosed at 18 years of age during his first year at college. His childhood was notable for several episodes of brief counseling for behavioral issues in school and at home, with a brief trial of methylphenidate (Ritalin) at 11 years of age. Patient A graduated from high school with his peers, but once at college, he developed delirious mania, paranoia, and psychosis. Treatment with olanzapine and valproic acid (Depakote) was initiated, but compliance has been an ongoing issue. During the past 16 years, the patient has had numerous episodes requiring hospitalization, one suicide attempt, and three arrests for breach of peace. He is now on probation and has been unable to maintain employment. He is living with his mother, who has communicated that he will have to leave the house if he does not take his medication. Patient A presents for medication management, stating that he does not like the weight gain he has experienced with many of the medications he has used in the past.

The nurse takes and documents a full history. On mental status exam, Patient A is alert and oriented. He scores 27 on a Mini-Mental State Exam (MMSE) and is mildly grandiose. His speech is slightly pressured but interruptible. At the time of presentation, the Patient A is not taking any medications, having disagreed with his last provider's prescription of olanzapine, a drug that had been effective in the past.

Patient A is 6 feet 1 inch tall and weighs 235 pounds. His blood pressure is 124/86 mm Hg. Laboratory studies are requested, and all return normal. An EKG reveals a normal QTc and sinus rhythm.

The nurse asks Patient A what he wants to gain in his medication management, and his stated goals are to continue to live with his mother, to avoid future arrest, and to be able to maintain a job. The nurse discusses available typical and atypical oral and decanoate antipsychotics. After a long discussion, Patient A decides to try long-acting injection risperidone (Risperdal Consta). Patient education includes the risks of extrapyramidal reactions (e.g., movement disorders), weight gain, and prolactin elevation, which can lead to gynecomastia, as well as risk mitigation strategies if any of these develop.

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A baseline AIMS test is conducted and is negative for any existing issues. The oral trial of risperdone is initiated, as required before using any long-acting injectable to demonstrate tolerance. The patient is titrated up to an oral dosage of 3 mg twice daily, which appears to resolve the patient's paranoia, pressured speech, and hypomania. Patient A reports that he is functioning better, but he reiterates that he does not think he will be able to comply with daily oral medication. The decision is made to progress to long-acting injected risperidone, which requires a three-week overlap with the oral medication.

While there is no exact dosage equivalency, the manufacturer recommends that a 6-mg total oral daily dose of risperdone should be converted to a bimonthly injectable dose of 37.5–50 mg long-acting risperdone. The patient is started at 37.5 mg IM every two weeks. After three weeks, the patient is stable and able to wean off the oral risperdone, decreasing to 4 mg in two divided doses for three days, then 2 mg in divided doses for three days, before total cessation. During this time, the nurse maintains frequent contact with Patient A to verify stability and compliance.

After six weeks, laboratory studies are ordered, including blood glucose level, lipids, and prolactin level, and a repeat EKG is done. All findings are normal. The nurse continues to administered the AIMS test every three months and to check weight and vital signs at every visit. While Patient A continues with this therapy, laboratory values are rechecked every three to six months.

Patient A responds well to treatment and is able to remain living with his mother. After six months, he has gained employment at a fast food restaurant and has avoided any contact with law enforcement.

ANTIDEPRESSANT MEDICATIONS

Depressive disorders affect approximately 17.3 million, or 1 in 6, Americans each year [34; 35; 36]. Major depressive disorder is present in approximately 22.2 million American adults, or about 7% of the U.S. population 18 years of age and older in a given year. The lifetime incidence of depression in the United States is 20% in women and 13% in men, or about 17% of all Americans.

There are five major classes of antidepressants available in the United States: tricyclic antidepressants (TCAs), MAOIs, SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs), and atypical antidepressants (***Table 5***). Modern antidepressants were introduced in the 1950s following serendipitous discovery of antidepressant effects with TCAs and MAOIs. SSRIs were introduced in the late 1980s, followed by atypical antidepressants and SNRIs [37]. The monoamine hypothesis, proposed to explain the unexpected effects of TCAs/MAOIs in the 1950s, posits that depression results from deficient brain serotonin and/or norepinephrine levels. This remained the dominant paradigm of depression and the basis of nearly all FDA-approved antidepressants for the next five decades [38; 39]. However, limitations of the monoamine hypothesis and mechanistic homogeneity of standard antidepressants are now understood. Major depressive disorder is more complex and diverse than previously assumed, and novel pathways that underlie its pathophysiology have been identified [40; 41].

Unlike psychotic disorders, first-line therapy for mild depression should include nonpharmacologic interventions, such as cognitive behavioral therapy, guided self-help, interpersonal psychotherapy, and other lifestyle and psychosocial interventions. Evidence-based guidelines recommend that the process of treatment selection involve shared decision making between provider, patient, and family members, and that the values, priorities, and goals of the patient be included in discussions of risks and benefits of treatment options [42]. Ongoing communication with other providers involved in the care of a patient is essential for coordination and monitoring and can involve different care providers in the same primary care clinic or the primary care provider and therapist or psychiatrist [43].

Combining pharmacotherapy and psychotherapy treatments should be considered for patients with major depressive disorder when practical, feasible, available, and affordable. Both approaches combined show better outcomes than either as monotherapy. When unable to combine therapy because of patient preference or problems with availability or affordability, consider psychotherapy when the presentation is mild-to-moderate, and antidepressants when depression is severe or chronic [44]. Patients with major depressive disorder with psychotic features should receive an antipsychotic and an antidepressant medication or ECT. Lithium can be added in patients unresponsive to antipsychotic/antidepressant therapy [43]. Other specific factors should be considered in treatment planning, including the presence of substance abuse, specific features, and other comorbid disorders. If a patient displays signs of potential suicide, increasing the treatment intensity, including hospitalization if needed, should be considered, and pharmacotherapy and psychotherapy should both be provided [43].

Prior to the prescription of antidepressants, patients should have a full history and physical exam and any relevant medical conditions (e.g., heart failure, renal disease) should be noted. A full medication reconciliation should be conducted, with special attention to potential interactions.

Treatment with antidepressant medications can involve dosage adjustments and/or trials of a different medication at some point to maximize response and minimize side effects [43]. Patient adherence to the medication regimen is essential in achieving the maximum clinical benefit. Providers should closely monitor patients for worsening depressive symptoms and emergent suicidality; appropriate intervention includes

ANTIDEPRESSANT MEDICATIONS[a]				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
MAOIs				
Selegiline (Emsam, Zelapar)	6–12 mg transdermal patch every 24 hours	6 mg transdermal patch every 24 hours	Serious food and drug interactions	Also used in treatment of Parkinson disease
Isocarboxazid (Marplan)	10–40 mg/day	10 mg BID		May take 3 to 6 weeks to see effects. Dose should be reduced once maximum clinical effect is seen. If no response obtained within 6 weeks, additional titration is unlikely to be beneficial.
Phenelzine (Nardil)	15–30 mg every 8 hours	15 mg every 8 hours		—
Tranylcypromine (Parnate)	10–60 mg BID	10–30 mg BID		—
Moclobemide	300–600 mg/day	300 mg/day in 2 divided doses		—
Tricyclic Antidepressants				
Amitriptyline	50–300 mg/day	25–50 mg/day as a single dose at bedtime or in divided doses	Xerostomia, sedation	Follow levels and EKG/QTc
Clomipramine (Anafranil)	12.5–250 mg at night	12.5–50 mg at night		Approved for OCD, off-label for MDD
Doxepin (Silenor)	25–300 mg at night or in divided doses	25–50 mg at night		Usually reserved for treatment-resistant MDD
Imipramine	25–300 mg at night or in divided doses	25–50 mg at night or in divided doses		—
Trimipramine	25–300 mg at night or in divided doses	25–50 mg at night or in divided doses		—
Amoxapine	25–600 mg total (may be BID dosing)	25–50 mg at bedtime or BID		The maximum dose in outpatients is 400 mg/day; in hospitalized patients, it is 600 mg/day.
Desipramine (Norpramin)	25–300 mg daily or in divided doses	25–50 mg/day		—
Nortriptyline (Pamelor)	25–150 mg/day	25 mg at night		—
Protriptyline	10–60 mg daily divided in 3 to 4 doses	10–20 mg daily divided in 3 to 4 doses		—

Table 5 continues on next page.

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ANTIDEPRESSANT MEDICATIONS[a] *(Continued)*				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
SSRIs				
Citalopram (Celexa)	20–40 mg/day	20 mg/day	GI upset	Few drug interactions Lower maximum daily dose (20 mg) recommended for patients at risk for QTc prolongation
Escitalopram (Lexapro)	10–20 mg/day	10 mg/day	GI upset	Also approved for generalized anxiety disorder
Fluoxetine (Prozac)	20–80 mg/day	20 mg/day	GI upset, activation syndrome	Also approved for bulimia, panic disorder, generalized anxiety disorder, OCD, and PMDD
Fluvoxamine, immediate-release	50–300 mg at night	50 mg at night	Nausea	Approved for OCD, off-label for MDD
Fluvoxamine, controlled-release	100–300 mg at night	100 mg at night		
Paroxetine (Brisdelle, Paxil, Pexeva)	20–50 mg/day	20 mg/day	Sedation	Also approved for generalized anxiety disorder, panic disorder, OCD, PTSD, PMDD, social anxiety disorder, and vasomotor symptoms of menopause
Paroxetine, controlled-release (Paxil CR)	25–62.5 mg/day	25 mg/day	Sedation	
Sertraline (Zoloft)	50–200 mg/day	50 mg/day	GI upset	Also approved for OCD, panic disorder, PMDD, PTSD, and social anxiety disorder
SNRIs				
Venlafaxine (Effexor)	37.5–375 mg BID	37.5–75 mg BID	Nausea, hypertension, xerostomia, drowsiness	Use with caution in patients with glaucoma
Venlafaxine, extended-release (Effexor XR)	37.5–225 mg/day	37.5–75 mg/day	Nausea, xerostomia, hypertension	Use with caution in patients with glaucoma Also approved for generalized anxiety disorder, panic disorder, and social anxiety disorder
Levomilnacipran (Fetzima)	20–120 mg/day	20 mg/day	Orthostatic hypotension (dose related), nausea	—
Desvelafaxine (Pristiq)	50–100 mg/day	50 mg/day	Dizziness, insomnia, hyperhidrosis, nausea, xerostomia, anxiety	No evidence that dosing over 50 mg more effective In patients who are sensitive to side effects (particularly anxiety), consider lower starting dose of (25 mg/day)

Table 5 continues on next page.

ANTIDEPRESSANT MEDICATIONS[a] *(Continued)*				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
Duloxetine (Cymbalta, Drizalma Sprinkle)	40–120 mg/day	40–60 mg/day	Activation syndrome, weight loss, GI upset, headache	Also approved for fibromyalgia, generalized anxiety disorder, chronic musculoskeletal pain, and diabetic neuropathic pain Avoid in patients with renal impairment (CrCl <30 mL/min)
Milnacipran (Savella)	25–100 mg BID	25–50 mg BID	Nausea, headache, constipation, insomnia	Approved for fibromyalgia, off-label for MDD
Atypical Antidepressants				
Buproprion (Aplenzin)	75–450 mg/day in divided doses	100 mg BID	Increased seizure threshold, weight loss, GI upset, agitation	Also approved for smoking cessation and seasonal affective disorder No sexual side effects
Buproprion, sustained-release (Wellbutrin SR)	150–200 mg BID	150 mg/day in the morning		
Buproprion, extended-release (Forfivo XL, Wellbutrin XL)	150–450 mg/day in the morning	150–175 mg/day in the morning		
Mirtazapine (Remeron)	15–45 mg at bedtime	15 mg at bedtime	Weight gain, increased appetite, drowsiness	Weight gain may limit satisfaction and compliance
Trazodone	50–600 mg BID	50 mg BID	Drowsiness, dizziness, xerostomia, GI upset	—
Nefazodone	50–600 mg in divided doses	50–100 mg BID	Headache, xerostomia, drowsiness	Should not be initiated in individuals with active liver disease or elevated baseline serum transaminases
Brexanolone (Zulresso)	—	60-hour continuous IV infusion (Total dose: 270 mg/kg)	Drowsiness, sedation, xerostomia, dizziness	Used only for inpatient treatment of postpartum depression Requires REMS
Esketamine (Spravato)	56–84 mg intranasal twice weekly	56–84 mg intranasal twice weekly	Dissociation, anxiety, nausea, dizziness	Reserved for treatment-resistant MDD or MDD with suicidality Requires REMS

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ANTIDEPRESSANT MEDICATIONS[a] *(Continued)*				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
Multimodal Agents				
Vilazodone (Viibryd)	10–40 mg/day	10 mg/day	Headache, GI upset	Alternative agent
Vortioxetine (Trintellix)	5–20 mg/day	5–10 mg/day	Nausea, sexual dysfunction	
[a]All information provided is for reference only. Unless otherwise stated, all agents are approved for the treatment of major depressive disorder, unipolar. BID = twice daily, EKG = electrocardiogram, GI = gastrointestinal, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PMDD = premenopausal dysphoric disorder, PTSD = post-traumatic stress disorder, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.				
Source: [17; 19]				*Table 5*

stopping or modifying the drug therapy or hospital admission [44]. Providers should instruct patients and caregiver(s) to be alert for emerging agitation/irritability, suicidality, and worsening depression, and to report this immediately to a healthcare provider [44].

The treatment efficacy of antidepressants in major depressive disorder is broadly similar. Other factors to help guide medication selection include previous patient or family member response to antidepressants (if any); impact on psychiatric or medical comorbidities; clinician familiarity; patient preference; safety in overdose; availability and cost; and drug-drug interactions [44]. Most second-generation antidepressant drugs are recommended as first-line treatment due to the quality of published data, side effect tolerability, and safety in overdose relative to TCAs and MAOIs [43; 44; 45].

The three most distressing side effects for patients treated with antidepressants are sleep disturbance, sexual dysfunction, and weight gain [46]. Choice of medication should be guided by knowledge of comparative side effects and patient priorities; some patients will be more concerned about sexual side effects, while for others, nausea, sleep disturbances, or weight gain may be more distressing [47]. In addition, available evidence regarding the optimal pharmacotherapeutic selection for the treatment of dimensions of depression and DSM-5 specifiers should be considered.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

What are advantages of using SSRIs in the treatment of depression?

SSRIs are thought to act by inhibiting serotonin transporters (SERT) that reuptake serotonin (5-HT) into the presynaptic cell, increasing 5-HT in the synaptic cleft. SSRIs have advantages of low overdose lethality and better tolerability than first-generation antidepressants, which can improve adherence. SSRIs are particularly effective in patients with obsessive-compulsive symptoms, but may initially worsen anxiety or panic symptoms [35; 43; 44]. This class includes the agents fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), and vortioxetine (Brintellix). Escitalopram may have fewer drug-drug interactions than other SSRIs, and fluoxetine may be a better choice in patients with poorer adherence due to its long half-life [35; 43; 44].

Common Side Effects

The most common side effects with SSRIs are gastrointestinal (nausea, vomiting, and diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, and sleep disturbances), sexual, headache, fatigue, and weight gain [35; 43; 44]. Many of these side effects dissipate over time. Sertraline is particularly associated with diarrhea, and paroxetine with weight gain [35; 43].

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs act by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and therefore an increase in neurotransmission [35; 43; 44]. Most SNRIs, including venlafaxine (Effexor), desvenlafaxine (Pristiq), levomilnacipran (Fetzima), and duloxetine (Cymbalta), are several-fold more selective for serotonin than norepinephrine.

Safety, tolerability, and side effect profiles of SNRIs resemble SSRIs, with the exception that the SNRIs have been associated (rarely) with sustained elevated blood pressure. SNRIs can be used as first-line agents, particularly in patients with significant fatigue or comorbid chronic pain, and have an important role as second-line agents in patients who have not responded to SSRIs [35; 43; 44].

Venlafaxine is especially beneficial in treating anxiety and panic attacks in patients with depression, and acts like an SSRI at lower doses (75 mg/day) but more like an SNRI at doses ≥150 mg/day [35; 43; 44].

Common Side Effects

SNRIs are associated with greater likelihood of increased pulse rate, dilated pupils, dry mouth, excessive sweating, and constipation [44]. Venlafaxine has a greater incidence of nausea and vomiting than SSRIs and may be associated with an increased risk for cardiovascular events [35; 43].

TRICYCLIC ANTIDEPRESSANTS

TCAs are predominantly serotonin and/or norepinephrine reuptake inhibitors that act by blocking the serotonin transporter and the norepinephrine transporter, respectively, which results in an elevation of the extracellular concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. TCAs also have varying but typically high affinity for the H1 and H2 histamine receptors and muscarinic acetylcholine receptors. As a result, they also act as potent antihistamines and anticholinergics. These properties are generally undesirable in antidepressants, however, and likely contribute to their large side effect profiles [48].

TCAs are classified by the nature of the final amine group on the side chain, with the tertiary amines amitriptyline (Elavil), clomipramine (Anafranil), doxepin (Sinequan), trimipramine (Surmontil), imipramine (Tofranil), and lofepramine (Lomont); the secondary amines nortriptyline (Pamelor), desipramine (Norpramin), and protriptyline (Vivactil); and the tetracyclic antidepressants amoxapine (Asendin) and maprotiline (Ludiomil).

TCAs are comparable in efficacy to SSRIs/SNRIs, but their side effect profile makes them seldom used as first-line therapy [35; 43; 44]. TCAs may initially worsen anxiety or panic symptoms. Due to side effect potential of cardiac arrhythmia, TCAs should be used very cautiously, if at all, in patients with heart problems. Secondary amine TCAs cause less orthostatic hypotension and sedation than tertiary amines, which should be avoided in elderly patients due to the risk for orthostatic hypotension, sedation, cognitive problems, and cardiac effects. The secondary amine nortriptyline is especially effective for elderly patients with moderate-to-severe depression. Clomipramine is particularly effective in patients with obsessive-compulsive symptoms [35; 43; 44].

Common Side Effects

Anticholinergic and antihistamine activity accounts for many side effects, including dry mouth, blurred vision, reduced gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature [35; 43; 44]. Other side effects may include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypersensitivity, changes in appetite and weight, sweating, sexual dysfunction, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and arrhythmia. Tolerance to side effects often occurs if treatment is continued. Side effects may also be less troublesome if treatment is initiated with low doses and gradually increased [48; 49].

MONOAMINE OXIDASE INHIBITORS

MAOIs inhibit monoamine oxidase (MAO), an enzyme that degrades and inactivates 5-HT, norepinephrine, and dopamine. This increases monoamine levels and activity. Earlier MAOIs were irreversible MAO inhibitors, deactivating the enzyme until slowly replenished over a two-week period [50; 51]. MAOIs includes phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan), linezolid (Zyvox, Zyvoxam, Zyvoxid), moclobemide (Aurorix, Manerix), pirlindole (Pirazidol) (approved for use in parts of Europe), and selegiline (Deprenyl, Eldepryl, Emsam).

Most MAOIs appear broadly effective in a range of depressive and anxiety disorders, and may be more effective than other antidepressant classes in major depressive disorder with pronounced anxiety or panic symptoms [35; 43; 44]. Major depressive disorder with atypical features may preferentially respond to MAOIs over other antidepressant classes. Although effective, MAOIs are rarely the first- or second-line treatment choice due to serious side effect potential from medication interactions and dietary restriction. The selegiline transdermal patch (Emsam) used at the lowest strength (6 mg delivered over 24 hours) may lack the dietary restrictions required of oral MAOIs [52].

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Common Side Effects

With oral ingestion, MAOIs inhibit the catabolism of dietary amines. When foods containing tyramine are consumed, the individual may suffer from hypertensive crisis [50]. If foods containing tryptophan are consumed, hyperserotonemia may result. The amount required to cause a reaction varies greatly from individual to individual and depends on the degree of inhibition, which in turn depends on dosage and selectivity.

MAOIs should not be combined with psychotropic drugs or with any other psychoactive substance except under expert care. This includes a wide range of prescribed, over-the-counter, and illicit drugs and nutritional supplements, such as St. John's wort. Common side effects include orthostatic hypotension, weight gain, sexual dysfunction, sedation, headache, and insomnia [50].

ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are diverse in monoamine activity and do not fit the profile of other classes. They include bupropion (Wellbutrin), nefazodone (Serzone), mirtazapine (Remeron), and trazodone (Desyrel). Nefazodone and trazodone block postsynaptic serotonin type-2 receptors and inhibit presynaptic serotonin reuptake. Bupropion inhibits activity of norepinephrine and dopamine transporters, and the active metabolite hydroxybupropion contributes to the drug's effects. Mirtazapine is a potent antagonist at 5-HT2, 5-HT3, alpha2, and H1 histamine receptors. As a group, these agents show low toxicity in overdose and may have an advantage over the SSRIs by causing less sexual dysfunction and gastrointestinal distress [35; 43; 44].

Each agent has apparent benefits and drawbacks, with some better suited for specific patient populations. Bupropion is associated with a risk of seizure at higher doses, especially in patients with a history of seizure or eating disorders, and should be used cautiously in anxious patients [35; 43; 44]. It may be more effective for atypical major depressive disorder than other antidepressants.

Mirtazapine can be very sedating and promotes appetite and weight increase, which in some patients may be desirable. It has a faster onset of action than fluoxetine, paroxetine, or sertraline, and may be superior to SSRIs in depression associated with severe insomnia and anxiety. Trazodone is also very sedating and is usually used as a sleep aid rather than as an antidepressant [35; 43; 44].

Common Side Effects

The side effects of atypical antidepressants vary considerably. With bupropion, the most common side effects are agitation, jitteriness, mild cognitive dysfunction, insomnia, gastrointestinal upset, and possible increased risk for seizures [35]. Patients taking mirtazapine may experience dry mouth, sedation, weight gain, and increased serum cholesterol [43].

Sedation is the most common side effect associated with trazodone, followed by cardiovascular side effects (such as orthostasis) and sexual side effects [43]. Finally, nefazodone is associated with sedation, dry mouth, nausea, constipation, orthostasis, visual alterations, and possible increased risk of hepatotoxicity have led to nefazodone being seldom prescribed [35].

MULTIMODAL ANTIDEPRESSANTS

Vilazodone and vortioxetine are multimodal antidepressants that combine SSRI properties with other pharmacologic actions affecting monoamine and non-monoaminergic targets. Evidence does not suggest greater efficacy than SSRI/SNRIs, but these agents may improve tolerability or efficacy on specific clinical domains [53].

Vilazodone, approved in 2011, primarily acts as a SERT inhibitor and 5-HT1A receptor partial agonist, and modestly inhibits dopamine and norepinephrine transporters. This antidepressant may be most helpful in patients lacking response to initial SSRIs. Vilazodone must be taken with food, which increases its absorption and bioavailability by 72% [54; 55].

Vortioxetine, approved in 2013, acts through various serotonin receptors as an antagonist (5-HT3/7/1D), partial agonist (5-HT1B), or agonist (5-HT1A), and inhibits SERT. It also activates the glutamate system in the frontal cortex. Vortioxetine displays a specific clinical efficacy in the treatment of cognitive deficits associated with major depressive disorder. The most common side effects are nausea, vomiting, and constipation [53].

CLASS-WIDE ADVERSE EFFECTS

Sexual Dysfunction

All commercially available antidepressants are associated with sexual side effects. SSRI/SNRIs show the highest rates of sexual dysfunction, including impaired sexual motivation, desire, arousal, and orgasm affecting men and women. Prescribers greatly underestimate the prevalence and patient burden of sexual side effects from antidepressants and other medications [56]. Among antidepressants, prevalence rates of sexual side effects are highest with venlafaxine and SSRIs; moderate with TCAs and MAOIs; low with bupropion, trazodone, nefazodone, mirtazapine, agomelatine, and vilazodone; and lowest with the reversible MAOI moclobemide [57; 58]. Compared to spontaneous patient reporting, systematic inquiry increases the rate of identifying sexual side effects by ≥60% [58].

Management of sexual side effects in men includes the use of phosphodiesterase-5 inhibitors such as sildenafil, vardenafil, tadalafil, and avanafil as first-line treatment or switching to bupropion [59]. In women, sexual side effect management considers symptoms, age, and potential hormonal contribution when peri- or post-menopausal.

Increased Suicidality

Several papers documenting an increased risk of suicidal thoughts and behavior with antidepressants, primarily SSRIs, have been published over the past decade. A review of the literature found that antidepressant use, including SSRIs, carried a small short-term risk of inducing suicidal thoughts and suicide attempts in persons younger than 25 years of age, with persons 30 to 40 years of age having a lower risk than those younger than 25 years. This risk should be balanced against the well-known beneficial effects of antidepressants that include reduced suicidal ideation and behavior, particularly in the long term. Clinical decision making should weigh the benefits and potential risks and strive to keep the potential risks of antidepressant treatment to a minimum [60; 61].

Discontinuation Symptoms

Antidepressant discontinuation (more appropriately termed withdrawal) symptoms are described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly, and may occur with any antidepressant [62; 63; 64; 65]. SSRI withdrawal symptoms are far more frequent with paroxetine. Common symptoms include dizziness, nausea, headache, confusion, low energy, weakness, sleep disturbance, flu-like symptoms, restlessness, agitation, anxiety, panic, anger, and irritability. Less common and more severe symptoms include electric-shock sensations, vertigo, paresthesia, intensified suicidal ideation, aggression, derealization, depersonalization, and visual/auditory hallucinations. Gradual tapering is a reasonable strategy but does not prevent the onset of SSRI withdrawal [66]. SSRI withdrawal syndrome is least likely with fluoxetine and vortioxetine [62].

Symptoms usually begin within five days of treatment cessation or occasionally during taper or after missed doses [67; 68]. Symptoms may be severe enough to interfere with daily functioning, and although a four-week taper is usually suggested, some patients may require longer periods, particularly with paroxetine and venlafaxine [69]. Treatment is pragmatic. If symptoms are mild, reassure the patient that this is a common occurrence and that the symptoms will pass in a few days. If symptoms are severe, reintroduce the original antidepressant or a replacement from the same class with a longer half-life, and taper gradually while monitoring for symptoms. Patients should be emphatically informed that the possible or actual emergence of discontinuation symptoms is not a manifestation of addiction to the antidepressant [70]. SSRI withdrawal can also be approached by switching to a course of fluoxetine, such as 10 mg for several weeks, which is slowly tapered and discontinued [43].

PEDIATRIC CONSIDERATIONS

Among the antidepressants, only fluoxetine is approved for use in treating major depressive disorder in pediatric patients. In addition, fluoxetine, sertraline, fluvoxamine, and clomipramine are approved for obsessive-compulsive disorder (OCD) in pediatric patients. Other than these indications, all other use of antidepressants in children is off-label [71]. However, these off-label uses are relatively common, particularly among adolescents and pediatric patients with more severe disease.

Beginning in 2003, data have suggested an increase in attempted and completed suicides in children treated with antidepressants [72]. There is also compelling research indicating that the decrease in prescribing of antidepressant medications to adolescents in the period after 2003, both in the United States and the Netherlands, led to an increase in suicide rate [72]. In the Netherlands, the rate increased by 49% between 2003 and 2005, during which time there was a significant decrease in pediatric SSRI prescriptions.

Data for pediatric efficacy (defined as improvements in depressive symptoms) are strongest for fluoxetine, which is approved for children older than 8 years of age [72]. The best results are achieved with a combination of pharmacotherapy and cognitive-behavioral therapy. Due to the risks and complexities involved in the treatment of children with depression, it is recommended that a multidisciplinary team approach be utilized in the treatment of these patients.

Pediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose [71].

TREATMENT-RESISTANT DEPRESSION

What are contributors to treatment-resistant depression?

Standard antidepressants fail to produce adequate response in 30% to 50% and remission in up to 70% of patients with major depressive disorder [73; 74; 75]. Partial response, instead of full remission, leaves patients with impairing residual symptoms and high risk of relapse. Each relapse increases symptom severity, decreases treatment response, and heightens risk of treatment-resistant depression [76].

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Treatment-resistant depression is a problem increasingly encountered by primary care and mental health providers. Contributors to treatment-resistant depression include illness severity, medical and psychiatric comorbidity, and the limitations of FDA-approved drug options. The definition of treatment resistance lacks consensus, but the most common definition is inadequate response to two or more antidepressants. This does not consider adjunctive strategies or distinguish patients with partial versus non-response [62; 77].

The American Psychiatric Association recommends optimizing the medication dose as a reasonable first step for patients treated with an antidepressant who have not responded fully to treatment if the side effect burden is tolerable and the upper limit of a medication dose has not been reached.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed July 7, 2020.)

Strength of Recommendation: II (Recommended with moderate clinical confidence)

In addition to augmentation strategies, a diverse and growing range of interventions are available as options for treatment-resistant depression [78; 79; 80]. Most engage novel therapeutic targets.

Neurostimulation Therapies

The limitations of standard antidepressants, frequent treatment resistance, and the paradigm shift in psychiatry away from specific neurotransmitter focus and toward an integrative neural network perspective has prompted the development of novel depression treatment approaches, such as neurostimulation therapy. Repetitive transcranial magnetic stimulation (rTMS) is a nonpharmacologic approach to the treatment of depression approved in 2008, and multiple randomized controlled studies have shown its use to be safe and effective [81]. Patient selection for rTMS is complex and should be done in conjunction with the specialist administering the therapy as well as the patient. Most clinicians refer patients after they have failed to improve on at least one antidepressant.

Electroconvulsive Therapy

The use of ECT in the treatment of treatment-resistant depression is long and varied. While there was historical misuse and abuse of this modality, particularly in the unethical care of patients in institutions, it has a proven record of efficacy for patients with severe or refractory depression.

ECT is effective as acute treatment, but multiple treatments are required and many who respond experience symptoms again within six months [82]. ECT generates electrical stimuli for seizure induction through electrodes applied to the scalp, with the patient under general anesthesia and pre-medicated with a muscle relaxant. Clinical outcomes are highly influenced by electrode placements, electrical intensity, and pulse width [83].

As first-line treatment, ECT is used for severe melancholic, catatonic, psychotic, or refractory depression and for patients who refuse to eat or drink, have very high suicide risk or severe distress, pregnant women with severe depression, or who have a previous positive ECT response [47; 82; 84].

Full ECT response requires at least four to six sessions delivered two to three times per week. Twice weekly ECT requires longer treatment duration, but more than three treatments per week is not recommended due to the greater cognitive side effect risk [83].

Headaches (45%), muscle soreness (20%), and nausea (1% to 25%) during ECT are transient and treated symptomatically; 7% of patients with major depression switch into a manic or mixed state [83]. Most distressing to some patients is loss of autobiographic memory recall, infrequently reported to persist beyond six months [84]. ECT lacks absolute contraindication, but increased safety risk is associated with space-occupying cerebral lesion, increased intracranial pressure, recent cerebral hemorrhage, or aneurysm [83; 85].

Pharmacotherapy

Ketamine is an *N*-methyl-D-aspartate receptor (NMDA-R) antagonist that was approved for use as an anesthetic in 1970. Demonstration that a single IV dose in patients with treatment-resistant depression reliably produced rapid, robust antidepressant effects for one week was a breakthrough discovery for research and a turning point for patients for whom all other treatment approaches had failed [86]. The short-term efficacy of ketamine treatment of refractory major depressive disorder and bipolar depression is now established; more than one dozen placebo-controlled trials have shown that patients with refractory unipolar or bipolar depression have significantly greater response, remission, and depressive symptom reduction to single-dose IV ketamine than placebo from 40 minutes through days 10 to 12 post-treatment [87; 88]. The approach has become standardized, using a sub-anesthetic dose: 0.5 mg/kg IV over a 40-minute infusion. In a 2015 analysis, ketamine was designated as one of two psychiatric treatments that had the highest potential impact on patient outcomes. This designation was based on the serious unmet need for fast-acting, well-tolerated antidepressants with efficacy in refractory major depression and bipolar depression [40].

In 2019, a ketamine derivative—esketamine—was approved by the FDA as an adjunctive agent for treatment-resistant depression. In 2020, the additional indication for short-term treatment of suicidal thoughts was added. This agent is administered by nasal spray and must be given under the direct supervision of a healthcare provider. Patients should be monitored for adverse effects for at least two hours following administration [19; 89]. Due to an increased potential for abuse and misuse, it has an associated REMS program.

CASE STUDY

Patient B, 46 years of age, presents with a history of mild-to-moderate depression for the past six months. He has been undergoing cognitive-behavioral therapy, and while he has made some gains, he continues to experience depressive symptoms, as documented by a mood map and reports from his therapist. In addition, he is overweight and complains of insomnia.

The nurse does a complete psychiatric history and orders baseline laboratory studies and EKG. The patient reports no history of suicidal ideation and has never been hospitalized. He states that he is functioning well in his job but has been unable to maintain a steady relationship, despite a desire to have a long-term partner.

Patient B's main complaints are depressed mood and insomnia. He does not endorse anxiety or panic attacks and denies any drug or tobacco use. The patient is relatively healthy, has received regular medical care, and does not take any other medications. He has no history of seizure disorder. After a long discussion with the patient, the nurse decides to start a trial of sertraline 50 mg/day and trazodone 25 mg at night.

Patient B returns in two weeks and reports that his sleep has improved and the medications are well tolerated. He agrees to return in four more weeks to determine if the medications are helping his mood, which currently has not improved. During that period, he will continue working with his therapist weekly. The nurse and therapist are in good communication, with an understanding that any changes in symptoms or tolerability should be shared immediately.

After four weeks, Patient B comes back to the office. His mood is still described as depressed by both him and his therapist, so the sertraline dosage is increased to 100 mg/day, with a plan for the patient to return in one month.

When Patient B returns in four weeks, he reports that he is feeling better and has been going out and socializing. However, he is experiencing sexual side effects (erectile dysfunction). Several options are discussed, including transitioning from sertraline to a trial of bupropion or adding a trial of sildenafil. The patient decides that he would like to switch to bupropion, because he does not like the idea of having to take another medication.

After decreasing the dose of sertraline to 50 mg for two weeks, the patient is stable and plans are made to discontinue the sertraline and start bupropion (Wellbutrin XR) 150 mg every morning. When Patient B presents in two weeks, he is happy with the new medication, reporting full resolution of the sexual side effects, but reports some residual depressed mood. The dose of bupropion is increased to 300 mg every morning.

In another four weeks, Patient B's depression is in remission and his sleep quality is significantly improved. The medications remain well-tolerated. The patient also notes that he has lost about 5 pounds, which he attributes to decreased appetite. The patient continues to work with his therapist and agrees to return monthly for at least the next three months for continued monitoring.

MOOD STABILIZERS AND BIPOLAR DISORDER

What is the typical starting dose for lithium in the treatment of bipolar disorder?

Perhaps no diagnosis in psychiatry has undergone such a rapid change in diagnostic standards and pharmacologic management as bipolar disorder in the last 30 years. Intravenous chlorpromazine was first noticed to decrease mania in surgical patients with bipolar disorder. Shortly thereafter, chlorpromazine and other antipsychotics became mainstays in the treatment of primary psychotic disorders. At the same time, the treatment of bipolar disorder was revolutionized by the discovery of lithium.

Lithium is perhaps the oldest drug still in clinical use. While its utilization was formally standardized in 1954, its use in psychiatry dates to the mid-19th century [6]. One of the earliest recorded medical uses of lithium, for the treatment of gout, was in 1847 in London. Lithium continued to be prescribed for the treatment of gout and renal calculi into the 1930s. Psychiatric interest in lithium can be traced to the late 1800s. William Hammond is believed to be the first physician to prescribe lithium for mania (in 1871) [6]. As noted, the United States was the 50th country to approve lithium for clinical use in 1970 [6]. Lithium was originally studied in the prevention of depression and continues to be used off-label as an antidepressant [6; 90].

Today, management of bipolar disorder may consist of lithium, anticonvulsants, and/or antipsychotic medications (***Table 6***). Antianxiety medications may be prescribed short term to improve sleep and manage agitation/anxiety. Lithium is one of the few drugs used in the treatment of bipolar disorder with proven efficacy in the prevention of suicide [79].

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MEDICATIONS USED IN THE TREATMENT OF BIPOLAR DISORDER				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
Lithium (Lithobid)	600–1,800 mg/day in divided doses	300 mg BID	Xerostomia, tremor, thyroid-stimulating hormone elevation, leukocytosis, nausea	Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels. Monitoring should be available before initiating therapy.
Anticonvulsants				
Valproic acid (Divalproex)	250–1,500 mg BID based on levels	250–500 mg PO BID	Weight gain, hair loss, GI upset	Drug levels, complete blood count, and hepatic function should be followed.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol)	100–800 mg BID	100–200 mg BID	Weight gain	Hepatic function, drug level, and CBC should be followed.
Lamotrigine (Lamictal, Subvenite)	Titrate to maximum 200 mg/day	25 mg/day	Nausea, tremor, rash, Stevens Johnson syndrome	—
Atypical Antipsychotics				
Aripiprazole (Abilify)	2.5–30 mg/day	2.5–5 mg/day	Weight gain (least likely in this class), extrapyramidal symptoms, constipation, sedation	Available in long-acting IM formulation
Asenapine (Saphris, Secuado)	2.5–10 mg BID	2.5–5 mg PO BID	Weight gain, extrapyramidal symptoms, constipation, sedation	—
Cariprazine (Vraylar)	1.5–6 mg/day	1.5 mg/day	Weight gain, extrapyramidal symptoms, constipation, sedation	—
Lurasidone (Latuda)	40–160 mg/day	40 mg/day	Weight gain, extrapyramidal symptoms, constipation, sedation	—
Olanzapine (Zyprexa)	2.5–30 mg either BID or at night	2.5 mg/day	Weight gain (very likely), extrapyramidal symptoms, constipation, sedation	—
Olanzapine/fluoxetine (Symbyax)	Up to 18 mg/day olanzapine and 75 mg/day fluoxetine	6 mg/day olanzapine and 25 mg/day fluoxetine	Weight gain, extrapyramidal symptoms, constipation, sedation	Usually given at night
Quetiapine (Seroquel)	50–800 mg/day	50–100 mg daily or BID	Weight gain, extrapyramidal symptoms, constipation, sedation	Available in extended-release formulation
Risperidone (Perseris, Risperdal)	0.5–6 mg/day (may be given BID)	0.5–1 mg daily or BID	Weight gain, extrapyramidal symptoms, constipation, sedation, increased prolactin, male gynecomastia	Available in long-acting IM formulation
Ziprasidone (Geodon)	40–80 mg BID	40 mg BID	Weight gain, extrapyramidal symptoms, constipation, sedation, increased prolactin	Taken with food to improve absorption
BID = twice per day, CBC = complete blood count, GI = gastrointestinal, IM = intramuscular, PO = oral.				
Source: [19; 80]				*Table 6*

EVIDENCE-BASED PRACTICE RECOMMENDATION

When using any psychotropic medication for bipolar disorder, the National Collaborating Centre for Mental Health recommends that clinicians ensure that the person is given information that is suitable for their developmental level about the purpose and likely side effects of treatment including any monitoring that is required, and give them an opportunity to ask questions. The choice of medication is made in collaboration with the person with bipolar disorder, taking into account the carer's views if the person agrees. The overall medication regimen is regularly reviewed so that medications that are not needed after the acute episode are stopped.

(https://www.nice.org.uk/guidance/cg185. Last accessed September 28, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

CASE STUDY

Patient C, 23 years of age, presents with a history of increasing mood instability, with periods of depression lasting three to four months followed by periods of increasing disorganization, lack of need for sleep, and risky behaviors (e.g., gambling, shoplifting). After her third shoplifting arrest, Patient C agreed to a plea deal that requires her to seek and comply with psychiatric care.

The clinician conducts a full psychiatric history that is significant for school and employment problems. She attempted outpatient treatment at 16 and 21 years of age, both of which were ended by the patient due to her dislike for medications and their side effects and a perceived "loss of energy" when treatment was initiated with olanzapine during a manic episode at 19 years of age.

The workup reveals a healthy woman, normal laboratory studies, normal EKG, and no medical problems. She is gravida 0 para 0 and has a progestin intrauterine device for birth control. She describes her current mood as depressed, rated 3 on a Likert scale. She describes hypersomnia, sleeping about 10 hours per day. She is currently unemployed and living with her parents. She denies any psychotic symptoms and has never attempted suicide. The patient feels her parents are supportive but firm in stating that she must engage in treatment to continue living with them. She is a nonsmoker and has no known drug use, other than occasional cannabis (less than once per week), which she does not view as problematic. She has genetic loading, with an uncle and a sister who have been diagnosed with bipolar disorder.

Patient C is currently not seeing a therapist or receiving psychotherapy. In discussing goals of care, her main goal is compliance with her probation stipulations. She also indicates that she would like to be employed and to eventually move out of her parents' house. Weight gain is identified as an intolerable side effect of pharmacotherapy; the patient states she would like to lose weight. After much discussion, Patient C agrees to see a social worker for cognitive support and to assist with employment goals.

Given the patient's goals and concerns, antipsychotics are determined to be undesirable. The clinician and patient discuss the risks and benefits of valproic acid and lithium. Patient C states that her uncle did well on lithium and that she would like to try it. In preparation for lithium prescription, the patient's thyroid hormone and calcium levels are reviewed along with kidney function; all are normal. Patient C expresses a strong desire to take pills only once per day and does not think she can remember to take a morning dose. The clinician reviews literature, which indicates that once daily dosing of lithium results in similar efficacy, with lower total doses, decreased renal toxicity, and decreased urinary frequency [91]. The patient is started on controlled-release lithium 450 mg taken at night. Eventually, she is titrated to 900 mg daily, with an average serum lithium level of 0.7 mEq/L.

As part of the patient education process, the clinician emphasizes the need for reliable birth control, as lithium crosses the placenta and is associated with serious fetal malformations following exposure in the first trimester [92]. This conversation is documented fully, including a recommendation that the patient use dual birth control (e.g., add condoms). The need to use a different medication during any planned pregnancy is reviewed.

After 12 months of therapy, Patient C has not experienced any episodes of mania. However, she describes her mood as depressed and complains of amotivation, sadness, hypersomnia, and a 10-pound weight gain. Her lithium level is stable and within the therapeutic range, and the clinician is concerned that raising the lithium dose could increase the risk of toxicity.

To address these issues, bupropion (Wellbutrin XL) 150 mg/day is added to the patient's regimen. Augmentation with low-dose bupropion appears to have the lowest risk of inducing mania among available antidepressants [93]. In six weeks, Patient C reports a gradual improvement in mood, a slight weight loss (2 to 3 pounds), and no signs or symptoms of mania. She continues to meet with her social worker and has attained employment as a front desk clerk at a hotel. She is pursuing her goal of living independently and has had no further contact with law enforcement.

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ANTIANXIETY MEDICATIONS

Anxiety disorders are characterized by states of chronic, excessive dread or fear of everyday situations. The fear and avoidance can be life-impairing and disabling. Anxiety disorders result from the interaction of biopsychosocial factors, whereby genetic vulnerability interacts with situations, stress, or trauma to produce clinically significant syndromes. Under the umbrella of anxiety disorders are specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, and separation anxiety disorder.

Each year in the United States, anxiety disorders impact approximately 42 million adults, or 19% of the population [94; 95]. The pattern of sex distribution is consistent among anxiety disorders, and the overall female-to-male ratio is approximately 2:1 across all age ranges [96]. Guidelines for the treatment of anxiety disorders typically support combined psychotherapy (e.g., mindfulness, exposure therapy, cognitive therapy) and pharmacotherapy [97].

The first report of antidepressant use in anxiety treatment was published in 1962. In this account, patients with agoraphobia who were given the TCA imipramine showed reductions in panic attacks and improved exposure to feared situations [98]. The benzodiazepine chlordiazepoxide (Librium) was introduced to the U.S. market in 1960. This was followed by diazepam (Valium) in 1963, which became the most prescribed drug in the United States from 1969 to 1982; in 1978, more than 2.3 billion diazepam doses were sold in the United States [99]. Panic disorder was first formalized as a psychiatric disorder in the 1980 DSM-III, and alprazolam (Xanax) became the first the FDA-approved drug for panic disorder treatment in 1981, remaining the most-prescribed benzodiazepine to date [100].

In the past two decades, antidepressant drugs have displaced benzodiazepines as the most widely prescribed and recommended anxiety disorder pharmacotherapy (***Table 7***). Antidepressants are generally recommended as first-line therapy for panic disorder because, unlike benzodiazepines, antidepressants treat comorbid depression and lack abuse risk and potential side effects of excessive sedation, cognitive impairment, and ataxia. All major antidepressant classes are comparably effective, but SSRIs and, increasingly, SNRIs are recommended over TCAs and MAOIs due to better safety and tolerability [101].

ANTIDEPRESSANTS

Although all major antidepressant classes are comparably effective against anxiety disorders, which class is recommended due to better safety and tolerability?

SSRIs are considered first-line therapy for generalized anxiety disorder and panic disorder [101; 103]. TCAs have comparable efficacy to SSRIs in panic disorder and generalized anxiety disorder [104; 105]. TCAs are lethal in overdose and, compared with SSRIs, have a markedly broader, more problematic, and less tolerable side effect profile [101]. Nonetheless, TCAs may work when first-line agents do not [106]. Also, some patients with panic disorder are sensitive to both beneficial and adverse effects of TCAs, so cannot tolerate imipramine doses >10 mg/day but still experience panic blockade [101].

MAOIs are effective for panic disorder and SAD and are thought by some to be superior options for severe, treatment-resistant anxiety disorders. As noted, MAOIs have a substantial side effect profile and impose the greatest safety burden of all antidepressants. Therefore, they are usually reserved as the last treatment option after other drug therapies have failed to achieve remission [107]. Clinicians do not routinely prescribe MAOIs for anxiety disorders, although they are probably not considered often enough in treatment-resistant patients [106].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Mental Health asserts that all patients prescribed antidepressants for the management of anxiety should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug.

(https://www.nice.org.uk/guidance/cg113. Last accessed September 28, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

BENZODIAZEPINES

Since their introduction in the early 1960s, benzodiazepines have been the most prescribed drugs for anxiety over the majority of the past half-century. Although SSRI/SNRI agents have replaced benzodiazepines as the top-prescribed anxiolytics, benzodiazepine prescribing remains common. In 2016, alprazolam and lorazepam were among the top 25 most frequently prescribed psychotropic medications in the United States; alprazolam ranked second, and lorazepam ranked ninth [108; 109].

MEDICATIONS USED IN THE TREATMENT OF ANXIETY DISORDERS				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Indication(s)**
Antidepressants				
Escitalopram (Lexapro)	10–20 mg/day	10 mg/day	Few	GAD
Fluoxetine (Prozac)	10–80 mg/day	10–20 mg/day	Few	OCD, PD
Fluvoxamine	100–300 mg/day	100 mg/day	Few	OCD, SP
Paroxetine (Brisdelle, Paxil, Pexeva)	10–50 mg/day	10–20 mg/day	Few	GAD, OCD, PD, SP
Sertraline (Zoloft)	25–200 mg/day	25–50 mg/day	Few	OCD, PD, SP
Duloxetine (Cymbalta, Drizalma Sprinkle)	30–120 mg/day	30–60 mg/day	Hypertension, headache	GAD
Venlafaxine (Effexor)	37.5–225 mg/day	37.5–75 mg/day	Hypertension, headache	GAD, PD, SP
Clomiparmine (Anafranil)	25–250 mg/day	25 mg/day	QTc prolongation	OCD, PD
Doxepin (Silenor)	25–300 mg/day	25–50 mg/day	QTc prolongation	NSA
Imipramine	50–200 mg/day	50–100 mg	QTc prolongation	PD
Phenelzine (Nardil)	45–90 mg/day	45 mg/day	Drug- and food-drug interactions	PD
Benzodiazepines				
Alprazolam (Xanax)	0.25–4 mg 2 to 3 times per day	0.25–1 mg/day	Dependence, rebound anxiety, increased dementia risk, increased risk of opioid overdose with concomitant use	NSA, PD
Chlordiazepoxide (Librium)	5–25 mg 3 to 4 times per day	5–10 mg/day		NSA
Clonazepam (Klonopin)	0.25–2 mg 2 times per day	0.25–1 mg/day		PD
Diazepam (Diastat, Valium, Valtoco)	2.5–10 mg 2 to 4 times per day	2.5–5 mg/day		NSA
Lorazepam (Ativan)	0.5–2 mg given 2 to 3 times per day	0.5–1 mg/day		NSA
Miscellaneous Agents				
Hydroxizine (Vistaril)	25.5 mg 2 to 4 times per day	25–50 mg/day	Xerostomia, drowsiness	NSA
Buspirone	10–20 mg 2 to 3 times per day	10 mg/day	Dizziness, headache	GAD

GAD = generalized anxiety disorder, NSA = nonspecific anxiety, OCD = obsessive-compulsive disorder, PD = panic disorder, SP = specific phobia.

Source: [19; 102] *Table 7*

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Pharmacology and Short-Term Effects

Numerous benzodiazepines are available and have similar pharmacodynamic properties and clinical actions; they mainly differ in pharmacokinetic properties (absorption, distribution, metabolism, elimination). Benzodiazepines bind to a specific receptor site in the gamma-aminobutyric acid (GABA) receptor complex. GABA is the primary inhibitory neurotransmitter in the CNS, and benzodiazepines cause non-selective GABA-A inhibitory effects throughout the brain that include drowsiness, cognitive impairment, dampening of fear and anxiety, memory impairment, anticonvulsant actions, and impairment of balance, motor control, muscle tone, and coordination. Adverse reactions to alprazolam also include amnesia, aggression, mood changes, and hostility. The newer Z drugs (e.g., zolpidem, zopiclone) have similar actions to benzodiazepines but are marketed for insomnia due to their pharmacokinetic profile, with high doses required for anxiolytic effects. There is evidence the Z drugs share similar risks to benzodiazepines [110; 111].

Meta-analyses suggest alprazolam, lorazepam, and diazepam are effective but comparable in generalized anxiety disorder efficacy, while clonazepam shows much greater efficacy in the treatment of panic disorder than alprazolam, lorazepam, and diazepam, which all have modest efficacy [112].

Appropriate Prescribing

Benzodiazepine treatment of anxiety disorders is controversial. While effective in rapid anxiety reduction, the potential drawbacks with long-term use are substantial. These agents are indicated when potent, short-term anxiolytic effects are necessary to permit infrequent exposure to feared stimuli and potentially severe anxiety, such as airplane travel [103; 106; 113]. Clonazepam, lorazepam, and alprazolam are effective for short-term use in panic disorder, generalized anxiety disorder, and SAD, but ineffective for, and potentially worsening, comorbid depression [114]. The rapid anxiolytic effects make benzodiazepines highly appealing to patients with anxiety, but aside from this specific context, benzodiazepine prescribing for as-needed use is discouraged [106; 115; 116]. Benzodiazepines can reinforce pill taking, serve as a safety signal that undermines self-efficacy, and become incorporated into conditioned fear responses; these concerns are heightened with as-needed use. On-demand dosing links pill taking to rapid anxiety reduction, powerfully reinforcing avoidance in anxiety-provoking situations and encouraging longer-term reliance on the drug. This iatrogenic effect also contributes to poor CBT response.

The current recommended prescribing is for time-dependent use, instead of panic response-dependent use, to minimize the risks [103]. This would also seem to maximize risk of withdrawal syndrome from uninterrupted versus intermittent drug exposure.

Benzodiazepines are also useful in the initial weeks of SSRI/SNRI initiation, to rapidly reduce anxiety and possible early anxiogenic medication side effects before the onset of SSRI/SNRI anxiolytic effects [103; 106; 113]. However, patients may discontinue the antidepressant when co-prescribed a rapidly effective benzodiazepine, believing the benzodiazepine's symptom relief makes the SSRI/SNRI unneeded. Supportive therapy with regular visits or phone contacts may also help patients remain adherent until the delayed onset of antidepressant benefits appears or early antidepressant side effects lessen [117].

Another indication for benzodiazepine use is for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress. Perhaps the greatest prescribing challenge with benzodiazepines is preventing short-term use from insidiously developing into long-term use. Patients with the most severe anxiety may obtain the greatest relief and become most hesitant to discontinue use [118]. In many cases, clinicians ignore the recommended two- to four-week prescribing limit, mainly because alternative options with superior anxiolytic effects are not available [119]. Clinicians intending to prescribe alprazolam should carefully consider the likelihood that its use will remain restricted to the very short term—a few days to a couple weeks—to see the patient through a crisis [118].

Benzodiazepines may be prescribed to augment SSRI/SNRI therapy for improved response in select patients with significant residual anxiety or non-response. In one study, patients with SAD and sertraline nonresponse after 10 weeks were given sertraline plus clonazepam (≤3 mg/day), venlafaxine (≤225 mg/day), or sertraline plus placebo for 12 weeks. Those with sertraline augmented by clonazepam showed greatest reduction in SAD symptoms and a better overall response rate than comparator groups, although remission rates did not differ significantly [120]. These agents are third- or fourth-line treatment in patients unresponsive or intolerant to other anxiolytic drugs who remain highly symptomatic [103; 106; 113]. Generally, patients with a history of substance abuse, personality disorder, or chronic pain should not be treated with benzodiazepines because of the high risk for overuse of these medications [113]. While benzodiazepines should usually be reserved for patients lacking response to at least two treatments (i.e., non-response to an SSRI/SNRI and a psychologic treatment), concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing, and impairing anxiety symptoms [121].

It seems the most appropriate guidance for benzodiazepine prescribing involves occasional, context-specific use or cautious use during SSRI/SNRI initiation [121; 122]. Otherwise, benzodiazepines should be reserved for patients lacking response to three or more treatments, such as an SSRI, an SNRI, and a psychologic intervention, who remain highly symptomatic.

Risks/Drawbacks

While alprazolam remains the most-prescribed benzodiazepine for anxiety disorders, evidence suggests that relative to other benzodiazepines, alprazolam is no more effective and may have specific drawbacks [100]. Alprazolam may have greater potential for dependence than other benzodiazepines due to its rapid onset of anxiolysis and short half-life. With the short half-life, persons prescribed fixed-interval alprazolam (e.g., every six to eight hours) can experience morning withdrawal symptoms following the last nighttime dose. This is frequently mistaken as relapse in anxiety for which the drug was originally prescribed, confirming the continuing need for the drug [118]. The alprazolam product monograph states that such emergence of interdose symptoms reflect insufficient plasma levels, best managed by adding the same dose for four times daily administration (but breakthrough anxiety and alprazolam withdrawal are not differentiated). The document also states that alprazolam treatment of panic disorder differs from sub-syndromal anxiety, in that recommended dosing is as close to around-the-clock as possible, or three or four times per day [123].

Long-term benzodiazepine use can result in added symptoms during stable-dose maintenance, including increasing anxiety and withdrawal-associated symptoms such as perceptual disturbances and paresthesia. This emerging withdrawal syndrome despite ongoing benzodiazepine use is much more likely with highly potent and rapidly eliminated alprazolam or lorazepam and is temporarily alleviated by dose escalation. As craving, dysphoria, and other withdrawal symptoms develop over time between doses, the motivation to continue benzodiazepine use for anxiolysis gradually merges with the need to avoid withdrawal symptoms [124].

Benzodiazepine prescriptions are associated with nonmedical use and the development of benzodiazepine use disorder unrelated to co-occurring drug use or anxiety disorder diagnosis/severity [109]. Acute cognitive-impairing side effects are drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. In one study, long-term use of an average 17 mg/day diazepam equivalent led to substantial cognitive decline that did not resolve three months after cessation [125]. Motor vehicle accident risks during benzodiazepine therapy are comparable to driving with a blood alcohol concentration of 0.050% to 0.079% [126]. Hip fracture risk is increased by ≥50% in older persons who take benzodiazepines; with zolpidem, the risk is increased 200% in persons older than 65 years of age [127]. The risk of overdose is particularly great when benzodiazepines are combined with sedative drugs such as opioids or alcohol.

Personality traits associated with long-term use, emotional dependence, and more severe/protracted benzodiazepine withdrawal have been described. Long-term benzodiazepine users often have poor stress coping abilities. Benzodiazepines compensate for these deficits, but their use interferes with learning stress coping strategies, including behavioral therapy for agoraphobia. Passive-dependent personality traits and lack of internal and external stress coping resources increases vulnerability to withdrawal symptoms and motivation for continued use. In these patients, benzodiazepine deprivation renders them unprotected from stress and re-exposes their coping deficits. Chronically anxious people have been found innately hypersensitive to punishing stimuli and punishment; benzodiazepines can be described as "depunishing" drugs [124].

Withdrawal

Despite comparable dosing, patients with which anxiety disorder often show greater difficulty tapering off of benzodiazepines?

Withdrawal symptoms following benzodiazepine cessation are appropriately concerning and a liability of this drug class that all prescribers should understand. In patients with panic disorder discontinuing alprazolam following 1.5 to 22 months of treatment, 33% to 100% were unable to completely taper [43]. These data did not include the 50% of long-term benzodiazepine users who do not consent to withdrawal studies or who later quit the study. The experience of benzodiazepine withdrawal is known to deter patients from future attempts [128]. An estimated 25% to 76% of patients prescribed benzodiazepines are long-term users. Defining high-dose benzodiazepine varies, but users of high-dose benzodiazepines commonly have comorbid disorders and are unlikely to benefit from current discontinuation and withdrawal strategies that expose them to greater risk of impairment and injury [128].

Despite comparable dosing, patients with panic disorder often show greater difficulty tapering than patients with generalized anxiety disorder. Problems during alprazolam tapering are most severe during the last half of the taper. Patients with panic disorder receiving diazepam or alprazolam had fewer problems during taper of the top 50% of daily dose. However, with abrupt discontinuation of the remaining dose, alprazolam caused significantly more anxiety, relapse, and rebound. This may reflect greater problems withdrawing from short half-life, high-potency benzodiazepines like alprazolam [43].

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CASE STUDY

Patient D, 33 years of age, presents with a chief complaint of anxiety. He describes increasing anxiety symptoms for the last eight months, including persistent worrying that he finds challenging to control, overthinking plans, inability to let go of a worry, difficulty concentrating, fatigue, difficulty falling asleep, irritability, and nervousness. He is employed as a corrections officer with two young children. A medical workup is normal. He has engaged with a therapist for the past three months, and while he has made some gains with cognitive-behavioral therapy, his therapist has suggested a medication consultation to help with his ongoing symptoms.

Upon review of symptoms and consultation with the patient's therapist, a diagnosis of generalized anxiety disorder is confirmed. The clinician discuses goals of care with the patient; he states that he wants to avoid the medication side effects of daytime sedation or impaired concentration due to his job. Available medications are reviewed, and the decision is made to start escitalopram to address the continued symptoms of generalized anxiety. Treatment is initiated at a daily dose of 10 mg. Patient D asks about alprazolam (Xanax), as a friend told him that this medication worked for him. The clinician spends time on patient education explaining that alprazolam has a known risk of addiction and a potential for sedation. The patient agrees to the trial of escitalopram.

When Patient D returns for follow-up in four weeks, he reports improvement in his anxiety symptoms and is continuing his cognitive-behavioral therapy. After three months, the patient indicates that his symptoms are manageable and he has not experienced any adverse effects of the pharmacotherapy.

PHARMACOTHERAPY FOR SUBSTANCE USE DISORDERS

Which agents are approved for the treatment of alcohol use disorder?

Although perhaps the most concerning drug of abuse in the United States today is opioids, substance use disorders (as defined by the DSM-5) are not limited to one specific drug. Even commonly used substances, such as alcohol and nicotine, may initiate use disorders. Substance use disorders are diagnosed based on the presence of at least two of the following criteria in the previous year [129]:

- Using the substance in larger amounts
- Wanting to cut down use but unable to
- Spending large amounts of time involved in procuring and using as well as recovering from use of the substance
- Cravings for the substance
- Not functioning normally at work, home, or school
- Continued use despite harm to relationships
- Decreasing other activities, including work or socialization
- Continued use despite harm or risk of harm
- Continued use despite medical or psychological problems made worse by continued use
- Increased tolerance leading to escalating dosages
- Withdrawal symptoms

The main stages of substance use disorder treatment are crisis intervention, harm reduction, detoxification/withdrawal, active treatment, and relapse prevention. To this end, a variety of medications are have been approved to assist in cessation of use of opioids, alcohol, and nicotine (***Table 8***). Some are used for detoxification, and others are used to prevent relapse. Research has shown that medications are most effective when used in conjunction with other therapies.

In addition to these approved medications, a variety of medications are used off-label for the management of several substance use disorders, including cocaine, methamphetamine, and cannabis.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Addiction Medicine recommends that all FDA-approved medications for the treatment of opioid use disorder should be available to all patients. Clinicians should consider the patient's preferences, past treatment history, current state of illness, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone.

(https://www.asam.org/Quality-Science/quality/2020-national-practice-guideline. Last accessed September 28, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

MEDICATIONS USED IN THE TREATMENT OF SUBSTANCE USE DISORDERS				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Route(s)**
Opioid Use Disorder				
Buprenorphine/naloxone (Bunavail, Suboxone, Zubsolv)	Buprenorphine: 0.7–24 mg/day Naloxone: 0.18–6 mg/day	4/1 mg/day	Pain, headache, nausea, diaphoresis	Buccal film, sublingual film, sublingual tablet
Methadone (Dolophine, Methadose, DISKETS)	20–120 mg/day	20–30 mg/day	Pruritus, constipation, cardiac abnormalities	PO, IV
Naltrexone (Vivitrol)	PO: 25-50 mg/day IM: 380 mg/week	PO: 25 mg/day IM: 380 mg/week	Injection site reactions, anxiety, syncope	PO, IM
Buprenorphine (Belbuca, Buprenex, Butrans, Probuphine, Sublocade)	SQ: 100–300 mg/month SL: 2–24 mg/day	SQ: 300 mg/month Implant: 4 implants SL: 2–4 mg/day	Few	Sublingual tablet, subdermal implant, SQ injection
Alcohol Use Disorder				
Acamprosate (Campral)	666 mg TID	666 mg TID	Diarrhea	PO
Naltrexone (Vivitrol)	PO: 25–100 mg/day IM: 380 mg/month	PO: 50 mg/day IM: 380 mg/month	Injection site reactions, anxiety, syncope	PO, IM
Disulfiram	125–500 mg/day	250 mg/day	Bitter taste, impotence, drowsiness	PO
Nicotine Use Disorder				
Bupropion, sustained-release (Zyban)	150 mg daily or BID	150 mg/day	Weight loss, constipation, agitation, xerostomia, nausea	PO
Nicotine	Gum: Up to a maximum 30 pieces/day Inhaler: 6–16 cartridges/day Lozenge: Titrate to 1 lozenge every 4 to 8 hours Nasal spray: Maximum 80 sprays/day Patch: One patch/day for 8 weeks	Gum: 1 to 2 pieces/hour (2 mg/piece) Inhaler: 6 cartridges/day Lozenge: One lozenge every 1 to 2 hours Nasal spray: 1 spray in each nostril once or twice per hour Patch: One patch/day	Oral irritation, headache, dyspepsia, nasal discomfort, cough, rhinitis	PO, intranasal, transdermal
Varenicline (Chantix)	1 mg BID up to 12 weeks	0.5 mg/day	Nausea, abnormal dreams, headache	PO

BID = two times per day, IM = intramuscular, IV = intravenous, PO = oral, SL = sublingual, SQ = subcutaneous, TID = three times per day.

Source: [19] *Table 8*

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CASE STUDY

Patient E, 54 years of age, presents with active opioid use disorder. He began using prescription opioids for back pain after having served in the infantry. His usage eventually resulted in his leaving military service prior to retirement, and he currently works in construction. The patient reports having relied on prescription opioids until three years ago, when he started using heroin. He buys 10 bundles per day of what is described as heroin but is most likely synthetic fentanyl. He has accidently overdosed on two occasions, and emergency medical services used naltrexone nasal spray to revive him. He is seeking care at an intensive outpatient program for treatment.

After reviewing goals of care with the patient, the clinician identifies that he has residual chronic back pain in addition to cravings for opioids when not using. The patient is diagnosed with opioid use disorder.

Patient E states that he recently sought care for his back pain and was referred to physical therapy and advised to take nonsteroidal anti-inflammatory drugs (NSAIDs) as needed for pain management. The possibility of methadone maintenance is discussed, but the patient does not want to have to go daily for dosing and is afraid that it will impair his ability to work around heavy machinery. Safety issues are also reviewed, and nasal naltrexone is prescribed for emergency use. The patient's partner receives education on use as well.

The patient states he does not wish to take a medication, but he starts attending daily 12-step meetings and working with a drug counselor. Within five days, Patient E is able to successfully complete detoxification. However, after about six weeks he experiences a relapse. His partner administers nasal naltrexone after finding him unconscious.

When Patient E returns for follow-up, various options for medication-assisted therapy are discussed, and he decides to enroll in buprenorphine/naloxone therapy, with a goal of eventually being maintained on monthly buprenorphine injection. The clinician emphasizes the need for continued counseling and the need to understand that, like all chronic diseases, patients with opioid use disorder are subject to relapse. The patient is advised of the importance of seeking help early in the event of a relapse. The biologic basis of substance use disorder is stressed; there is no judgement or shame.

Patient E does well on buprenorphine/naloxone therapy and is attending physical therapy for his back pain. He has continued with regular 12-step meetings and individual psychotherapy. At each follow-up appointment, the need to keep naltrexone nasal spray available for emergency use is emphasized.

CONCLUSION

In the management of patients with mental health disorders, pharmacotherapy remains a vital part of optimal treatment. Only a portion of the psychopharmacologic options available have been discussed in this course. When providing care to special populations, such as pediatric patients and patients who are or may become pregnant, clinicians should consult the latest literature.

Customer Information/Evaluation insert located between pages 88–89.

Pituitary and Adrenal Disorders

Audience
This course is designed for nurses in all practice settings.

Course Objective
As health care becomes more complex, it is essential that the theoretical concepts of the basis of illness (pathophysiology) be well understood. The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing struggle with their pituitary or adrenal illness.

Learning Objectives
Upon completion of this course, you should be able to:

1. Describe the anatomy and physiology of the pituitary and adrenal glands.
2. Outline the action of the hormones excreted by the pituitary and adrenal glands.
3. Describe key aspects of the assessment of patients with pituitary or adrenal disorders, including appropriate diagnostic tools.
4. Discuss the presentation and diagnosis of diabetes insipidus.
5. Outline the options for the treatment of diabetes insipidus.
6. Review the presentation and management of syndrome of inappropriate antidiuretic hormone secretion (SIADH).
7. Evaluate the signs/symptoms, diagnosis, and treatment of growth hormone deficiency.
8. Identify acromegaly and gifantism and appropriate approaches to their treatment.
9. Describe the clinical presentation and diagnosis of Addison disease.
10. Evaluate approaches to the treatment of Addison disease, including identification and management of adrenal crises.
11. Discuss the identification and diagnosis of Cushing syndrome.
12. Evaluate various treatment options for Cushing syndrome, including surgical considerations.
13. Review the signs/symptoms, diagnosis, and treatment of primary aldosteronism.
14. Analyze the clinical presentation, diagnosis, and treatment of pheochromocytoma.
15. Identify psychosocial/lifestyle considerations for patients with pituitary or adrenal disorders.

Faculty
Amanda Perkins, MSN, DNP, is a DNP-prepared registered nurse with a focus in healthcare leadership. Prior to obtaining her DNP, she obtained an MSN with a focus on nursing education. She currently works full-time as an Associate Professor of Nursing at Vermont Tech and per-diem at Gifford Medical Center on the medical-surgical unit and in the long-term care facility. Dr. Perkins also sits on the editorial board, writes, and peer-reviews for the journal *Nursing Made Incredibly Easy!* She has experience in a variety of settings, including long-term care, residential care, medical-surgical, women and children, intensive care, and inpatient psychiatric units.

Jane C. Norman, RN, MSN, CNE, PhD, received her undergraduate education at the University of Tennessee, Knoxville campus. There she completed a double major in Sociology and English. She completed an Associate of Science in Nursing at the University of Tennessee, Nashville campus and began her nursing career at Vanderbilt University Medical Center. Jane received her Masters in Medical-Surgical Nursing from Vanderbilt University. In 1978, she took her first faculty position and served as program director for an associate degree program. In 1982, she received her PhD in Higher Education Administration from Peabody College of Vanderbilt University. In 1988, Dr. Norman took a position at Tennessee State University. There she has achieved tenure and full professor status. She is a member of Sigma Theta Tau National Nursing Honors Society. In 2005, she began her current position as Director of the Masters of Science in Nursing Program.

Faculty Disclosure
Contributing faculty, Amanda Perkins, MSN, DNP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Jane C. Norman, RN, MSN, CNE, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner
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Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

Body activities, homeostasis, and the response to stress are controlled by two distinct, but interacting systems: the nervous system and the endocrine system. The nervous system creates an immediate but short-lived response, operating on the principles of electricity, through impulse conduction. The endocrine system has a slightly slower onset and a longer duration of action and uses highly specific hormones to control its response chemically.

The endocrine system is composed of many glands scattered throughout the body; these glands secrete unique and potent hormones directly into the bloodstream. Most hormones direct their action to target glands or tissues at distant receptor sites, thereby regulating critical body functions such as urinary output, cellular metabolic rate, and growth and development. Hormonal secretions typically are regulated by negative feedback; information about the hormone level or its effect is fed back to the gland, which then responds accordingly.

Endocrine diseases result from an abnormal increase or decrease in the secretion of hormones. This divergence from normal hormone quantities may be the result of hyperplasia, hypertrophy, or atrophy of an endocrine gland. Changes in gland size that affect the gland's production and secretion of a hormone often result from an insult to the gland, such as infection, radiation, trauma, surgical intervention, or inflammation.

As noted, the principal functional units in the system are the endocrine glands: the pituitary, thyroid, parathyroid, adrenal, and pineal glands; the cells of the islets of Langerhans in the pancreas; the gonads (ovaries and testes); and the thymus. The kidneys also perform an endocrine function. Some of these glands are solely endocrine in function, whereas others form parts of larger organs that may have both endocrine and nonendocrine functions. The pituitary, thyroid, parathyroid, pineal, and adrenal glands have distinct endocrine functions. This course will focus on the pathophysiology of the pituitary and adrenal glands.

Because of the complex actions of the pituitary and adrenal glands, as well as their interaction with each other and with other body systems, their dysfunctions have a variety of causes and clinical manifestations. Pituitary disorders encompass a diverse set of conditions, including diabetes insipidus, SIADH (syndrome of inappropriate antidiuretic hormone secretion), acromegaly, and growth hormone deficiency. Common adrenal disorders include Cushing syndrome, Addison disease, hypoaldosteronism, and hyperaldosteronism. Because the pituitary and adrenal glands work together closely, there is often overlap in the pathophysiology of these disorders.

Dysfunction of the pituitary or adrenal gland is associated with many physical and mental symptoms, with significant impact on patients, families, health services, and society. When caring for patients with these types of disorders, there are key skills necessary to accurately interpret diagnostic testing, identify comorbidities, and effectively manage care.

ANATOMY AND PHYSIOLOGY

HYPOTHALAMUS

The hypothalamus plays an important role in the regulation of homeostasis within the body. It is necessary for automatic functions of the nervous system, regulation of the glands of the endocrine system, emotional responses, and behaviors [1]. It may help to think of the hypothalamus as a control center—it monitors information about the body and makes necessary changes based on the information obtained.

The hypothalamus functions as an integral part of both the endocrine and nervous systems. In its neural role, it receives and processes innervations from the thalamus, cerebral cortex, spinal cord, and brainstem. This results in the control of such bodily functions as temperature, respiration, arterial blood pressure and circulation, and metabolism. The hypothalamus also controls certain behavioral functions, including the emotional states of fear, anxiety, anger, rage, pleasure, and pain, as well as the states of sleep, wakefulness, and alertness. The hypothalamus, as it is influenced by the autonomic nervous system, affects all the unconscious actives of the body [2; 3]. In its endocrine role, the hypothalamus has two regulatory functions:

- Regulating the anterior pituitary gland by producing and secreting releasing factors
- Producing and secreting two hormones (oxytocin and antidiuretic hormone [ADH]) stored in the posterior pituitary gland

Hypothalamic-releasing factors are proteins that act on the anterior pituitary gland to stimulate or inhibit the release of tropic hormones. Other inhibiting factors and releasing factors have been identified; it is thought, although still unproven, that the hypothalamus may produce both an inhibiting and a releasing factor for each of the anterior pituitary hormones [2; 3].

The release or inhibition of these hypothalamic hormones is controlled by various neurotransmitters, such as serotonin, acetylcholine, norepinephrine, and dopamine. The tropic hormones released from the anterior pituitary gland then act upon a target gland or tissues to produce a specific response. In regulating the secretion of these releasing factors, the hypothalamus processes input from both the circulatory and nervous systems [2; 3].

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PITUITARY GLAND

Where do most of the disorders affecting the pituitary gland originate?

The pituitary gland (hypophysis) is located in the sella turcica at the base of the skull. It lies just below the hypothalamus and is connected to it by a stalk containing blood vessels and nervous tissue. The pituitary gland is composed of an anterior and posterior lobe (adenohypophysis and neurohypophysis, respectively), each of which performs specific functions, as well as a rudimentary intermediate lobe [4].

In response to the releasing factors from the hypothalamus, the anterior pituitary gland secretes several hormones, some of which control hormonal secretions by other glands. The anterior pituitary hormones secreted include thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone, luteinizing hormone (also called interstitial cell-stimulating hormone in men), follicle-stimulating hormone, and prolactin. In general, growth hormone, ACTH, and TSH are concerned with metabolic activities, whereas luteinizing hormone, follicle-stimulating hormone, and prolactin are concerned with reproduction. ACTH, TSH, follicle-stimulating hormone, and luteinizing hormone exert their effects on target glands, either increasing their size or their secretions. Prolactin and growth hormone directly affect the metabolism of specific target tissues [5].

Most of the disorders affecting the pituitary gland originate in the anterior lobe. The effects of pathology on the anterior pituitary gland can be broadly summarized as hyperpituitarism and hypopituitarism [6; 7].

The most common cause of hyperfunction of the anterior pituitary gland is a neoplastic secreting tumor, usually a benign adenoma. Tumors of the pituitary gland exert their effects through either pressure on structures in the brain, causing visual symptoms and headaches, or excessive secretion of one or more of the anterior pituitary hormones, which results in increased stimulation of one or more target glands.

One of the pathophysiologic manifestations of these tumors is hypersomatotropism, which can result in acromegaly in adults and gigantism in children. Other effects of hypersomatotropism include goiter (from stimulation of the thyroid) and diabetes mellitus (from the diabetogenic effect of growth hormone). Cardiomegaly and hypertension can also occur. Visual impairment and eventual blindness are possible because of compression of tissues by an expanding tumor. Amenorrhea in women and loss of libido and potency in men may occur because compression from the expanding tumor leads to gonadal deficiencies from loss of healthy gonadotropin-producing cells [6; 7].

Hyperfunction of the anterior pituitary gland can be secondary to pathology of the anterior pituitary gland or to injury to the hypothalamus resulting in a decrease or absence of hypothalamic-releasing factors. Hypothalamism may be manifested by isolated hormonal deficiencies or by a deficiency of both the anterior and posterior pituitary hormones (panhypopituitarism). The exact hormonal deficit and its etiology are important to understanding patients' symptoms and signs [6; 7].

ADRENAL GLANDS

The adrenal glands are paired and located in the retroperitoneal space at the upper pole of the kidney. Because of this position, they may be referred to as the suprarenal glands. Each adrenal gland consists of an outer portion (the cortex) and an inner portion (the medulla), which differ in both anatomic structure and function [8].

The adrenal cortex is composed of three zones, or groups of different cells: the zona glomerulus (the outer layer of cortical cells that secretes the mineralocorticoids), the zona fasciculate (the middle layer of cortical cells that secretes the glucocorticoids), and the zona reticularis (the layer of cortical cells proximal to the medulla that secretes the adrenal sex hormones androgens and estrogen). The adrenal glands receive an abundant blood supply. The medulla of the adrenal gland functions as part of the sympathetic nervous system, whereas the cortex has only minimal nervous system innervation [8].

In response to stimulation by ACTH from the anterior pituitary gland, the adrenal cortex secretes three major types of hormones: glucocorticoids (cortisol), mineralocorticoids (aldosterone), and sex hormones (androgens, estrogen, and progesterone). These hormones affect metabolism, fluid balance, and the development of secondary sex characteristics, respectively. All three types of hormones secreted by the adrenal cortex are structurally similar steroids, which results in some overlapping of their effects [5; 9].

The primary causes of hypercortisolism (Cushing syndrome), originating from within the adrenal cortex itself, include neoplastic and bilateral hyperplasia. In iatrogenic hypercortisolism, an exogenous source (e.g., prolonged use of glucocorticoids or ACTH) is responsible for the hypercortisolism. The normal adrenal glandular tissue may be atrophic, and ACTH levels are suppressed [10].

Hyperfunction of the adrenal cortex results in three major disorders: Cushing syndrome, primary aldosteronism, and excessive production of sex hormones characterized by virilizing changes in women, feminizing changes in men, and precocious sexual development in children. These changes often cause serious psychologic issues related to self-esteem and body image.

Hypofunction of the adrenal cortex, or adrenal insufficiency, results in a decreased secretion of glucocorticoids, mineralocorticoids, and sex hormones. The causes of adrenal insufficiency can be grouped into two categories: primary (based on pathology occurring within the gland itself) and secondary (arising from an undersecretion of ACTH due to pathology in the pituitary gland or the hypothalamus). Primary causes may be acute or chronic [11].

Primary adrenal insufficiency (Addison disease) is characterized by a failure of the adrenal cortex to produce sufficient corticosteroids. Acute severe symptoms of Addison disease are referred to as addisonian or acute adrenal crisis.

The adrenal medulla is considered a part of the sympathetic division of the autonomic nervous system, which controls the secretion of its hormones. Because the functions of the sympathetic nervous system and the functions of the hormones of the adrenal medulla are the same, they can compensate for each other. Thus, the medullary hormones are not essential to life but play an important role in the body's response to stress. About 15% of the hormonal secretion by the adrenal medulla is norepinephrine and 75% is epinephrine [5].

Pathophysiology of the adrenal medulla is rare and is usually associated with hyperfunction. The clinical manifestations seen in hyperfunction of the adrenal medulla are related to the excessive secretion of epinephrine and norepinephrine [12]. Pheochromocytoma is the most common cause of adrenal medulla hyperfunction. Other disorders associated with hyperfunction of the adrenal medulla include neurofibromatosis carcinomas (of the thyroid) and hyperparathyroidism [12].

HORMONES

What are the major influencers of secretion of hormones by the endocrine glands?

A hormone may be defined as a "chemical substance synthesized by an endocrine gland and secreted into the bloodstream, which carries it to other sites in the body where its actions are exerted" [5]. Hormones may function independently, in conjunction with other hormones, or as a step in a series of related actions. They may influence the action, metabolism, synthesis, and/or transport of another hormone, which is one of the integrative aspects of the endocrine system. Hormones can be differentiated into two major categories: local (with specific local effects) and general (transported by the circulation to distant sites, where they have a physiologic effect) [13].

Only target cells have the capability to respond to a specific hormone in a characteristic way. Their response depends on the presence of specific receptors for a particular hormone. This response is called hormone-target cell specificity, and the process is known as hormone-receptor binding. The initial interaction between a hormone and its target cell receptor initiates a chain of biochemical events that eventually provokes a cellular response. This often involves a hormone-induced change in the activity of a specific enzyme found in the target cell that might change the rate of reactions within the cell, change the growth of the cell, or control the cell's secretion. Because cells are exposed to many hormones, complex hormone-hormone interactions can occur in target cells. These interactions may be inhibitory, synergistic, or permissive (i.e., one hormone, by its presence, potentiates the effect of the second hormone) [13].

Hormones include steroid, polypeptide, amino acid, catecholamine, or iodothyronine structures. The steroidal hormones are aldosterone, cortisol, and the estrogens and androgens. The receptors involved in hormonal-receptor binding differ for steroidal and nonsteroidal hormones. The receptors for most nonsteroidal hormones are located on the outer surface of the plasma membrane of the target cells, whereas the receptors for the steroidal hormones are soluble proteins within the cytoplasm of the target cell. The physiology of hormone receptors is an expanding area of research in endocrinology [13].

Most hormones are not secreted at a constant rate. After secretion into the bloodstream, they circulate in a free form or are bound to proteins. Polypeptide hormones and the catecholamines are essentially unbound in the circulation. These free hormones are directly available to the target tissues, and only they can affect the target cells. The protein-bound forms are thought to represent a hormonal reserve, because the protein binding may prevent excretion of the hormone by the kidney. The amount of circulating free hormone is usually quite small and exists in equilibrium with the bound fractions [13].

There are five major influences of the secretion of hormones by the endocrine glands: the hypothalamus, hypothalamic-releasing factors, anterior pituitary hormones, the autonomic nervous system, and nutrient and ion concentrations in the plasma. The hypothalamus affects hormone secretion by secreting a series of peptides called releasing factors, which stimulate or inhibit the release of hormones by the anterior pituitary gland. The hypothalamus also directly manufactures oxytocin and antidiuretic hormones (ADH or vasopressin). The hypothalamic-releasing factors cause the interior pituitary gland to secrete growth hormone, prolactin, TSH, the gonadotropic hormones follicle-stimulating hormone, luteinizing hormone, and ACTH. The anterior pituitary hormones directly control the release of thyroid hormone (T3 and T4),

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cortisol, testosterone in men, and estrogen and progesterone in women [13]. In some patients with excessive hormone levels caused by a tumor of the involved endocrine gland, feedback inhibition does not suppress the overproduction of the hormone, and the tumor functions autonomously [14; 15].

Diurnal variation is another of the control mechanisms affecting hormonal secretion. A 24-hour cyclical variation in the secretory rates of certain hormones can be seen. For example, growth hormone levels are highest in the first 90 minutes after sleep begins. These circadian rhythms have been found to be different for each hormone. It is evident that the endocrine system affects all aspects of the organism. Through the hormonal secretion of its glands, the system controls and regulates the metabolic processes of anabolism and catabolism, the function of muscles, growth and reproduction, energy production, stress reactions, electrolyte balances, and personality development [14; 15].

Antidiuretic Hormone (ADH)

The storage and release of ADH are influenced by such factors as plasma osmolality, blood volume, physiologic and psychological stress, and input from the central nervous system. ADH is produced in the hypothalamus and then transported to the posterior pituitary gland where it is stored. In the posterior pituitary gland, oxytocin and ADH are bound to the protein neurophysin and released into the circulation in response to specific physiological stimuli [3].

ADH plays an important role in the reabsorption of water by the kidneys; decreased ADH leads to diuresis, and increased ADH leads to fluid retention [16]. ADH is typically responsible for osmoregulation, but this changes when a person has a reduction in blood volume, which shifts ADH from osmoregulation to blood volume regulation [17]. ADH induces water reabsorption via vasopressin 2 receptors in the kidneys [18]. The main osmotic stimulus for ADH secretion is increased plasma osmolality and the main non-osmotic stimulus is hypovolemia [18]. The osmotic threshold for ADH is approximately 280–290 mOsm/Kg [17]. As such, ADH levels will significantly decrease when plasma osmolality drops below this level. Plasma osmolality greater than 280–290 mOsm/kg will lead to increased ADH release [17].

Growth Hormone

Growth hormone, also referred to as somatotropin, is produced in the pituitary gland [19]. An estimated 50% of the cells in the anterior pituitary are somatotrophs (cells that secrete growth hormone) [20]. Secretion of growth hormone by the anterior pituitary gland occurs in a pulsatile manner, and the majority (up to 70%) occurs at night during non-REM (typically stage 3) sleep [21; 22]. Therefore, the amount and quality of sleep plays an important role in growth and development.

Growth hormone-releasing hormone (GHRH) is secreted from the hypothalamus, so growth hormone levels are primarily under hypothalamic control [22; 23]. Growth hormone activates hormone-sensitive lipase (which results in metabolism of fat for energy), affects insulin sensitivity, and stimulates the formation of insulin-like growth factor in the liver [20; 24].

Growth hormone can first be detected in the fetus near the end of the first trimester, with levels peaking at 20 weeks and decreasing after birth [21]. It will fall to adult levels until puberty, when levels increase [21]. After puberty, the levels decrease again and remain relatively stable until mid-adulthood, when they undergo another drop [21]. Levels of growth hormone may be increased during fasting or exercising and decreased in those with central obesity [21; 23].

In addition to its role in normal development, growth hormone is necessary for the maintenance of bone health. It stimulates osteoblast differentiation and proliferation and increases calcium absorption in the intestines [23]. Further, it plays a role in appetite, cognitive function, energy, memory, mood, neuroprotection, and sleep [25].

Glucocorticoids

The glucocorticoids function in carbohydrate, fat, and protein metabolism and play an important role in the body's response to stress and emotional well-being. The principal glucocorticoid secreted by the adrenal cortex is cortisol, which constitutes 95% of cortical production; corticosterone and cortisone are also produced.

Glucocorticoids act on all cells in the body [26]. Cortisol, the main glucocorticoid, is secreted based on the circadian rhythm and in response to stress; for this reason, it is also known as the stress hormone. When the body is experiencing stress, the pituitary gland secretes ACTH, which stimulates the production and release of cortisol [27]. Cortisol also plays a role in nutrient metabolism, immune response to inflammation, regulation of blood pressure, blood glucose levels, and body fluid homeostasis [28; 29].

Mineralocorticoids

The principal and most potent mineralocorticoid secreted by the adrenal cortex is aldosterone. Desoxycorticosterone and corticosterone are also secreted, but their actions are of minor importance. Aldosterone enters the circulation and travels to the kidney, where it binds to a specific receptor in the cytoplasm of the epithelial cells of the distal convoluted tubules. This receptor initiates a series of biochemical events that result in the major physiologic action of aldosterone [5; 9].

Aldosterone increases the reabsorption of sodium and the secretion of potassium. This is accomplished as an exchange of sodium ions for potassium or hydrogen ions, which results in the excretion of potassium and hydrogen into the urine and the retention of sodium. As sodium is reabsorbed into the blood, it brings with it water and chlorides, which mechanically increases the blood volume. This action of aldosterone is vital to the maintenance of the extracellular fluid volume. Aldosterone also promotes sodium reabsorption to a lesser degree from the sweat glands, salivary glands, and gastrointestinal (GI) tract [2; 3].

Aldosterone is an important factor in the maintenance of circulatory blood volume homeostasis through its effect on the electrolyte balance and its control of blood volume. It is the most potent hormonal regulator of electrolyte excretion. The secretion of aldosterone is regulated by three (or possibly four) major mechanisms: the renin-angiotensin system, ACTH, plasma potassium levels, and perhaps prostaglandins.

Although chiefly affecting the secretion of cortisol, ACTH is also thought to affect aldosterone production for short periods. This appears to be related to crises, during which ACTH causes an increase in the secretion of glucocorticoids and stimulates the production of aldosterone. This effect of ACTH is thought to be minor and secondary to that of the renin-angiotensin system and serum potassium levels [3].

The ratio of serum sodium levels to serum potassium levels is another important regulator of aldosterone secretion. If the serum potassium level rises or the serum sodium level decreases, changing the sodium-potassium ratio, the adrenal cortex will be stimulated to produce aldosterone. Prostaglandins are also thought to be involved in aldosterone secretion through the relation of sodium and water excretion and the release of renin [5; 9].

Adrenal Medullary Hormones

The primary hormones secreted by the adrenal medulla are norepinephrine and epinephrine. Norepinephrine increases the contraction of the blood vessels, which increases peripheral resistance and causes the blood pressure to rise. This hormone also dilates the pupils of the eyes, increases the force and rate of myocardial contraction, and inhibits the activity of the GI system. It causes peripheral vasoconstriction, which diverts blood away from less-needed areas (e.g., the GI tract) toward the heart and skeletal muscles in a "fight-or-flight" response. Because of the length of time norepinephrine is retained in the circulation (two to three circulation times), it has an effect ten times larger than that of the sympathetic nervous system [5].

Epinephrine increases body metabolism and, in conjunction with glucagon, elevates the plasma glucose levels by glycogenolysis (the conversion of glycogen to glucose). Epinephrine also inhibits the secretion of insulin and elevates blood lipid levels by promoting lipolysis. These actions provide the body with a plasma glucose source for increased energy expenditure. Epinephrine is also able to constrict the arterioles of the skin selectively (causing pallor) while dilating the blood vessels of the heart and skeletal muscles, again vital to the stress response [5].

It is important to remember the permissive role of the glucocorticoids with respect to catecholamines. In the absence of cortisol, the vasoconstrictive and metabolic responses mediated by norepinephrine and epinephrine will not occur [5; 9].

Through innervation from the sympathetic nervous system, the secretion of the adrenal medullary hormones is influenced by emotional stresses (e.g., fear, anxiety) and physiologic stresses (e.g., childbirth, injury, cold, hypoxia, immobilization, physical exercise). The relation between the psychologic-emotional state and the endocrine system is one of the body's major homeostatic mechanisms for protecting the individual from harm and physiologic stresses in a way that preserves integrity [9].

NURSING ASSESSMENT

Assessment of pituitary and adrenal issues should begin with a nursing history, followed by a physical examination. Exams should include determination of the patient's signs and symptoms, past medical history, family history, and any medications or supplements that the patient is taking. During the physical assessment, nurses should use the skills of inspection, olfaction, auscultation, percussion, and palpation. Vital signs and the patient's weight should also be obtained during the patient assessment.

PHYSICAL ASSESSMENT

Vital Signs

Patients with suspected pituitary or adrenal disorder should have their height and weight assessed and compared with growth charts. A careful developmental and familial growth history may help in the interpretation of abnormalities. Blood pressure should be measured in both arms initially and in at least two positions (e.g., supine and seated). Apical and radial pulse rates, rhythm, and quality should be evaluated, along with respiratory rate, rhythm, and depth. The patient's temperature should also be recorded [30].

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General Appearance

Whether a patient's appearance closely matches his or her chronologic age should be noted. The symmetry and proportionality of the body parts should be assessed. Weight distribution and any abnormal movements of the extremities or face (e.g., spasms or twitching of facial muscles) should be noted. A plethoric (round, erythematous), "moon" face suggests Cushing syndrome [30].

Skin, Hair, and Nails

Pituitary and adrenal dysfunction can affect the temperature and texture of the skin. For example, pheochromocytoma is associated with increased skin temperature with sweating. Ecchymoses often accompany Cushing syndrome, and vitiligo has been seen in patients with adrenal insufficiency. Other possible skin lesions include skin infections (e.g., furuncles, carbuncles), ulcerations, and diabetes-related skin changes (e.g., candidiasis, diabetic dermopathy, diabetic xanthoma) [30]. The texture and distribution of body hair should also be considered.

Eyes

Nurses should pay careful attention to any changes in visual acuity or visual fields defects. Patients whose disorders induce hyperglycemia may display diabetic retinopathy (e.g., retinal edema, microaneurysms, retinal hemorrhages, exudates). Patients with these conditions require immediate referral to an ophthalmologist [30].

Cardiorespiratory System

The patient's heart rate and rhythm should be assessed, with attention to murmurs or extra heart sounds. In pheochromocytoma, hypertension, tachycardia, and atrial fibrillation may be noted. Cushing syndrome often leads to congestive heart failure, as manifested by lethargy, dyspnea on exertion, paroxysmal nocturnal dyspnea, and cough. Hypertension can accompany Cushing syndrome, and hypotension can accompany adrenal insufficiency. Because of the interrelation between cardiac and respiratory systems, cardiac pathology often produces changes in the lungs (e.g., pleural effusions, congestive heart failure). Therefore, the lungs should be assessed for abnormal breath sounds, rales, rhonchi, wheezes, and pleural friction rubs [30].

Abdomen and Genitals

The abdomen should be assessed for any asymmetry that might indicate ascites, enlargement of an organ, or a mass. Auscultation may detect bruits (especially over the renal arteries), and palpation can uncover abdominal pain [30].

Assessment of the genitalia is important in the evaluation of patients with pituitary/adrenal dysfunction, because changes in sexual development and reproductive function often occur. The appearance and any abnormalities of the patient's genitals should be noted. The presence or absence of secondary sex characteristics is recorded, including agreement between the genital, hormonal, and psychologic sex of the patient [30].

Neuromuscular System

Patients should be evaluated for current and past fractures, as may be seen in Cushing syndrome. Other issues may include bone pain, joint pain, and generalized muscle weakness. The neurologic and endocrine systems work closely together to maintain the homeostasis of the internal environment and to help cope with stress. Therefore, pathology in the nervous system often affects endocrine function (e.g., a benign tumor of the pituitary gland can cause hypersecretion of anterior pituitary hormones) and pathology in the endocrine system can be reflected in the nervous system [30].

Nurses should conduct a careful neurologic evaluation, including assessment of mental status, cranial nerves (as dysfunction of cranial nerves I and II is associated with enlargement of the pituitary gland), motor and sensory function, the cerebellum, and deep tendon and superficial reflexes. Ataxia can occur in hypocalcemia and acromegaly. Thoroughness in examination and accuracy in recording findings are essential, and all abnormal findings require additional evaluation [30].

DIAGNOSTIC TESTS

Single measures of endocrine function are rarely sufficient to support a diagnosis but nevertheless should be an integral part of the whole data base. In pituitary and adrenal testing, be aware of the importance of patient preparation and adhere strictly to the testing protocols. Patient and environmental influences that might modify the test results are important nursing considerations [31]. This section will focus on some of the most commonly used tests; general screening tests, such as complete blood count and basic metabolic panel, will not be discussed but are usually part of the workup.

Serum and Urine Osmolality

Which medications are associated with decreased urine osmolality?

Serum osmolality testing provides information about the number of particles dissolved in the serum, while urine osmolality provides information about the kidney's ability to concentrate urine [32]. Serum and urine osmolality are controlled by ADH [33]. The release of ADH reduces the amount of fluid output by the kidneys, increasing blood volume and decreasing serum osmolality while simultaneously increasing urine osmolality. Serum osmolality is also increased in patients with hypernatremia and decreased in those with hyponatremia. The opposite is true for urine

MEDICATIONS THAT IMPACT SERUM AND URINE OSMOLALITY	
Effect	**Medications/Drugs**
Increased serum osmolality	Corticosteroids Glycerin Insulin Mannitol
Decreased serum osmolality	Carbamazepine Chlorpromazine Hydrochlorothiazide Cyclothiazide Doxepin Lorcainide MDMA/Ecstasy
Increased urine osmolality	Anesthetic drugs Furosemide Mannitol Octreotide Vincristine
Decreased urine osmolality	Captopril Demeclocycline Glyburide Lithium Octreotide Tolazamide Verapamil
Source: [32]	*Table 1*

osmolality—it is increased with hyponatremia and decreased with hypernatremia. Certain medications can affect serum and urine osmolality (***Table 1***).

Cumulatively, serum and urine osmolality will help to estimate the ability of the kidney tubules to concentrate or dilute urine and can be used to aid in the diagnosis of diabetes insipidus and SIADH [33]. The normal range for serum osmolality is 280–300 mOsm/kg, and the normal range for urine osmolality is approximately 250–900 mOsm/kg [32; 33]. Normal reference ranges may vary slightly depending on the source or laboratory. Diabetes insipidus is associated with elevated serum osmolality, while decreased values would be indicative of SIADH.

Urine osmolality tests use the first-voided urine specimen, which is thought to represent the maximum concentration ability of the kidneys [34]. Prior to this test, the patient should be asked about recent alcohol use and blood transfusions, as both can interfere with the results [33]. Alcohol should be avoided for at least 12 hours prior to the collection of the serum sample [33].

Water Deprivation Test

A water deprivation test involves withholding water from the patient for 6 to 17 hours while monitoring body weight, vital signs, urine volume, and urine osmolality every 1 to 2 hours [16; 35]. Blood samples are also obtained two hours after the start of fluid deprivation and before giving desmopressin [35]. At the end of the test, desmopressin is given and urine osmolality is tested [18]. Water deprivation typically leads to more concentrated urine and increased weight [16]. Extended deprivation results in a urine osmolality level greater than 800 mOsm/kg (considered maximally concentrated) [18]. In patients with complete central diabetes insipidus, urine osmolality will remain less than 300 mOsm/kg during water deprivation but will increase by more than 50% after the administration of desmopressin [18]. With nephrogenic diabetes insipidus, urine osmolality will remain less than 300 mOsm/kg throughout the test and administration of desmopressin will not induce an increase in urine osmolality [18]. Although the test is fairly easy, interpreting the results can be a challenge [35].

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If any of the following develop during a water deprivation, the test should be halted [35]:

- Body weight decreased by more than 3%
- Symptoms of orthostatic hypotension, with a heart rate increase of 15% or a mean arterial blood pressure decrease of 15%
- Increase in plasma sodium level to 150 mmol/L or more

Hypertonic Saline Test

The hypertonic saline test can be used to aid in the diagnosis of diabetes insipidus. This procedure involves the administration of a 250-mL bolus of 3% hypertonic saline; the patient is given a 5% glucose infusion and is instructed to drink 30 mL of water per kg of body weight within one hour. Rapid sodium measurements are taken every 30 minutes; plasma osmolality, serum sodium, urea, and glucose are also monitored [18; 35]. If the sodium level rises above 147 mmol/L, the infusion should be stopped. If copeptin is being measured, it should be done at this point [18]. With the hypertonic saline test, a plasma copeptin measurement of 4.9 pmol/L or less indicates complete or partial central diabetes insipidus [35].

The advantages of measuring copeptin are that small amounts of serum are needed, the samples collected are stable for one week at room temperature, and results are available within two hours [18; 35]. The release of copeptin is triggered by osmotic stimuli and volume depletion [18]. Research has shown that measuring osmotically stimulated copeptin is a useful diagnostic tool [35]. Levels may be measured with a water deprivation or hypertonic saline test, but results are more accurate with hypertonic saline than water deprivation [35]. Baseline copeptin levels should be obtained followed by levels prior to desmopressin [35]. Basal plasma copeptin levels of less than 2.6 pmol/L are indicative of complete central diabetes insipidus [35]. If the ratio of copeptin to plasma sodium is less than 0.02 pmol/L, partial central diabetes insipidus is suggested [35].

Growth Hormone Stimulation Test

As noted, growth hormone is secreted by the anterior pituitary gland periodically throughout the day, with levels highest at night. Due to the episodic nature of growth hormone secretion, random checks are rarely useful [32]. However, to assess for growth hormone deficiency or acromegaly, a growth hormone test is often completed together with a growth hormone suppression test, growth hormone stimulation test, and insulin-like growth factor test [33]. Before testing, the patient should avoid eating, drinking, and exercising for 10 hours [33]. The typical normal value is less than 5 ng/mL in men, less than 10 ng/mL in women, and 0–10 ng/mL in children [33]. Decreased levels are associated with a deficiency, and increased levels are associated with acromegaly.

The growth hormone stimulation typically takes two to five hours to complete and is typically started in the morning with a baseline blood sample [36]. Medication (arginine, glucagon, or insulin) will be given intravenously to stimulate the pituitary gland to release growth hormone [36]. Blood samples may be obtained at baseline and 30, 60, 90, and 120 minutes after administration of the testing agent [33]. Prior to growth hormone stimulation and suppression tests, patients should avoid strenuous activity for at least 12 hours [32]. If the patient has normal values throughout this test, growth hormone deficiency can be ruled out. However, failure of growth hormone levels to increase as expected is an indicator that the patient may have a growth hormone deficiency.

Insulin Tolerance Test

Because hypoglycemia stimulates growth hormone secretion, an insulin tolerance test may also be used to assess growth hormone sufficiency [21]. An insulin tolerance test involves hypoglycemia induced by an intravenous (IV) injection of insulin [37]. With this test, regular insulin is administered intravenously to drop the patient's glucose levels below 40 mg/dL [21]. Within 30 to 60 minutes, growth hormone levels are measured and should reflect a peak. Throughout the course of this test, the patient may experience signs and symptoms of hypoglycemia, including dizziness, anxiety, tremors, sweating, and tachycardia. Seizure and/or loss of consciousness are possible, so close monitoring during the test is necessary [21].

Cortisol Levels

The body typically responds to stress by triggering the pituitary to make ACTH, with a resultant elevation in cortisol [37]. Blood is drawn at the start of the test and every 30 minutes for 2 hours [37]. In patients with Cushing syndrome, cortisol levels are higher than expected [32]. This test is not appropriate for persons taking insulin or on hemodialysis [32]. Patients should be instructed to report signs and symptoms of hypoglycemia.

Growth Hormone Suppression Test

Growth hormone suppression tests are used to aid in the diagnosis of acromegaly. After the baseline blood sample is obtained, the patient is instructed to drink a solution containing glucose within five minutes [38]. Blood samples are then obtained after 60 and 120 minutes [33]. If possible, glucocorticoids should be halted prior to the test [38]. In general, this test is not used for screening—it is only ordered if a patient presents with signs and symptoms of acromegaly [38]. If growth hormone levels stay the same or increase during the test, acromegaly is suggested [38].

Insulin-like growth factor regulates the effects of growth hormone, but it remains stable throughout the day [39]. Testing Insulin-like growth factor levels is indicated for patients with suspected acromegaly or to monitor the effectiveness of growth hormone treatment [39; 40]. Elevated levels in the presence of elevated growth hormone levels are indicative of acromegaly [39].

ACTH Stimulation Test

ACTH stimulation testing involves the infusion of cosyntropin (a synthetic form of ACTH) as either intravenous or intramuscular injection [32]. Cortisol levels are collected at baseline, 30 minutes, and (in some cases) 60 minutes after the medication bolus [32]. Normal baseline cortisol levels are greater than 5 mcg/dL; normal levels at 30 to 60 minutes are 18–20 mcg/dL [32]. In response to the cosyntropin infusion, the adrenal cortex should release two to five times the amount of normal plasma cortisol levels within 30 minutes [24]. Prior to undergoing ACTH stimulation testing, patients should abstain from nicotine, alcohol, cortisol-affecting medications, and strenuous activity for at least 12 hours [32]. Some patients may be instructed to remain in bed for one hour prior to the test [32].

Urinary Free-Cortisol Test

For the 24-hour urinary free-cortisol test, urine is collected over 24 hours to measure the amount of unbound cortisol filtered by the urinary system [41]. The accuracy of this test is dependent on the patient's glomerular filtration rate and urinary volume [41]. Normal cortisol levels in a 24-hour urine collection are 450–700 nmol/L [42]. Elevated levels indicate Cushing syndrome, while low levels could indicate Addison disease.

Low-Dose Dexamethasone Suppression Test

The low-dose dexamethasone suppression test (LDDST) is completed by administering low doses of dexamethasone at night, followed by a blood draw in the morning [28]. For this test, the patient is given 1 mg of dexamethasone orally at 11 p.m. and cortisol levels are measured at 8 a.m. [32]. Alternately, dexamethasone may be given every 6 hours for 48 hours, followed by a blood sample 6 hours after the last dose [28]. Cortisol levels are expected to be less than 1.8 mcg/dL when the sample is taken [32]. Administration of dexamethasone decreases cortisol levels, so an elevated finding is indicative of abnormality. This test is used to distinguish between Cushing syndrome and Cushing disease (specifically caused by a pituitary tumor that secretes excessive ACTH) [32]. However, certain medical conditions can affect the results of the test, including severe obesity, pregnancy, dehydration, uncontrolled diabetes, severe weight loss, alcohol withdrawal, severe injury, and stress [33].

Corticotropin-Releasing Hormone Stimulation Test

The corticotropin-releasing hormone stimulation test can help to distinguish between Cushing syndrome and Cushing disease [32]. Corticotropin-releasing hormone is given intravenously and eight cortisol and ACTH levels are collected, one at baseline and the others at 5, 15, 30, 60, 120, and 180 minutes after administration [32]. The expected result in healthy individuals is a peak in cortisol (greater than 20 mcg/dL) and a two- to four-fold increase in ACTH within 30 to 60 minutes [32]. Higher cortisol levels are associated with Cushing disease; cortisol levels that fail to increase may indicate ectopic ACTH secretion [32].

Inferior Petrosal Sinus Sampling

Bilateral inferior petrosal sinus sampling (IPSS) can be used to distinguish Cushing disease from ectopic ACTH secretion [43]. This test is guided by fluoroscopy, typically while the patient is under general anesthesia, and will take 60 to 90 minutes [43; 44]. Catheters are inserted through both the left and right femoral veins and advanced to the petrosal sinuses [43]. Samples are drawn simultaneously from the inferior petrosal sinus and the peripheral veins for plasma ACTH five minutes and one minute before administration of 1–100 mcg corticotropin-releasing hormone in a peripheral vein. Samples for plasma ACTH are collected at 2, 5, and 10 minutes after administration. A peripheral sample for plasma cortisol is also taken along with each sample for plasma ACTH.

ACTH should be in higher concentrations when measured from a sample collected close to the gland [43]. Possible complications associated with this test include a groin hematoma and rarely subarachnoid hemorrhage, brainstem injury, brainstem stroke, and infection [43]. Though less accurate, jugular vein sampling is a less-invasive alternative to IPSS [43].

If a tumor is the cause of excess ACTH, this test will help to identify the location [44]. Additionally, comparing results from the right and left sides can help identify the best approach to remove the tumor while maintaining some functional pituitary tissue [44].

Other Tests and Imaging

The late-night salivary cortisol test measures cortisol in the saliva at night, when the levels typically drop; levels will remain elevated in patients with Cushing syndrome [28]. Serum or urinary cortisol, aldosterone, and/or ACTH may also be assessed.

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The diagnostic investigation of anterior pituitary dysfunction often involves an x-ray, computed tomography (CT), or most commonly, magnetic resonance imaging (MRI) scan of the skull. A cerebral flow brain scan or echoencephalogram also may be used. In the presence of a pituitary tumor, a widening of the sella turcica (the bony seat of the pituitary gland) may be visualized. To further detect the presence of a brain tumor, a complete neurologic evaluation may be done, including assessment of the patient's visual fields [34].

NURSING DIAGNOSES

The nursing diagnosis forms the basis of the plan of care for the patient and provides guidelines for its implementation and evaluation. Because pituitary/adrenal dysfunction has widespread effects, many nursing diagnoses can be used in caring for these patients. Each patient's actual problem is unique, however, and requires a skillful assessment. Recognition of the specific problem and its etiology is integral to a comprehensive, well-executed nursing care plan [46].

INEFFECTIVE INDIVIDUAL COPING

Because of the profound physiologic and psychosocial stresses on the patients with these conditions, it is not unusual for them to be fearful and have difficulty coping. Feelings of anxiety can be directly related to the disorder (as in pheochromocytoma) or exogenous, resulting from feelings of unexplained apprehension about the situation [46].

Pituitary/adrenal disorders often require the patient and family to make major changes in lifestyle. Patients may require lifelong pharmacotherapy and medical/nursing supervision. They also may face the possibility of major surgery and may have some degree of transitory or permanent sensory loss [46].

ALTERATION IN THOUGHT PROCESSES

Central nervous system involvement may produce a variety of problems in patients, ranging from headaches and lethargy (e.g., with pheochromocytoma) to outright psychosis (e.g., Cushing syndrome). Alterations in thought processes and perception pose difficulties not only for patients but for their families and friends as well [47].

ALTERATION IN COMFORT

Some patients with pituitary or adrenal dysfunction will have problems with thermal regulation. For example, patients with pheochromocytoma or hypoglycemia often experience excessive sweating. Those with acromegaly often experience joint pain [46; 47].

DISTURBANCE IN SELF-CONCEPT

Changes in the skin and hair occur in patients with pituitary or adrenal dysfunction and can contribute to disturbances in body image. Increases in skin pigmentation may occur in patients with Addison disease. Ecchymosis develops in patients with Cushing syndrome due to changes in the fragility of the capillaries. Facial flushing is often a sign of pheochromocytoma. Hirsutism is a problem for patients with adrenal tumor or hyperplasia and is an especially bothersome body image issue for women [46; 47].

Patients with these disorders may have an impaired ability to manage self-care or maintain their home environment. They are at increased risk for injury because of weakness, fatigue, and visual disturbances. For example, weakness of the musculoskeletal system is seen in patients with acromegaly and Cushing syndrome. Patients with Cushing syndrome have an increased incidence of fractures. Fatigue often accompanies adrenal insufficiency, hypoglycemia, and acromegaly. Patients with pituitary tumors may have some level of visual impairment [46; 47].

Sexual dysfunction may occur as loss of libido or impotence. Menstrual problems are also relatively common [46; 47].

ALTERATION IN NUTRITION AND BOWEL ELIMINATION

Anorexia and weight loss are common in patients with adrenal insufficiency, pheochromocytoma, and hyperkalemia [46; 47]. Alteration in bowel elimination, specifically diarrhea, may be seen in patients with Addison disease, while constipation can occur in patients with hypercalcemia and pheochromocytoma [46; 47].

ALTERATION IN FLUID VOLUME

Actual or potential fluid volume deficits occur in patients with posterior pituitary disorders. In addition, patients with Cushing syndrome may develop congestive heart failure. Patients with hypercalcemia and hyperaldosteronism may have polydipsia and polyuria [46; 47].

DIABETES INSIPIDUS

Diabetes insipidus is a rare disorder of the posterior pituitary caused by insufficient production or utilization of ADH and characterized by polyuria, polydipsia, and hypernatremia. It is seen in approximately 1 out of 25,000 people and is more common in adults but can develop in individuals of all ages [45]. Risk factors for the development of diabetes insipidus include tumors, trauma, medications, and alcohol consumption [16].

PATHOPHYSIOLOGY

The underlying cause of diabetes insipidus is generally either pituitary (central) or nephrogenic. More rarely, it may develop during pregnancy or related to a mental disorder.

Central Diabetes Insipidus

Approximately 50% of patients have primary central diabetes insipidus, also known as pituitary or primary diabetes insipidus. This form is associated with familial and congenital factors as well as with subclinical encephalitis. Secondary diabetes insipidus is diabetes insipidus arising from a variety of causes, including hypophysectomy, tumors (e.g., metastatic carcinoma of the breast, craniopharyngiomas), trauma (e.g., basilar skull fractures), vascular lesions (e.g., hemorrhage, aneurysm), infection (e.g., syphilis, encephalitis, meningitis), histiocytosis, and granulomatous disease (e.g., sarcoidosis, tuberculosis) [46; 47].

Patients with central diabetes insipidus have an impaired ability to synthesize and secrete vasopressin (ADH) [26]. In most healthy people, ADH is secreted by the pituitary gland when plasma osmolality increases, but this does not occur in those with central diabetes insipidus [48]. Central diabetes insipidus is classified as either complete or partial, depending on the level of ADH present in the body [18].

A variety of factors can lead to central diabetes insipidus, including genetic mutation, medications (e.g., beta-adrenergic agents, ethanol, halothane, phenytoin, opioid antagonists), head (pituitary) trauma, intracranial tumor, infection (e.g., meningitis, encephalitis, tuberculosis), autoimmune disease, disorders of the hypothalamus or pituitary gland, and brain surgery [26; 48]. Rarely, central diabetes insipidus may be the result of snakebite. One genetic cause is Wolfram syndrome, an autosomal dominant disorder associated with diabetes mellitus, diabetes insipidus, optic nerve atrophy, and sensorineural hearing loss [48]. The most common causes are trauma and malignancy.

Lesions and autoimmune disorders can lead to the destruction of vasopressin neurons in the hypothalamus, while surgery and trauma can damage or destroy the vasopressin neurons [49]. It is important to note that the body's ability to synthesize vasopressin is greater than the body's needs, so up to 80% to 90% of the vasopressin neurons in the hypothalamus can be destroyed before diabetes insipidus develops [49].

A transient form of polyuria may develop in patients post-trauma or post-surgery, but it usually resolves within four days [49]. In rare cases, these patients may develop a permanent form of diabetes insipidus [49].

Nephrogenic Diabetes Insipidus

In patients with nephrogenic diabetes insipidus, the kidneys do not respond normally to vasopressin [26]. The underlying etiology of this condition may be genetic/congenital, medication-induced kidney damage (e.g., with amphotericin, cisplatin, clozapine, demeclocycline, furosemide, lithium [most common], methicillin), renal or urinary tract infection, or chronic disease processes (e.g., amyloidosis, chronic renal failure, polycystic kidney disease, sickle cell disease, Sjögren syndrome) [18; 26; 50]. Acquired nephrogenic diabetes insipidus is more common than the hereditary form [50].

The genes associated with the hereditary form of nephrogenic diabetes insipidus prevent the kidneys from responding to ADH [50]. Infants with hereditary nephrogenic diabetes insipidus will develop signs and symptoms of the disease within a few months of birth [50].

Gestational Diabetes Insipidus

Gestational diabetes insipidus is a type of transient diabetes insipidus that develops in 2 to 4 of every 100,000 pregnancies [51]. During pregnancy, ADH production is increased and plays a role in the increased blood volume. At the same time, placental vasopressinase, which metabolizes ADH, is increased [51]. This is more commonly seen in pregnancies with multiple fetuses because of the increased placental mass [18; 51]. In the majority of cases, the patient will have a normal delivery and healthy newborn [51]. After delivery, vasopressinase levels will decrease by approximately 25% each day, reaching undetectable levels at four to six weeks postpartum and resulting in resolution of the disorder [51].

It is important to note that some patients may have undiagnosed diabetes insipidus prior to pregnancy, with symptoms not becoming apparent until after they become pregnant [51]. If the patient has undiagnosed diabetes insipidus discovered during pregnancy, it is classified as central or nephrogenic, depending on the underlying pathophysiology.

Psychogenic Diabetes Insipidus

In rare cases, patients may develop a psychiatric condition involving the consumption of large amounts of fluids [26]. This is not true diabetes insipidus, but it can be life-threatening and has been associated with increased morbidity and mortality. In psychogenic cases, the function of the pituitary gland and kidneys remain intact, and extracellular fluid dilution develops and inhibits ADH secretion, leading to diuresis [52]. The increased fluid intake leads to functional diabetes insipidus [52].

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This condition can be seen in patients with a variety of mental health disorders, including autism, schizophrenia, schizoaffective disorder, and bipolar disorder [53]. Schizophrenia is a common cause, with 11% to 20% of patients with schizophrenia developing psychogenic diabetes insipidus [53].

For some patients, increased fluid intake is a compulsion rather than a response to thirst [53]. Another subset of patients believes that increased water intake is healthy [53]. These individuals typically do not have a mental health disorder but are rather misinformed about the risks of overconsumption of water.

SIGNS AND SYMPTOMS

What are the signs and symptoms of diabetes insipidus?

Patients with diabetes insipidus present with polyuria, nocturia, polydipsia, increased serum osmolality, decreased urine osmolality, and decreased urine specific gravity [16; 26]. Many report extreme thirst, even at night, leading to increased fluid intake at all hours [52]. In addition to drinking throughout the day, patients with diabetes insipidus often have a preference for cold or ice water [18]. An intact thirst drive will often prevent severe dehydration and maintain homeostasis in those affected [48]. In some cases, the thirst mechanism is faulty because of damage to osmoreceptors in the hypothalamus, leading to decreased fluid intake and severe dehydration [49].

Patients with diabetes insipidus will have dilute and light-colored urine. Polyuria will develop regardless of normal contributing factors to urine output, such as fluid intake. Patients may urinate as much as 10–20 L/day [26]. In most cases, the urine will be hypotonic and serum osmolality will increase [16; 26]. In patients with a serum osmolality of 300–330 mOsm/kg, symptoms may not be apparent [49]. Patients with severe dehydration may develop weakness, postural dizziness, confusion, azotemia, hyperglycemia, secondary hyperaldosteronism with hypokalemia, and coma [49]. Under normal circumstances, an increase in serum osmolality would result in a drop in blood pressure and subsequent secretion of ADH [16]. Additionally, when a patient has increased serum osmolality they will often be very thirsty [16]. Thirst will lead to increased fluid intake, which increases fluid in the vasculature and restores fluid balance. However, in patients with diabetes insipidus, this does not occur, further increasing the risk for dehydration and hypovolemic shock [16].

Serum sodium levels will be normal or increased, with hypernatremia typically developing if the patient does not drink enough water to account for the increased urine output [26]. Patients with hypernatremia may present with altered mental status, myoclonus (muscle jerking), seizures, and focal deficits [26]. If untreated, the patient may progress to an altered level of consciousness or death [16].

Infants with congenital nephrogenic diabetes insipidus present with enuresis, poor intake, poor weight gain, poor growth (failure to thrive), irritability, fevers, diarrhea, and vomiting [50]. If a child with this condition develops dehydration on multiple occasions, it can lead to problems with growth and development [50].

As many as 50% of patients with underlying diabetes insipidus will have increased signs and symptoms during pregnancy [51]. Patients with underlying diabetes insipidus do not have increased levels of ADH during pregnancy, so the symptoms of diabetes insipidus may become apparent [51]. Patients are at increased risk for dehydration and hypernatremia if they experience diabetes insipidus during pregnancy [51]. However, during pregnancy, thirst is triggered at lower serum osmolality levels, which can act as a protective factor [51].

Patients with an exacerbation of a mental illness may also increase their fluid intake; this increase is not related to the regulation or maintenance of homeostasis [53]. Patients with psychogenic diabetes insipidus drink more than 3L of fluids per day [52]. In patients with compulsive fluid intake, drinking fluids calms an acute anxiety and the compulsion can be so strong that they will drink from inappropriate and unhealthy water sources (e.g., toilets) [53]. Individuals who compulsively drink fluids may also have comorbid nicotine, alcohol, and/or eating disorders [53]. Patients with psychogenic diabetes insipidus urinate as often as every 30 minutes, and the urine is dilute, with decreased specific gravity and decreased osmolality [52]. These patients may also report fatigue and constipation [52].

Patients with psychogenic diabetes insipidus typically do not drink fluids at night, which can help differentiate it from true cases of diabetes insipidus [53]. Most patients with diabetes insipidus will develop hypernatremia due to the fluid deficit, but patients with psychogenic diabetes insipidus may develop hyponatremia [53]. If hyponatremia develops in these patients, it is important to determine if it is the result of excessive fluid intake or another cause (e.g., medication) [53]. Patients with schizophrenia and diabetes insipidus typically have lower body weight and increased rates of alcohol consumption and smoking compared with patients without diabetes insipidus [53].

DIAGNOSIS

The diagnosis of diabetes insipidus can be a challenge, and misdiagnosis carries the risk for severe complications [35]. Diabetes insipidus is diagnosed by routine screening tests, such as specific gravity of urine, plasma sodium levels, osmolality tests, and water-deprivation and water-loading tests. If serum osmolality is greater than 300 mOsm/kg and urine osmolality is less than 300 mOsm/kg, the diagnosis is likely diabetes insipidus [48]. Diagnosis is confirmed if a deficiency of ADH is demonstrated and the patient's kidneys

are shown to respond normally to ADH. In response to a water-deprivation challenge, patients with diabetes insipidus will demonstrate an inability to increase the specific gravity and osmolality of the urine [54; 55]. Differential diagnosis involves other causes of polyuria. A brain scan, skull x-rays, visual field testing, and full neurologic examination may be indicated to rule out the presence of a tumor.

Differentiation between the types of diabetes insipidus can be a challenge but is essential because treatment will vary based on the type identified [18]. Patients with central diabetes insipidus will respond to vasopressin with decreased urine output and increased urine osmolality [48]. If the patient has nephrogenic diabetes insipidus, there will be no response to the vasopressin [48].

A newer diagnostic tool is copeptin, a surrogate marker for ADH [18]. High basal copeptin levels are accurate in diagnosing nephrogenic diabetes insipidus [18]. The copeptin test can also be used during pregnancy, unlike the water deprivation test [51]. In nonpregnant patients, the copeptin test can be combined with the water deprivation test, which increases diagnostic accuracy of both tests [18]. It can also be combined with the administration of hypertonic saline [18].

Diagnosis of psychogenic diabetes insipidus usually requires a multidisciplinary approach [52]. The care team may include primary care, endocrinologists, nephrologists, and psychologists.

TREATMENT

The treatment plan for patients with diabetes insipidus depends on the type and the associated signs and symptoms.

Central Diabetes Insipidus

What is the most common adverse effect of desmopressin use?

For patients with mild cases of central diabetes insipidus, treatment may be as simple as increasing fluid intake [56]. However, most patients will require ADH replacement therapy. In acute cases, patients are given intravenous or subcutaneous vasopressin [16]. Long-term treatment involves the administration of desmopressin orally, subcutaneously, or intranasally [16]. The most common adverse effect of desmopressin administration is hyponatremia, although fluid retention can also develop [48]. Intranasal desmopressin can result in eye irritation, headaches, dizziness, rhinitis, epistaxis, coughing, and flushing [48]. If diabetes insipidus is caused by pituitary tumor, hypophysectomy may be required [16].

The Society for Endocrinology recommends that for those patients with central diabetes insipidus and normal serum sodium and who require maintenance intravenous fluid therapy, the type and volume administered should be equivalent to the daily requirements appropriate for other patients without central diabetes insipidus. This should be given together with the agreed, prescribed dose of desmopressin.

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6013691. Last accessed August 5, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

For infants with congenital central diabetes insipidus, the preferred treatment is usually thiazide diuretics [48]. Thiazide diuretics work by inhibiting the amount of sodium lost by the kidneys, which can lead to decreased water loss [57]. However, thiazide diuretics can paradoxically decrease urine flow in some [16]. As such, urine output should be closely monitored in these patients.

Nephrogenic Diabetes Insipidus

Poorly managed nephrogenic diabetes insipidus can cause pain, infection, damage to the genitourinary system, and kidney failure [50]. Appropriate treatment will help to prevent these complications. In many cases, treatment is palliative [57]. A low-sodium diet may be prescribed to help decrease the amount of urine made by the kidneys [56]. As with all types of diabetes insipidus, fluid intake should be increased. Hydrochlorothiazide may be given to help manage symptoms and decrease urine output [56]. Patients may also be prescribed indomethacin, a nonsteroidal anti-inflammatory drug that increases urine concentration [57].

Most of the secondary causes of nephrogenic diabetes insipidus can be reversed [18]. If medications are the cause, their use should be reconsidered. If the underlying cause is lithium, it can take months to years for renal function to recover completely [18].

Infants with nephrogenic diabetes insipidus should intermittently be offered water. Patients unable to take in enough fluid to replace urine output may require a feeding tube [57]. School-aged children should have a plan in place with their school to ensure adequate access to a bathroom and to fluids. The school nurse and teachers should be included in the plan.

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Gestational Diabetes Insipidus

Desmopressin is the treatment of choice for gestational diabetes insipidus, with minimal side effects for the patient and fetus [51]. It is important to consider that the dosage should usually be increased as the pregnancy progresses [51]. It is also important to correct any hypernatremia that develops. Patients with diabetes insipidus during pregnancy are at increased risk for recurrence during any future pregnancies [51].

Psychogenic Diabetes Insipidus

For patients with psychogenic diabetes insipidus, behavioral therapy may be beneficial [52]. Medication reconciliation should be done to eliminate agents that impair water excretion, if possible [53]. The treatment of psychogenic diabetes insipidus in children should involve parents/caregivers [52]. In general, adequately addressing the underlying mental health issue will help to resolve the diabetes insipidus. Patients with psychogenic diabetes insipidus due to health misinformation should be given education on appropriate water intake [53].

In some cases, clozapine may be given to help normalize sodium levels and decrease fluid intake [53]. The choice to use this medication should be made carefully, because it is associated with significant side effects [53]. Vasopressin V2 receptor (V2R) antagonists (vaptans) may also be given to normalize serum sodium levels [53]. These medications should be used cautiously and the patient observed closely because they can lead to dehydration and renal damage [53].

Unlike the treatment of other diabetes insipidus types, these patients may be placed on fluid restriction [53]. Weight measurements can help identify patients who will benefit from fluid restriction. If the patient's weight increases, it may be an indicator for fluid restriction. Providing ice chips may also help control fluid intake for patients with psychogenic diabetes insipidus [53].

Surgical Resection

If diabetes insipidus is caused by a pituitary tumor, this must be addressed in order to resolve symptoms. Hypophysectomy can involve the resection of a small tumor or the complete removal of the pituitary gland. The major indications for hypophysectomy are a primary neoplasm of the pituitary gland (adenoma) and the need to halt the growth and spread of other endocrine-dependent malignancies (e.g., breast, ovary, or prostate cancer).

Though historically used, transcranial and transsphenoidal approaches to hypophysectomy are major surgical procedures and have largely been replaced by less invasive options, such as radiation therapy. However, in some cases, surgical resection is required. Because of the risk of damaging the pituitary and the proximity of the optic nerves, optic chiasm, carotid arteries, cavernous sinus, and hypothalamus to the operative area, the surgery involves some risk.

The surgical approach is most commonly transsphenoidal selective tumor resection guided by fluoroscopy [58]. With this type of surgery, the tumor is approached through the sphenoid sinus, avoiding brain tissue. A cut is made along the nasal septum or under the upper lip, near the base of the nose. In addition to the avoidance of brain tissue, this procedure is often associated with fewer side effects and cosmetic effects compared with other surgery types [59]. Drawbacks are that it is more time-consuming and is difficult to perform on large tumors, which often require craniotomy for removal [59]. After a transsphenoidal approach, the patient may report sinus congestion and headaches lasting for one to two weeks postoperatively [59].

Transfrontal craniotomy is indicated when the tumor extends beyond the pituitary fossa and is impinging on the optic chiasm, because this procedure provides the best view of the operative field [60]. With this technique, an opening is made in the skull and the pituitary is accessed through the brain, increasing the risk of brain injury [59]. Complications can include brain damage, stroke, blindness, meningitis, leakage of cerebrospinal fluid, bleeding, diabetes insipidus, and adverse reactions to anesthesia [59].

Transient cerebrospinal fluid leaks can occur following removal of the nasal packings. Most leaks respond to conservative measures aimed at keeping the intracranial pressure low. Lifelong hormonal replacement is necessary if the entire gland is removed [60].

Prior to surgery, patients with diagnosed pituitary tumors should be observed for symptoms and signs of pituitary apoplexy, including severe headache, changes in level of consciousness, diplopia, loss of vision, and shock. Pituitary apoplexy occurs when there is spontaneous hemorrhage into the tumor secondary to rupture of the blood vessels or rapid enlargement of the adenoma with resulting infarction [61].

Postoperative care of patients who have undergone transfrontal craniotomy should also be closely observed for signs/symptoms of [61]:

- Increased intracranial pressure (e.g., hypertension, bradycardia, change in pupil size and reaction to light, changes in level of consciousness, changes in mental or neurologic status)
- Adrenal insufficiency
- Hypothyroidism (which may develop over several weeks)
- Meningitis (e.g., elevated temperature, headache, motor restlessness, photophobia, nuchal rigidity)
- Fluid imbalance (which may indicate transient or permanent diabetes insipidus)

Most patients recover rapidly from transsphenoidal surgery. Patients may report a temporary loss of smell. Oral hygiene is important to keep the oral mucosa moist. Tooth brushing is usually contraindicated because of possible tension on the suture line. Nasal packs are usually removed in 48 to 72 hours [62]. Headache may be a problem in the postoperative period and should be assessed as a possible symptom of meningitis.

A major complication in the postoperative period is hypopituitarism, which may develop into Addisonian crisis and transient or permanent diabetes insipidus. As such, these patients should be watched closely for symptoms and signs of Addisonian crisis (e.g., weakness, lethargy, fever, nausea, hypotension, dizziness) and diabetes insipidus. In the immediate postoperative period, intake and output should be measured and used as a guide to fluid balance; the specific gravity of urine should be checked after each voiding [62].

After total ablation of the pituitary gland, amenorrhea and infertility will result. For men, testosterone may relieve changes in libido and impotence secondary to the surgery. Estrogen may be prescribed for women to relieve atrophy of the vaginal mucosa. Human pituitary gonadotropins have been successful in treating infertility in patients posthypophysectomy, especially women [62].

Postoperative teaching should focus on mediations prescribed, including their purpose and side effects, and the importance of regular follow-up care.

Nursing Interventions

When caring for any patient with diabetes insipidus, close monitoring of the patient's fluid balance is necessary. Nurses should also monitor the patient for dehydration, especially if the patient is confused, unconscious, or otherwise unable to communicate (e.g., infants), because these patients are unable to make their needs known regarding fluid intake. This is best done with daily weights and frequent intake and output monitoring. Patients should be assessed for signs and symptoms of fluid deficit, such as poor skin turgor and dry mucous membranes.

Treatment of diabetes insipidus may include the administration of hypotonic intravenous fluids to increase fluid in the vasculature without increasing serum sodium levels [16]. These patients should be closely monitored for fluid overload [16]. Oral fluids should be encouraged for most patients with diabetes insipidus, except those with psychogenic diabetes insipidus. Nurses should also be vigilant for signs of hypovolemic shock, including hypotension and tachycardia. Any of these potential complications should be addressed promptly.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

What are risk factors for SIADH?

Clinically, SIADH is the opposite of diabetes insipidus, with ADH levels increased as opposed to decreased. It is seen more commonly as an individual ages but can develop at any age [17]. A major risk factor for SIADH is hospitalization, and a high number of SIADH cases develop in hospitalized patients older than 30 years of age [24].

PATHOPHYSIOLOGY

The syndrome of inappropriate antidiuretic hormone, or SIADH, is a condition characterized by autonomous release of ADH without regard to plasma osmolality. The body is unable to dilute the urine appropriately, so fluid is retained, which expands the extracellular fluid compartment and leads to hyponatremia. There may also be sodium loss by the kidneys because of a lack of aldosterone [26].

The cause of SIADH is multifactorial and may include genetic, nervous system, malignancy, pulmonary disease, surgery, and medication factors [16]. Hereditary SIDAH is referred to as nephrogenic SIADH and is the result of a functional mutation in the vasopressin 2 receptors in the kidneys that leads to these receptors staying in an active state [17].

Conditions that increase intracranial pressure can lead to the development of SIADH, including head trauma, stroke, meningitis, lesions, hemorrhage, and hydrocephalus [16; 24; 26]. Vasopressin-secreting tumors of the lung and brain are another potential cause of SIADH; small cell lung cancer is responsible for 70% of the cancer-related causes of SIADH [16; 26; 63]. Pulmonary disease (e.g., cystic fibrosis, chronic obstructive pulmonary disease) can lead to SIADH, although the exact mechanism is not fully understood [16].

Medications associated with SIADH include carbamazepine, oxcarbazepine, chlorpropamide, cyclophosphamide, selective serotonin reuptake inhibitors (SSRIs), antipsychotics, hormones (i.e., vasopressin, desmopressin, and oxytocin), and antihistamines [16; 26]. Of these medications, SSRIs and carbamazepine are the most commonly associated medications [24]. The illicit drug 3,4-methylenedioxy-methamphetamine (MDMA or Ecstasy/E/Molly) induces release of ADH and increases thirst, which causes SIADH and is linked to more severe signs and symptoms [17].

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SIGNS AND SYMPTOMS

SIADH is also associated with serum hypo-osmolality, concentrated urine, increased urine specific gravity, decreased urine output, weakness, lethargy, headache, anorexia, nausea, vomiting, mental status changes, seizures, cerebral edema, cerebral hemorrhage, asterixis, myoclonus, pulmonary edema, and coma [26; 64]. Hyponatremia and decreased extracellular fluid volume lead to a fluid shift into the cells [17]. The osmotic fluid shifts associated with this condition cause cerebral edema and subsequent increased intracranial pressure [26]. When cerebral edema occurs, there is also a loss of potassium and amino acids from brain cells [24].

In patients with chronic SIADH, solute loss is more prominent than water retention [17]. This can lead to the development of hyponatremia in a euvolemic state. In those with SIADH, ADH is secreted even in instances in which the ADH should be decreased, leading to the reabsorption of water, increased fluid in the bloodstream, dilutional hyponatremia, and an increase in the extracellular fluid volume. Dilutional hyponatremia may be manifested by a bounding pulse, increased or normal blood pressure, muscle weakness, headache, personality changes, nausea, diarrhea, convulsions, and coma [16]. The patient with hyponatremia may also develop gait disturbance, memory and cognition problems, dizziness, and an increased risk for falls.

Hyponatremia can be classified as mild (130–134 mEq/L), moderate (125–129 mEq/L), or profound (less than 125 mEq/L) [64]. In patients with mild-to-moderate hyponatremia, the only signs and symptoms may be nausea and malaise [17]. As hyponatremia worsens, patients will develop additional signs and symptoms, and serum sodium levels less than 120 mEq/L can lead to coma and respiratory arrest [17]. The speed at which the hyponatremia develops is correlated with the neurologic manifestations [26]. If the patient develops acute hyponatremic encephalopathy, the condition may be reversible, but it could also lead to permanent deficits [17]. Vomiting is considered an ominous sign [17].

Hyponatremia that develops quickly can lead to cerebral edema and potential brain herniation [63]. When the body has time to adapt to the cerebral edema, it displaces solutes (e.g., potassium) from the brain and into the extracellular spaces [63]. In those with chronic hyponatremia, the body adapts and the condition can be asymptomatic, even with serum sodium levels less than 120 mEq/L [17]. Although these patients may be asymptomatic, nausea and vomiting are seen in approximately one-third of patients [17]. However, rapid drops in sodium levels can result in delirium, confusion, and seizures, even if the drop is minimal [17].

DIAGNOSTIC TESTS

In all patients with suspected SIADH, hypothyroidism and adrenal insufficiency should be ruled out [17]. Patients should be asked about a history of head injury, chronic pain, smoking, weight loss, respiratory symptoms, drug use, and any new symptoms experienced [17]. The physical exam should include an assessment of the patient's volume status, skin turgor, mucous membranes, neurologic status, and vital signs. There is no specific diagnostic tool or test for SIADH, but the Bartter-Schwartz criteria, developed in 1967, are still used today to aid in diagnosis [17]. The following are the criteria for this tool [17]:

- Serum sodium <135 mEq/L
- Serum osmolality <275 mOsm/Kg
- Urine sodium >40 mEq/L
- Urine osmolality >100 mOsm/kg
- Absence of clinical evidence of volume depletion
- Absence of other causes of hyponatremia
- Correction of hyponatremia with fluid restriction

Selection of appropriate diagnostic tests is vital, because it will affect the successful correction of hyponatremia and patient success rates [65]. Although a variety of tests are used, the three cardinal tests assess urine osmolality, plasma osmolality, and urine sodium [65]. Patients with SIADH will have decreased serum sodium, increased urine sodium, decreased serum osmolality, increased urine osmolality, decreased blood urea nitrogen (BUN), and concentrated urine [16; 66]. Urine osmolality will be greater than 50 mOsm/Kg, and often greater than 100 mOsm/kg [64]. Serum ADH will also be increased.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Society of Endocrinology recommends that if clinical assessment indicates that the volume of extracellular fluid is not overtly increased and the urine sodium concentration is >30mmol/L, other causes of hypotonic hyponatremia should be excluded before implicating SIADH.

(https://eje.bioscientifica.com/view/journals/eje/170/3/G1.xml. Last accessed August 5, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

TREATMENT AND NURSING INTERVENTIONS

Treatment of SIADH is directed toward its underlying cause. Approaches will differ for acute and chronic disease [63]. One of the main goals of treatment is the correction of hyponatremia, with a target serum sodium level of more than 130 mEq/L [17]. Even mild cases of hyponatremia are associated

with a variety of safety risks, including gait instability, falls, osteoporosis, bone fractures, attention deficit, and increased mortality [67]. Although these risks are known, many patients admitted to the hospital with SIADH are discharged with continued hyponatremia [65].

In elderly patients a common cause of hyponatremia is chronic SIADH, and these patients may have aging-related safety risks exacerbated by low serum sodium levels [67]. Additionally, chronic SIADH is associated with a decreased bone mass, increasing the risk for fractures [63].

It is important to slowly increase sodium levels, because increasing the concentration too quickly can lead to osmotic demyelination syndrome and poor outcomes [17; 64]. Osmotic demyelination syndrome, also known as central pontine myelinolysis, is seen more often in those treated with hypertonic saline or tolvaptan [65; 68]. Rapid correction of sodium leads to a fluid shift and essentially dehydration of the brain cells, which causes degeneration and demyelination of the myelin [68]. Patients with euvolemic hyponatremia (as opposed to hypervolemic hyponatremia) have an increased risk for rapid sodium correction and the development of osmotic demyelination syndrome [66]. Other risk factors include alcohol use disorder, malnutrition, liver disease, hypokalemia, hyponatremia lasting longer than two days, and decreased serum sodium concentration in conjunction with decreased BUN prior to the start of therapy [66; 68]. With this in mind, these laboratory values should be assessed/considered prior to initiating treatment.

The signs and symptoms associated with osmotic demyelination typically arise in two to six days. The first signs and symptoms include changes in level of consciousness and difficulty or inability to speak [68]. Patients may also develop dysarthria, dysphagia, paraparesis, quadriparesis, spastic quadriplegia, confusion, disorientation, obtundation, pseudobulbar palsy, encephalopathy, and coma [68]. These signs and symptoms are the result of noninflammatory demyelination of the pons [68]. In severe cases, a type of locked-in syndrome can develop, whereby the patient is paralyzed and unable to communicate but fully awake [17]. The effects of this condition may be partially reversible, but in many instances, they are permanent. Prevention involves avoidance of sodium increases of more than 8 mEq/L in 24 hours or 0.5–1 mEq/L per hour [17]. Treatment focuses on addressing symptoms and lowering the serum sodium concentration [68].

Patients with mild-to-moderate SIADH may require fluid restriction, which will lead to the release of aldosterone and the conservation of sodium by the kidneys [17; 24]. The recommended fluid intake is often 600–800 mL per day, which can be a significant challenge for many patients [24; 67]. In fact, the major challenge with fluid restriction is noncompliance, and patient education will play an important role in the patient's plan of care. Fluid restriction should be used cautiously in patients with an increased risk for hypovolemia.

If fluid restriction is unsuccessful or if the patient is acutely ill and symptomatic, hypertonic 3% saline may be administered to help increase serum sodium levels; this is typically reserved for patients with severe hyponatremia [17]. This intervention should be completed cautiously, because when the solution is administered too rapidly the fluid shifts can damage the brain [24]. The initial dose is 100 mL hypertonic 3% saline bolus in the first three to four hours [17]. Serum sodium levels are then checked within two to three hours, and the results will help to guide continued treatment [17]. These patients should be closely monitored for fluid overload. Because of the risks of severe side effects, isotonic saline should only be used in hyponatremic emergencies [65].

In some cases, loop or thiazide diuretics may be ordered to help rid the body of excess fluid. Use of diuretics is often reserved for patients with cardiac symptoms [24]. Patients prescribed diuretics may take oral salt tablets or increase dietary salt intake to decrease the urine concentration [17].

Conivaptan is a vasopressin 2 receptor antagonist that may be ordered for severe cases of hyponatremia [16]. This agent is given intravenously and blocks the action of ADH at the kidney level [16; 66].

Tolvaptan is also a vasopressin 2 receptor antagonist, but it is given orally [17]. This medication is hepatotoxic and should be avoided in patients with pre-existing liver disease. Tolvaptan increases sodium levels at a faster rate than other methods, but it can increase the rates too rapidly, leading to osmotic demyelination syndrome [65]. Potential side effects include dry mouth, polydipsia, liver toxicity, and polyuria [63]. It is also important to consider that this medication can be quite costly.

Other medications that may be used in the treatment of this condition are lithium and demeclocycline [17]. Demeclocycline, an antibiotic that blocks the action of ADH at the tubules of the kidney, is administered at a dose of 600–1,200 mg/day in divided doses [24]. Both of these medications are nephrotoxic and associated with undesirable side effects.

If a secreting tumor is the underlying cause of SIADH, the tumor may need to be removed [16]. The removal and additional treatment of the tumor will depend on a variety of factors, including whether the tumor is malignant or benign. If medications are associated with this condition, they should be stopped, if possible.

Patients with SIADH should be monitored for patent airway. For patients without respiratory symptoms, the head of the bed should be kept low (i.e., 10 degrees or less) [24]. Keeping the head of the bed low will enhance venous return and left atrial filling pressure, leading to a decrease in the release of ADH [24].

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Other nursing interventions include closely monitoring intake and output, daily weight checks, assisting with hemodynamic monitoring, and neurologic checks. Because the most common indicator of SIADH is decreased serum sodium levels, the patient's laboratory values should be monitored closely [24]. Urinary output may be monitored hourly, with notation of color, clarity, and odor. In most patients with SIADH, urinary output will be decreased and urine will appear concentrated. If the patient on fluid restrictions complains of a dry mouth, hard candies, dry mouth lozenges, or moisturizing mouth swabs may be offered. Patients should also be educated on SIADH and treatment, with an emphasis on the importance of adhering to fluid restriction and increased salt intake.

GROWTH HORMONE DEFICIENCY

Growth hormone deficiency is usually the result of genetic mutations or structural defects in the brain and can affect children and adults [69]. Acquired growth hormone deficiency in adults is due to malnutrition, trauma (e.g., traumatic brain injury [TBI], Sheehan syndrome), infection (e.g., meningitis, encephalitis), radiation therapy, brain tumors, or the treatment of acromegaly [69; 70]. In children, malnutrition, neglect, and/or emotional stress can lead to a growth hormone deficiency [16]. Cases in which there is no identifiable cause are classified as idiopathic.

Worldwide, malnutrition is the most common cause of growth hormone deficiency [16]. The prevalence of growth hormone deficiency in children is 1.8 to 2.9 per 10,000 population [71]. Approximately 6,000 new cases of adult-onset growth hormone deficiency are diagnosed each year in the United States [21].

PATHOPHYSIOLOGY

What anatomic abnormalities are associated with congenital growth hormone deficiency?

Congenital growth hormone deficiency can be genetic or the result of structural changes in the brain. It appears to have a hereditary factor; approximately 5% to 30% of children with growth hormone deficiency have a first-degree relative with the disorder [20]. These patients have an increased risk for other pituitary hormone abnormalities and anatomic differences of the pituitary gland [20]. Three abnormalities are commonly seen in patients with congenital growth hormone deficiency: interrupted or thin pituitary stalk; absent or ectopic posterior pituitary gland (i.e., the posterior portion of the pituitary gland is in an abnormal position); and anterior hypoplasia or aplasia of the pituitary gland [20].

Genetic causes of growth hormone deficiency include growth hormone deficiency IA, IB, IIB, and III [69]. Growth hormone deficiency IA is an autosomal recessive disorder in which the fetus develops growth retardation in utero [69]. When these children are initially given growth hormone, they respond appropriately, but over time, they create antibodies to the growth hormone [69]. Growth hormone deficiency IB is an autosomal recessive disorder in which the child has some growth hormone and will respond to the administration of growth hormone [69]. Growth hormone IIB is an autosomal dominant disorder, and III is an x-linked disorder [69]. Both of these genetic disorders are similar to growth hormone deficiency IB [69].

Adult-onset growth hormone deficiency is typically caused by a pituitary tumor or brain trauma, but less common causes include surgery, radiation, infection, and hemorrhage [23; 69]. These contributing factors cause damage to the pituitary gland, leading to a growth hormone deficiency. Deficiency in adults can also be caused by persistent childhood growth hormone deficiency [23]. It is also important to consider that growth hormone secretion decreases with age [22].

Treatment of acromegaly suppresses growth hormone secretion and reduces insulin-like growth factor levels [22]. An estimated 30% to 75% of patients undergoing radiation therapy for acromegaly develop growth hormone deficiency, with increased risk associated with younger age, high doses of radiotherapy, and extended treatment [22]. This effect will be discussed in greater detail later in this course.

TBI has been associated with growth hormone deficiency; more severe TBI increases this risk [70]. However, growth hormone deficiency after a TBI is not well-known and can be easily missed [70]. The reported prevalence is variable due to a multitude of factors, but an estimated 2% to 30% of patients who have experienced a TBI will develop growth hormone deficiency within one month [25]. Further, an estimated 10% to 63.6% of patients in the chronic phase of TBI will develop growth hormone deficiency [25]. The underlying cause in these patients is ischemic injury to the pituitary gland, particularly the pituitary stalk, which is fragile and prone to injury [25]. In the secondary phase of TBI, ischemic, cytotoxic, and inflammatory changes can increase the risk for the development of a growth hormone deficiency [25].

In some cases, malnutrition, neglect, and/or emotional/environmental stress can lead to delayed growth [71]. This may be related to inflammation that develops due to chronic stress; increased inflammation is associated with decreased levels of insulin-like growth factor and growth hormone resistance [71].

Sheehan Syndrome

Sheehan syndrome is a rare postpartum pituitary dysfunction caused by pituitary necrosis [70]. This condition develops after severe hypotension and shock associated with hemorrhage during delivery [70]. A variety of hormonal deficiencies can develop in the patient with Sheehan syndrome, but growth hormone deficiency is one of the most common [72]. Although relatively rare in the United States, this disorder is still seen frequently in developing countries due to the lack of obstetric care [72].

Sheehan syndrome is characterized by hypopituitarism caused by ischemic pituitary necrosis developing after blood loss associated with childbirth [72]. The pituitary gland is susceptible to injury during and immediately after pregnancy because the anterior pituitary gland enlarges during pregnancy but does not develop an increased blood supply [72].

SIGNS AND SYMPTOMS

The signs and symptoms observed with growth hormone deficiency will vary depending on the age of the individual affected.

Children

Growth hormone deficiency can present in a variety of ways in children. Growth retardation, short stature, and delays in maturation are common signs [69]. Children with this deficiency typically have delays in longitudinal bone growth, and untreated growth hormone deficiency results in an average maximal height of 3–4 feet, although body proportions are normal. These children will also display slowed sexual maturation and, in some cases, cognitive deficits. Excess weight and a younger than expected appearance and voice may also be noted [73].

Children with growth hormone deficiency are typically within normal range for size at birth [69]. However, infants born with anatomic changes in the pituitary gland are more likely to be born breech and to have jaundice, hypoxia, and hypoglycemia [20]. As these children grow, they will present with delayed development of the facial bones, slowed tooth eruption, fine hair, poor nail growth, and delayed lengthening of the long bones [69]. If the growth hormone deficiency is associated with malnutrition, changes in the child's weight will often be observed before delayed growth [71]. In infants, the fontanelles may take longer than expected to close [69]. Additional signs and symptoms include poor appetite, decreased strength, decreased muscle development, low energy, poor endurance, sleep difficulties, trouble concentrating, and fatigue [73].

Growth hormone deficiency can impact a child's daily, emotional, and social life [73]. The child may report a decreased ability to play sports or participate in social activities [73]. Short stature may lead to bullying, leaving the child to feel as if he or she is different and socially isolated.

Adults

Adults with a growth hormone deficiency may present with fatigue, weakness, obesity, decreased muscle mass, weakened bones, sexual dysfunction, elevated cholesterol levels, and insulin resistance [16; 69]. Decreased bone turnover and decreased bone mass are common, and adults with a growth hormone deficiency have a risk for fracture that is two to three times higher than their counterparts without growth hormone deficiency [23]. Early onset of deficiency (i.e., in childhood) and cigarette smoking can further increase this risk [23].

These patients are at an increased risk for cardiovascular and neurologic disorders. Growth hormone deficiency is associated with increased abdominal subcutaneous tissue, insulin resistance, hypercoagulability, increased total and low-density lipoprotein (LDL) cholesterol levels, decreased high-density lipoprotein (HDL) cholesterol levels, decreased exercise performance, and atherosclerosis [21]. All of these changes can increase the risk for cardiovascular complications.

As with pediatric patients, growth hormone deficiency can decrease adult patients' quality of life, and treatment has been shown to improve satisfaction with life [21; 22]. These individuals are more likely to be unemployed, on sick leave, or on disability [21]. Patients who develop a growth hormone deficiency after a TBI are more likely to develop depression and report a decreased quality of life [25].

DIAGNOSTIC TESTS

The diagnosis of congenital causes of growth hormone deficiency is often delayed until slow growth is observed in a child [69]. It is common to see initial diagnosis around 5 years of age, when children start school or when puberty is delayed (10 to 13 years of age for girls, 12 to 16 years of age for boys) [69]. Diagnostic tests for a growth hormone deficiency include serum growth hormone levels, growth hormone stimulation test, pituitary MRI, and bone density tests.

The Endocrine Society recommends that the insulin tolerance test and the GHRH-arginine test have sufficient sensitivity and specificity to establish the diagnosis of growth hormone deficiency in adults.

(https://academic.oup.com/jcem/article/96/6/1587/2833853. Last accessed August 5, 2021.)

Strength of Recommendation/Level of Evidence: 1/⊕⊕⊕⊕ (Strong recommendation based on high-quality evidence)

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Although growth hormone levels can be measured, these tests can be unreliable because hormones are not secreted in consistent amounts throughout the day. Additionally, a variety of medications can affect growth hormone levels and interfere with diagnostic testing [32]. As such, a medication review should be conducted to determine if any could interfere with testing. Medications that can affect the results include insulin, estrogen, amphetamines, oral contraception, and corticosteroids; the herbal supplement St. John's wort can also impact findings [33].

A more reliable test is the growth hormone stimulation test, which measures the response of growth hormone to hypoglycemia [16]. Medications that may be used in stimulation testing are clonidine, arginine, and glucagon [20]. In the patient with a growth hormone deficiency, growth hormone levels would not elevate as expected.

An MRI is usually completed to assess for tumors, and a bone density test will provide information about bone strength and possible disorders (e.g., osteopenia, osteoporosis). In patients with congenital growth hormone deficiency, an MRI will help to identify abnormal pituitary anatomy rather than for definitive diagnosis. However, conducting an MRI can be challenging for pediatric patients and may require sedation to remain calm and still for approximately 45 minutes.

Diagnosis of a growth hormone deficiency after TBI can be challenging because many of the signs and symptoms associated with each condition overlap [25]. It is important to consider that increases in the severity of TBI likewise increase the risk of growth hormone deficiency [25]. As such, patients with a severe TBI should be evaluated. In these patients, plasma insulin growth factor is not a useful measure, because it lacks sensitivity and accuracy [25]. Instead, an insulin tolerance test, GHRH levels, and/or glucagon stimulation test should be used [25].

The diagnosis of growth hormone deficiency due to Sheehan syndrome is often delayed, in some instances for many years [72]. This is often because it is overlooked by healthcare professionals, and it should be considered as part of the differential diagnosis in women presenting with suggestive signs and symptoms [72].

TREATMENT AND NURSING INTERVENTIONS

The treatment of growth hormone deficiency is most commonly the administration of synthetic human growth hormone. If hormone replacement is initiated during childhood, the patient will usually reach a normal height in adulthood; even those with short stature can catch up [71; 74]. The goal is to start hormone replacement before the child drops below the third percentile for height [21].

Growth hormone replacement is also appropriate therapy for adults and can lead to increased bone turnover, expanded remodeling space, decreased fracture risk, and over time, increased bone density [23]. It is interesting to note that some research has shown that the positive effect on bone density is more pronounced in men than women [23].

Somatropin, a recombinant growth hormone, may be used for both children and adults with a growth hormone deficiency. This medication increases skeletal growth in children and increases bone density in adults [75]. Somatropin is administered as a subcutaneous injection, usually in the evening to mimic the body's normal rhythm [21]. The onset of action is typically within three months of the initiation of treatment [75]. Starting treatment early will help prevent delayed growth in children. In most cases, somatropin is administered to children when delayed growth is identified, with doses increased when the child is going through puberty and discontinued when skeletal maturation is reached [69]. However, testing should be completed to determine if the patient should continue treatment, as early cessation can lead to negative consequences in adulthood [69]. Adverse effects of somatropin include edema of the hands and feet, hyperglycemia, hypothyroidism, insulin resistance, pancreatitis, pain at the injection site, lipodystrophy, carpal tunnel syndrome, and arthralgia [21; 75]. Lipodystrophy can be prevented by rotating injection sites. Concurrent use of corticosteroids can decrease the effectiveness of somatropin [75].

During somatropin treatment, children should have growth (height and weight) assessed every three to six months [75]. In adolescence, patients' growth and puberty should be monitored every six months [74]. Because this medication has been linked to hypothyroidism, thyroid function should be periodically checked. Somatropin treatment is ineffective in the presence of hypothyroidism, so treatment of the condition is vital [75]. Patients should also be monitored for hyperglycemia, especially patients diagnosed with diabetes. In addition, patients given somatropin after epiphyseal closure should be monitored for signs and symptoms of acromegaly.

Somapacitan, a long-acting human growth hormone analog, was approved for use in adults with growth hormone deficiency in 2020 [76]. This medication is administered as a once-weekly injection [76; 77]. The initial dose is 1.5 mg, but the dose can be increased by 0.5–1.5 mg per week (to a maximum 8 mg per week) every two to four weeks based on clinical response and insulin-like growth factor-1 levels. Potential adverse effects include back pain, joint pain, indigestion, sleep disorders, dizziness, tonsillitis, edema of the extremities, vomiting, adrenal insufficiency, hypertension, increased blood creatinine phosphokinase, weight gain, and anemia [76]. The dose should be reduced if needed for adverse reactions or elevated insulin-like growth factor-1

levels. Somapacitan is contraindicated in patients with malignancy, diabetic retinopathy, and acute critical illness [76; 77]. Discontinuation of therapy should be considered if no apparent benefits are achieved after 12 to 18 months.

Growth hormone replacement therapy should continue over a prolonged period of time, in some cases for the patient's entire life. Patients receiving this treatment should be taught self-administration techniques.

Due to the length of treatment, adherence can be a challenge. Factors that may affect adherence include cost, length of treatment, and decreased understanding of treatment. Transition to adolescence is an important challenge to adherence [74]. Factors that may negatively affect adherence in adolescence include peer group conflict and loss of a sense of control. This is also a period of increased independence during which adolescents may want to take a more central role in managing their own care.

Poor compliance with or delayed therapy can lead to poor growth in children and to increased weight, changes to bone metabolism and density, and changes to cardiac structure and function (e.g., exercise intolerance, bradycardia, dilated cardiomyopathy) in adults [74]. Cognitive/psychological changes associated with poor compliance may include fatigue, sleep disturbance, decreased motivation, decreased self-esteem, and isolation [74].

With adherence in mind, empowering patients is important. For pediatric patient, parents/caregivers and the patient should be educated, offering choices (whenever possible), rewards, and age-appropriate educational materials [74]. Adolescent patients should be asked how they feel about their treatment and allowed to make decisions so they feel a sense of control. Adult patients should be encouraged to attend regular follow-up appointments and be provided with education on the benefits of treatment. Phone alerts or text or e-mail reminders may be beneficial [74]. Because cigarette smoking can increase the risk for fracture in adults with a growth hormone deficiency, patients should be advised to quit smoking and provided with cessation tools and resources.

DISORDERS OF HYPERSOMATOTROPISM

Hypersecretion of somatotropin by the anterior pituitary results in gigantism (before puberty) or acromegaly (after puberty). The crucial factor is the time onset of the disorder. If the hypersecretion of growth hormone occurs during the individual's growth period before the epiphyses of long bones have closed, gigantism will occur. Acromegaly occurs after epiphyseal closure [78; 79].

ACROMEGALY

Acromegaly is a rare condition, with approximately 3 to 14 of every 100,000 people diagnosed [80]. It is seen most commonly in adults between 30 and 40 years of age and more frequently in women than men [16; 24]. Acromegaly is most commonly caused by pituitary tumors (e.g., adenomas, hypothalamic adenomas), but pituitary hyperplasia and genetic mutation are other possible etiologies.

Pathophysiology

What is the cause of most cases of growth hormone hypersecretion?

As noted, acromegaly develops when there is excessive growth hormone after the closure of the growth plates [80]. Bones will specifically increase in width rather than length. Subcutaneous connective tissues, organs, and glands may also enlarge [16].

Patients with acromegaly have increased levels of somatotropin and insulin-like growth factor [22]. Insulin-like growth factor alters the metabolism of blood glucose and lipids, increasing the risk for type 2 diabetes, hypertension, and cardiovascular disease [80]. Patients with acromegaly may also have an abnormal production of glucocorticoids, mineralocorticoids, and gonadotropins [24].

The majority of cases of growth hormone hypersecretion (more than 90%) are caused by benign pituitary adenomas [19]. In the United States, approximately 45 million people are diagnosed with pituitary tumors each year; 25% of these tumors will lead to acromegaly [21]. It is possible for patients to develop a malignant pituitary adenoma that is responsible for acromegaly, but this occurs in less than 1% of cases [24]. The disorder may also be caused by hypothalamic adenomas that increase the amount of GHRH, which, in turn, increases growth hormone levels [19]. Other types of tumors, such as those found in the hypothalamus, pancreas, lungs, chest, or abdomen, can also lead to acromegaly [80]. These tumors can secrete their own growth hormone, although it is more common for them to produce GHRH [80]. Additional possible causes include pituitary hyperplasia and excess GHRH [16].

Acromegaly has been shown to run in families, and several mutated genes have been associated with acromegaly, including *AIP*, *MEN1*, *CDKN1B*, *PRKARIA*, *SDHx*, *GPR101*, and *GNAS* [81]. The most common genetic cause of acromegaly is familial isolated pituitary adenoma syndrome [81]. Less common causes are Carney complex, multiple endocrine neoplasia, and sporadic acromegaly [81]. The exact mechanisms behind familial isolated pituitary adenoma are not fully understood [81].

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Signs and Symptoms

The term acromegaly refers to enlargement of the acral parts—the head, hands, and feet—and these patients often present with enlargement of facial features, excessive growth of the hands and feet, and hypertrophy of soft tissues. The signs and symptoms may develop slowly and not become apparent for years [19].

Patients with acromegaly will have lateral changes to the bones of the face, and the mandible will enlarge and protrude. The space between the patient's teeth may widen and teeth may become displaced, which can lead to problems chewing and eating. The tongue and salivary glands often enlarge, leading to trouble with speaking and eating [16; 21]. In addition to the tongue thickening, the lips and nose also enlarge, impeding breathing and possibly causing sleep apnea [80]. The patient's hair and skin may become thick, coarse, and oily [80]. Approximately 70% of patients with acromegaly report oily skin with increased sweating and unpleasant odor [21]. Some patients describe skin tags that become larger and darker [80]. Joint changes are seen in approximately 70% of patients with acromegaly, and joint pain and osteoarthritis often develop [19]. Growth hormone can increase bone resorption and turnover, increasing the risk for fracture [21].

Patients with pituitary enlargement may complain of headaches and visual disturbances (e.g., diplopia) as a result of the adenoma pushing on the brain and cranial nerves III, IV, and VI [16; 19; 24]. If the tumor presses on other pituitary tissue, it can lead to menstrual changes, erectile dysfunction, thyroid hormone changes, and decreased circulating cortisol [80]. The headaches may be severe and can interfere with the patient's ability to perform daily tasks [21]. If cranial nerve V is involved, the patient may also complain of facial pain [21].

Patients with acromegaly often have a reduced life expectancy because of associated cardiovascular, respiratory, metabolic, and neoplastic conditions [22]. Cardiac disease, including cardiomyopathy, arrhythmias, hypertension, and diastolic overload, is seen in approximately 60% of patients with acromegaly [21]. As many as 50% of patients will develop hypertension [21].

The Endocrine Society suggests evaluating all patients presenting with acromegaly for associated comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnea.

(https://academic.oup.com/jcem/article/99/11/3933/2836347. Last accessed August 5, 2021.)

Strength of Recommendation/Level of Evidence: 2 | ⊕⊕○○ (Weak recommendation based on low-quality evidence)

Diagnosis

The slow progression of acromegaly often delays diagnosis and treatment [80]. This is a problem, because associated health conditions can develop and cause significant damage during this period [80]. The first step is in an accurate physical exam and history. Patients should be observed for any enlargement in facial features; it may be helpful to ask the patient to bring in an older photograph for comparison [24]. Patients should also be asked about any changes that they have noticed, such as an increase in ring or shoe size [16]. An oral exam may be significant for an enlarged tongue; if present, respiratory issues may be a concern. Patients should be asked about any problems chewing, eating, or swallowing or with sleep (e.g., snoring and excessive daytime sleepiness, which may be signs of sleep apnea). When speaking with the patient, assess for and note any difficulty speaking. The nurse should ask the patient about skin changes, sweating, increased body odor, changes to body hair, and skin tags, and an assessment of the patient's integumentary system should be conducted. Patients should be asked about a history of headaches or visual changes, either of which would warrant additional investigation.

Appropriate diagnostic tests include serum insulin-like growth factor, growth hormone levels, serum glucose, MRI, CT scan, bone density scans, and x-rays [24]. Insulin-like growth hormone levels are more than five times greater in patients with acromegaly than in those without the disease [24; 80]. For patients with moderately elevated insulin-like growth factor, an oral glucose tolerance test may also be ordered. This test consists of the patient drinking a sugary liquid, typically containing 75 mg of glucose, and blood samples taken after one and two hours to measure growth hormone [24; 80]. Under normal conditions, growth hormone levels would drop after consumption of glucose, but this will not occur in patients with acromegaly. Theoretically, blood tests of growth hormone levels would also be elevated, but these tests may be unreliable. Elevated blood glucose levels are also common in these patients.

Bone density testing is completed to identify any weakening of the patient's bones, and x-rays are done to identify bone enlargement. An MRI should be conducted to visualize pituitary and any other tumors.

Treatment and Nursing Interventions

The changes associated with acromegaly usually develop over 7 to 10 years, but the best outcomes are associated with early identification and treatment [24]. Left untreated, this condition can result in early mortality and decreased quality of life [80]. However, treatment allows patients with acromegaly a normal life expectancy and quality of life [80].

In most cases, the goal of treatment is to control the size of the underlying tumor, to return growth hormone and insulin-like growth factor levels to normal, and to improve symptoms and manage any associated conditions [80]. It is particularly important to address any cardiovascular complications, as these are the main cause of excess mortality [21].

Surgical Intervention

A common treatment option is the surgical removal of the pituitary adenoma by endoscopic, transnasal, or transsphenoidal route [24]. For 60% of patients, surgery will result in cure, and in many cases, pituitary function may be preserved [24]. However, some may require hypophysectomy, with fluoroscopy-guided removal of the pituitary gland along with any adenoma or other tumors [80].

Possible postoperative complications include bleeding, cerebrospinal fluid leaks, sodium imbalances, fluid imbalances, decreased pituitary hormones, diabetes insipidus, hypopituitarism, and meningitis [24; 80]. Postsurgical nursing interventions include [24]:

- Assess neurologic status
- Assess for pain
- Assess for nasal drainage
- Elevate the head of the bed
- Educate about the avoidance of activities that increase intracranial pressure
- Check blood glucose and serum sodium levels

If present, clear nasal drainage should be checked for glucose to ensure that it is not cerebral spinal fluid [24]. The head of the bed should be elevated to promote drainage and to make breathing easier. Patients should be advised to avoid coughing, straining for a bowel movement, or any other activity that can increase intracranial pressure for up to two months following the procedure. Tooth brushing can cause damage to the surgical incision site and should also be avoided. After the removal of pituitary adenoma, hypoglycemia may develop as growth hormone and insulin-like growth factor levels drop [24]. Approximately 20% of patients have associated pituitary damage and may require replacement of glucocorticoids, gonadotropins, and thyroid hormone [24].

Radiation Therapy

Radiation therapy is another treatment option for patients with acromegaly caused by malignancy. It is typically a second-line option if surgery and/or pharmacotherapy are ineffective [80]. It is important to understand that it can take years for this treatment to improve symptoms [80]. Further, this therapy can impair fertility and approximately 50% of patients will require hormone replacement [80].

Pharmacotherapy

Medications used in the treatment of acromegaly include somatostatin analogs, dopamine agonists, and growth hormone-receptor antagonists [80]. These medications are initiated in patients who do not have remission following surgical removal of adenoma or in patients for whom surgery and/or radiation therapy is contraindicated [24].

Somatostatin analogs (e.g., octreotide, lanreotide) work by slowing the release of growth hormone [80]. In some cases, these medications can effectively reduce the size of the pituitary tumor [80]. Octreotide suppresses growth hormone, insulin, and glucagon and helps to normalize growth hormone and insulin-like growth factor levels in patients with acromegaly [75]. Octreotide is available in short- and long-acting forms [24]. The short-acting form is given as a 100-mg subcutaneous injection three times daily; the long-acting form is given as a 10- to 30-mg intramuscular injection once monthly [24]. Lanreotide is a treatment option for patients with acromegaly who are not candidates for or who have not responded to other treatment options [75]. Lanreotide is given as a 60- to 120-mg subcutaneous injection monthly and is intended to be administered by a healthcare professional [75]. Potential side effects of somatostatin analogs include cramps, bradycardia, orthostatic hypotension, gas, diarrhea, gallstones, and hair loss [80]. Octreotide has been linked to dizziness, bradycardia, and orthostatic hypotension, so pulse and blood pressure should be monitored in these patients prior to and periodically throughout treatment. Patients should be advised to move slowly and not operate vehicles or heavy machinery until they know how they respond to the medication. Octreotide can also increase fertility in ovulating patients, so precautions to prevent pregnancy are necessary [75]. GI side effects are common when starting lanreotide but will often decrease with time [75].

Dopamine agonists (e.g., bromocriptine) are a treatment option to inhibit growth hormone production and tumor growth, but they are not as effective as somatostatin analogs [80]. Growth hormone-receptor antagonists (e.g., bromocriptine) decrease growth hormone levels and may be given orally. Potential side effects include GI upset, nausea, vomiting, headache, postural hypotension, dizziness, nasal congestion, and cold-induced vasospasm [21]. Laboratory changes may also be noted, including increased serum BUN, aspartate transaminase (AST), alanine transaminase (ALT), creatine phosphokinase (CPK), alkaline phosphatase, and uric acid levels [75]. Due to the risk of severe hypotension with the first dose, patients should be supervised when treatment is initiated.

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Growth hormone antagonists (e.g., pegvisomant) are given to lower insulin-like growth factor levels [24]. Pegvisomant is used for patients with acromegaly who do not respond to other therapies and are not candidates for surgery or radiation [75]. It binds to growth hormone receptor sites and blocks the effects of growth hormone, decreasing the manifestations of acromegaly [75]. Pegvisomant is given as a daily subcutaneous injection and takes two weeks to start working [24; 75]. Insulin-like growth factor levels should be checked within four to six weeks of the onset of therapy and every six months thereafter [75]. Side effects include hypertension, peripheral edema, lipohypertrophy, increased glucose tolerance, elevated liver enzymes, increased fertility, dizziness, and back pain [75].

If the therapy regimen includes injectable medications, patients should receive instruction on injection technique and should be able to demonstrate appropriate medication administration. Patients with acromegaly often experience changes to their self-concept [24]. Nurses should inquire about how the condition is affecting their life and help develop a plan of care based on the information obtained from the patient.

GIGANTISM

Gigantism starts in infancy or childhood and is characterized by continuous growth of the body until epiphyseal closure occurs. In adults, it is defined as a height greater than 80 inches; in children, it is defined as three standard deviations above the mean for the child's age as measured on a growth curve. Adults with gigantism may be as tall as 8 feet and weigh more than 300 pounds. Some individuals may develop associated acromegaly features (i.e., very large heads, hands, and feet) in adulthood [79].

Signs and Symptoms

Untreated, patients with gigantism have an increased death rate of approximately twice the normal average for the population. These patients experience progressive debilitation, but treatment can be very effective [78; 79]. They generally present with [78; 79]:

- Extremely large size
- Enlargement of the heart, liver, spleen, kidneys, pancreas, thyroid, parathyroid, adrenals, soft tissues, and/or peripheral nerves
- Increased metabolic rate
- Incomplete or slow development of secondary sex characteristics
- Glucose intolerance with resulting hyperglycemia and diabetes mellitus
- Possible excess secretion of other anterior pituitary hormones (e.g., prolactin, ACTH)

More advanced signs include extreme muscular weakness and crippling osteoarthritis, which may be associated with a severe kyphosis [78; 79].

The symptoms of gigantism are usually attributable to the effects of compression of the adjacent tissues by the pituitary tumor or by metabolic changes. Symptoms include headache, which may be mild to severe and persistent; bitemporal hemianopia and other visual field defects (e.g., changes in color perception, diplopia) due to pressure in the optic chiasm; and seizures and stroke resulting from increased intracranial pressure [78; 79].

Treatment

Because the underlying pathophysiology of gigantism is similar to acromegaly (usually pituitary tumor), the approach to treatment is generally the same. However, because most of these patients are children, patient and family education should be adjusted. Patients should be allowed opportunities to discuss their feelings and ask questions about the changes in their physical appearance. Children with gigantism require information about the reasons for the changes in physical appearance and also what might occur in the future. These patients are often coping with major differences in body size and shape as compared with peers, and this can result in bullying and insecurity [55].

ADDISON DISEASE

Addison disease, also known as primary adrenal insufficiency, develops when the adrenal glands do not produce enough of the hormones cortisol and aldosterone. In the United States, Addison disease affects approximately 4 out of every 100,000 people and is seen more commonly in women than men [27; 37]. This disorder is typically diagnosed among individuals 30 to 50 years of age, but it can develop at any age [37]. Addison disease may be caused by an autoimmune disease, genetics, infections, adrenalectomy, hemorrhage, cancer, amyloidosis, adrenoleukodystrophy (ALD), or medications, or as a side effect of the treatment of Cushing syndrome [45].

PATHOPHYSIOLOGY

What is the most common cause of Addison disease?

As discussed, the adrenal glands are found above each kidney and produce cortisol, a glucocorticoid and aldosterone, a mineralocorticoid. In patients with Addison disease, an abnormality of the adrenal cortex leads to inadequate amounts of circulating cortisol and, in some cases, aldosterone [82].

Autoimmune disease is the most common cause of Addison disease, accounting for approximately 80% to 90% of all cases [37]. Autoimmune Addison disease, also referred to as autoimmune adrenalitis, results in atrophied adrenal glands and an inability to produce hormones in sufficient amounts. Cells destroyed by the inflammatory response are replaced by fibrotic tissue [83]. In these patients, the cells in the adrenal cortex are damaged but the medulla remains intact [83].

Risk for Addison disease is increased in those with a family history of the disease, with heritability accounting for 97% of cases in a Swedish twin study [24]. In addition, other autoimmune conditions have been associated with an increased risk of Addison disease, including vitiligo, type 1 diabetes, and hypothyroidism [45].

Viral, bacterial, or fungal infection or parasitic infestation of the adrenal glands can lead to changes, and childhood infections may predispose a patient to Addison disease [83]. Worldwide, tuberculosis is the most common cause of Addison disease, although this is not routinely seen as a cause in developed countries [45; 83]. Many infections that damage the adrenal glands are opportunistic, meaning they develop in immunocompromised individuals [83]. Serious infections (e.g., sepsis) require that the body be able to rapidly activate glucocorticoid production, which can lead to adrenal failure and, in some instances, adrenal crisis [83]. However, it has been hypothesized that infections highlight or exacerbate existing adrenal insufficiency rather than initiating it [83].

Patient who undergo bilateral adrenalectomy, as may occur with Cushing syndrome treatment, require steroid replacement or they will develop adrenal insufficiency and subsequent adrenal crisis. However, unilateral adrenalectomy rarely causes Addison disease unless the patient experiences severe adrenal stress, in which case the reduced adrenal reserve may be depleted [84]. Conditions that increase the risk for adrenal stress include sepsis, cardiopulmonary disturbance, trauma, and postoperative complications [84].

Hemorrhage (usually in response to infection or trauma) or malignant cells in the adrenal glands can cause damage and negatively affect the glands' ability to secrete cortisol and aldosterone [45]. Amyloidosis is a condition whereby the protein amyloid accumulates and causes damage to the adrenal glands, leading to decreased amounts of cortisol in the body [45]. Medications (e.g., antifungals, general anesthesia) can also lead to the development of Addison disease [37; 45].

Adrenal crisis is a serious complication of Addison disease that can result in death if not identified and treated appropriately. Anything that increases the cortisol needs of the body can lead to this condition. In the patient with Addison disease, the body is unable to increase the amount of circulating cortisol in the body, leading to a cortisol deficit. The decline in cortisol and aldosterone directly affects the liver, stomach, and kidneys [85].

SIGNS AND SYMPTOMS

Addison disease is associated with vague, gradually developing (insidious) symptoms that can make diagnosis a challenge [37]. Signs and symptoms associated with this disorder are due to hormone deficiency, with the majority being attributable to decreased cortisol levels, although aldosterone plays a role as well [82]. In many cases, signs and symptoms do not develop until approximately 90% of the adrenal cortex is destroyed, and in some patients, symptoms are not recognized until adrenal crisis develops [45; 82].

The most common signs and symptoms of Addison disease are chronic fatigue, lethargy, muscle weakness, loss of appetite, weight loss, increased urination, increased thirst, and abdominal pain [37; 45]. Other potential signs and symptoms include nausea, vomiting, diarrhea, hypotension, irritability, depression, joint pain, salt cravings, hypoglycemia, dizziness, reduction in underarm and pubic hair, muscular pain, irregular or no menstruation, decreased libido, darkening of the skin, slowed growth in children, neurologic disturbances, depression, impaired concentration, and hypersensitivity to tastes and smells [37; 86].

Cortisol plays a significant role in glucose metabolism, and decreases in cortisol levels can lead to hypoglycemia. Aldosterone acts on the kidneys to increase water retention and blood volume, and decreases in aldosterone levels can lead to hypotension, tachycardia, and salt cravings [16; 32; 82].

Melanodermia, color changes of the skin, is a potential side effect of Addison disease and most often presents in areas of the body most exposed to sunlight, such as the face, neck, knuckles, elbows, knees, and creases of the palms [24; 86]. Darkening of scars may also be seen [85]. Pigment changes seen with Addison disease are due to the stimulant effect of excess ACTH on the melanocytes to produce melanin [82].

Electrolyte changes (e.g., hyponatremia, hyperkalemia, hypercalcemia) may occur with Addison disease [86]. As such, these patients should be closely monitored and may require supplementation and/or a modified diet. The patient with this disorder may also develop lymphocytosis and anemia [82].

Late symptoms of adrenal insufficiency are hypotension, dizziness, syncope, nausea, vomiting, diarrhea, abdominal pain, joint pain, back pain, muscle cramps, chronic exhaustion, skin changes, and decreased libido [45]. Signs and symptoms of adrenal crisis are hypotension, hypoglycemia, hyponatremia, hyperkalemia, vomiting, diarrhea, weakness, confusion, severe dehydration, severe pain in the lower back and abdomen, GI pain, and loss of consciousness [37; 86]. Patients with later stage Addison disease may present with pale, cold, clammy skin; sweating; rapid, shallow breathing; and severe muscle weakness [45]. Untreated, adrenal crisis can lead to coma and death.

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Patients in adrenal crisis lose large amounts of sodium and water, causing a fluid deficit with resulting hypotension and tachycardia [16]. The patient will often present with hyperkalemia, which can lead to cardiac abnormalities. The decreased cortisol levels in Addison disease will cause decreased glucose output by the liver and decreased digestive enzymes [85].

DIAGNOSTIC TESTS

For most patients with Addison disease, diagnosis will be made around 40 years of age, and it is not uncommon for these patients to see multiple physicians before a diagnosis is made [82]. In cases of primary adrenal insufficiency, diagnosis of Addison disease may be delayed up to one year in as many as half of all cases [86]. Misdiagnosis is also common due to the vague signs and symptoms associated with the condition [82].

As discussed, the diagnostic tests that may be used for suspected Addison disease include ACTH stimulation test, serum cortisol levels, insulin tolerance test, antibody testing, and a CT scan or MRI. Aldosterone, serum cortisol, urine cortisol, blood glucose, and electrolyte levels may also be assessed [16; 45]. In these patients, cortisol, aldosterone, sodium and glucose levels would all be low in persons with Addison disease; potassium will be elevated [45]. If the patient becomes dehydrated, BUN and hematocrit levels should be checked and will likely both be elevated. A complete blood count may be checked to determine if the patient has lymphocytosis or anemia.

After completion of the ACTH stimulation and insulin tolerance tests, an antibody test may be ordered. If the antibody test is positive, diagnosis of autoimmune Addison disease may be made with no further testing [37]. The CT scan or MRI may be helpful to evaluate the adrenal glands and/or pituitary gland. These imaging studies can determine if the glands are small in size or if they are enlarged due to infection, bleeding, or malignancy [37]. If tuberculosis is suspected, testing to rule out tuberculosis should be conducted.

TREATMENT AND NURSING INTERVENTIONS

What class of medications is usually prescribed for the treatment of Addison disease?

When a patient develops Addison disease, glucocorticoids are typically prescribed. Those with autoimmune Addison disease will require lifelong glucocorticoid treatment, and even with steroid replacement, these patients have an increased risk for morbidity, mortality, and decreased quality of life [83].

Hormone replacement should be carefully planned to ensure the best outcome for the patient. Under typical circumstances, two-thirds of the daily dose is given in the morning and one-third in the evening to mimic the natural circadian rhythm of cortisol levels [16]. Increased doses of hormones are required during times of stress, as this will mimic what normally happens in the body; this includes during illness, infection, accident, injury, invasive medical procedures, and strenuous exercise [45]. If the patient is vomiting, IV or intramuscular hydrocortisone may be necessary [27]. Patients should be educated on self-administration of injectable medications.

The most often prescribed corticosteroid for the treatment of Addison disease is hydrocortisone; however, prednisone or dexamethasone may be used [37]. In patients who are deficient in both cortisol and aldosterone, fludrocortisone is the agent of choice [37]. Fludrocortisone aids in the retention of sodium and loss of potassium, and patients taking this medication should be monitored for signs and symptoms of fluid overload. This involves daily weights and assessment of new onset of edema in the lower extremities. Patients who do not make sufficient amounts of aldosterone should be advised to consume high-salt foods, especially if they are craving salt and on hot days.

One side effect of long-term corticosteroid therapy is an increased risk for osteoporosis [37]. As such, calcium and vitamin D supplementation may be necessary, and patients should be educated about incorporating these nutrients into the diet. Corticosteroids can also lead to mood swings and insomnia [45]. Treatment for these side effects is guided by impact on the patient's life and patient preference.

It may also be necessary to restore fluid, electrolyte, and hormone imbalances [24]. The IV fluid typically used for these patients is 5% dextrose in 0.9% sodium chloride to address glucose and sodium imbalances [24]. Electrolyte disturbances are addressed by adding electrolytes to IV fluid, hanging individual bags of specific electrolyte(s), or oral supplementation.

Nursing assessments should include questions about any recent stressors, such as illness, infection, or traumatic events. It is important to inquire regarding the use of steroids or recent surgery, particularly on the adrenal and/or pituitary glands. Identifying associated signs and symptoms (e.g., increased urination, salt cravings) is important. Standard nursing care includes monitoring vital signs, daily weights, intake and output, and laboratory values. Patients who report increased urination should be monitored for dehydration and signs/symptoms of hypovolemia (e.g., hypotension, tachycardia). Understanding that stress can play a role in this disorder, patients should be assessed for coping abilities and educated about stress reduction strategies. It may also be helpful to ask about the patient's support systems. Patients should be encouraged to wear a medical alert bracelet or necklace to help ensure appropriate care, such as the administration of glucocorticoids if the patient is ill or injured and unable to provide a medical history [45].

Adrenal Crisis

When at all possible, it is important to prevent an adrenal crisis. Risk factors for adrenal crisis include GI infection, febrile infection, surgery, strenuous physical activity, discontinuation of glucocorticoids, psychiatric distress, and accidents [86]. If untreated, these patients can go into shock, followed by coma and death [85]. If adrenal crisis is suspected, treatment should be started quickly to restore fluid balance and cortisol levels [16; 87]. Replacement fluids should contain glucose. Cortisol levels are restored with the administration of intravenous glucocorticoids. If IV access is not readily available, glucocorticoids can be given intramuscularly [87]. Glucocorticoids are administered either on an around-the-clock schedule or as a continuous infusion [87]. If necessary, electrolytes should be replaced. For children with adrenal crisis, additional challenges include an increased incidence of hypoglycemia, ensuring weight-based dosing for medications, and difficulty attaining IV access [87].

Patient education is essential for the prevention of adrenal crisis. Patients should be aware of the risk factors in addition to associated signs and symptoms. Specific medication orders should be given for sick/stress days, and an emergency hydrocortisone kit should be available at all times [87].

CUSHING SYNDROME

As discussed, Cushing syndrome is a disorder of excess cortisol, and the effects of this disorder can be seen in nearly every body system [24]. It is most commonly seen in individuals between 20 and 50 years of age and is three times more common in women than men [88]. Cushing syndrome affects 40 to 70 people per 1 million population in the United States [28]. Nearly 90% of cases are among adults, but children can be affected [24].

PATHOPHYSIOLOGY

Cushing syndrome is further classified as iatrogenic (or exogenous), primary, secondary, or ectopic [24]. Iatrogenic Cushing syndrome is the most common form and is the result of long-term glucocorticoid therapy [21]. Both primary and secondary Cushing syndrome develop as a result of endogenous causes (e.g., adrenal tumor). Primary Cushing syndrome is typically caused by adrenal gland malignancy, while secondary Cushing syndrome (also referred to as Cushing disease) is the result of excessive secretion of ACTH by a pituitary tumor, usually an adenoma [24]. Ectopic Cushing syndrome arises from the endogenous production of ACTH by one of at least 25 different extrapituitary malignancies, including carcinoma of the lung and of several organs in the GI tract. Secondary Cushing syndrome is the most common (66%) endogenous type of the disease. When this condition is seen in infants, it is most commonly caused by an adrenal carcinoma [24].

As noted, Cushing syndrome is most commonly caused by long-term, high-dose glucocorticoid (e.g., prednisolone, dexamethasone) therapy, often used for the treatment of chronic conditions, such as asthma and chronic obstructive pulmonary disease (COPD) [21; 28]. Symptoms associated with exogenous Cushing syndrome typically do not develop until the patient has been taking corticosteroids for at least one month [24].

In comparison, endogenous Cushing syndrome is relatively rare, occurring in 2 to 3 out of every 1 million people [41]. Cushing disease (secondary Cushing syndrome) makes up approximately 70% of all endogenous cases [21]. It is important to note that the terms Cushing syndrome and Cushing disease are not synonymous. Cushing syndrome encompasses cortisol changes from a variety of internal (endogenous) or external (exogenous) causes, while Cushing disease is only endogenous disease caused by a pituitary tumor or hyperplasia of the pituitary gland [29; 88].

SIGNS AND SYMPTOMS

What are the signs and symptoms of Cushing syndrome?

A variety of signs and symptoms may be observed in patients with Cushing syndrome, including round ("moon") face; flushed face; weight gain above the collarbone and/or on the back of neck ("buffalo hump"); purple striae on the chest, armpits, and abdomen; acne; excessive facial hair; easy bruising; thin skin; rapid central weight gain; thin extremities; hypertension; skin ulcers; headache; muscle weakness; weak bones; menstrual irregularities; decreased libido; erectile dysfunction; hyperglycemia; emotional disturbances; and slowed growth in children [29; 88; 89]. Visceral fat deposits are one of the most common and often one of the first symptoms [21]. The distribution of fat deposits is different than what is typically seen with obesity [21]. For example, fat deposits are commonly seen on the face and clavicular area, both anterior and posterior; extremities often remain thin unless edema develops [21].

Many of the signs and symptoms associated with this disorder are due to the protein-wasting effect of cortisol [21]. Muscle wasting, thin skin, and striae develop because of the catabolic effect of cortisol on the tissues [16]. Purple/red striae occur then the skin becomes thin and stretched over areas of fat deposits [21]. This sign is most commonly seen on the abdomen, flank, breast, hips, and axillae [21]. The patient's skin may be red and warm to the touch due to inflammatory changes [21]. Patients with Cushing syndrome bruise easily and have fragile skin that is prone to tears. Wound healing is slowed due to the increased cortisol levels and subsequent hyperglycemia [21]. Lower extremity edema may develop and is often due to increased capillary permeability and sodium/fluid retention [21].

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Children and adolescents with Cushing syndrome may present with growth delay or arrest (most common), weight gain/obesity, virilism, hirsutism, delay of secondary sexual development, and muscle weakness [90].

Women with Cushing syndrome may display signs of androgen imbalance, including oligomenorrhea or amenorrhea; infertility; excess hair on the face, neck, chest, abdomen, and thighs; thinning of the hair on the scalp; and polycystic ovary syndrome [16; 28; 90]. In addition to increasing the risk for infertility, Cushing syndrome may also increase the risk for miscarriage, perinatal death, premature birth, intrauterine growth restriction, pre-eclampsia, and eclampsia [21; 58]. Men may experience erectile dysfunction and decreased fertility and libido [28].

The symptoms of Cushing syndrome often overlap significantly with metabolic syndrome [41]. These symptoms include obesity, glucose impairment, insulin resistance, dyslipidemia, and hypertension, all of which may persist after diagnosis and treatment of Cushing syndrome [41]. Patients with Cushing syndrome will have an increased risk for heart attack, cardiac failure, and left ventricular hypertrophy [41]. These persisting conditions can lead to a decreased quality of life and an increased risk morbidity and mortality.

Patients with this condition may also present with emotional, behavioral, and cognitive effects, such as mood changes, increased irritability, anxiety, depression, sleep problems, memory problems, and fatigue [29; 89]. Anxiety and bipolar disorder are the most common psychiatric disorders associated with Cushing syndrome [41]. In children, obsessive compulsive disorder may be seen, as well as a declining school performance [41].

The catabolic effect of cortisol can cause changes to the patient's bones [16]. Up to 40% of patients with Cushing syndrome will develop osteoporosis and 20% of patients with this disorder will develop compression fractures of the spine [21]. Patients may also have a spontaneous rupture of the Achilles tendon [90]. The patient may also develop kyphosis and decreased height. Individuals with Cushing disease are more prone to opportunistic infections [90].

Many patients with Cushing syndrome report a decreased quality of life. Appropriate diagnosis and treatment can lead to improvements in patient health and well-being.

DIAGNOSTIC TESTS

Diagnosis of Cushing syndrome may be difficult because cortisol levels are variable and will fluctuate throughout the day [89]. Misdiagnosis is common because the disease typically progresses slowly, making symptom identification more difficult [88]. Diagnosis is based on a medical history, physical exam, and laboratory tests. Through the diagnostic process, differential diagnosis is a consideration, as several conditions can mimic the syndrome. Patients should be evaluated for recent use of oral, cream, or inhaled steroids, most commonly hydrocortisone, prednisone, and dexamethasone [88]. Estrogen-containing oral contraceptive pills can increase cortisol and glucose levels, making diagnosis a challenge [21]. When testing for Cushing syndrome, estrogen therapy should be discontinued for six weeks prior to the test, if possible [21].

Diagnosis is especially challenging during pregnancy, because cortisol and glucose levels normally increase during this time [21]. Understanding that pregnancy and oral contraceptives may increase blood glucose and cortisol levels, Cushing syndrome testing should utilize saliva or urine samples in these patients [21].

After Cushing syndrome is diagnosed, it is necessary to determine the underlying cause [41]. This can often be accomplished with a dexamethasone-corticotropin-releasing hormone test [28]. This test can distinguish Cushing syndrome from non-Cushing causes of elevated cortisol. Similarly, bilateral inferior petrosal sinus sampling can be used to differentiate pituitary from ectopic Cushing syndrome [41].

CT or MRI is necessary to identify pituitary or adrenal tumors; MRI is the preferred imaging technique for Cushing syndrome [21]. CT scan can be used, but it is less reliable and may lead to false positive findings [21]. Additional laboratory tests may show neutrophilia and decreased lymphocytes and eosinophils [21].

TREATMENT

Surgery

What is the greatest postoperative concern after adrenalectomy?

As noted, the underlying cause of Cushing syndrome will guide the development of a plan of care [58]. If a tumor is the cause, surgery is often necessary. Surgery is effective and is associated with decreased morbidity and mortality [21]. Prior to surgery, hypertension and hyperglycemia should be well-controlled.

The Endocrine Society recommends initial resection of primary lesion(s) underlying Cushing disease, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess.

(https://academic.oup.com/jcem/article/100/8/2807/2836065. Last accessed August 5, 2021.)

Strength of Recommendation/Level of Evidence: 1/⊕⊕⊕⊕ (Strong recommendation based on high-quality evidence)

An adrenalectomy is the surgical removal or resection of one or both of the adrenal glands. In a subtotal adrenalectomy, only part of an adrenal gland is excised [60]. In most cases, the major goal of adrenalectomy is to reduce hyperfunction secondary to a tumor or hyperplasia of the glands (e.g., pheochromocytoma) or in advanced cases of cancer of the breast and prostate.

Laparoscopic adrenalectomy is the criterion standard for benign adrenal conditions [92]. A number of approaches are appropriate given the location of the adrenal glands, including posterior or lateral retroperitoneal, transthoracic, and lateral transperitoneal. Rarely, an open adrenalectomy may be required for large tumors or complicated cases.

Preoperative nursing care focuses on stabilization of the patient. In a patient with Cushing syndrome, this involves controlling hypertension, hyperglycemia, and hypokalemia. However, it also requires attention to decreased resistance to stress and infection, emotional liability, and edema [61]. The environment should be organized to provide maximum physical and emotional rest for the patient. Hyperadrenocorticism has an impact on the emotions, and patients may require additional support and reassurance. Patients should also be monitored for symptoms or signs of infection [61; 92].

Serum electrolytes and urinary glucose and acetone levels will be monitored at regular intervals. Any fluid and electrolyte imbalances should be corrected in the preoperative period, because they may be exacerbated in the postoperative period. Intake, output, and weights should be recorded to assess the degree of fluid retention [54].

In the postoperative period, dietary selections should be centered on controlling hypertension, hyperglycemia, and hypokalemia. If a patient with excessive hyperadrenocorticism has protein depletion (hypoproteinemia), as reflected by a low serum albumin level, he or she may be prescribed a high-protein diet [93].

Corticosteroids are administered preoperatively as well as during surgery to prevent renal insufficiency in the postoperative period. Intravenous fluids are usually started and infused slowly to allow prompt administration of corticosteroids and vasopressors if needed [54].

Patient teaching before adrenalectomy should include [54]:

- What to expect in the immediate postoperative period (i.e., the patient will be in the recovery room or intensive care unit until stable, and vital signs will be monitored regularly)
- The importance of coughing, deep breathing, and early ambulation for prevention of complications
- The nature of the procedure, its indication, and its expected outcome, including the need for lifelong medication and medical supervision

The greatest postoperative concern after adrenalectomy is adrenal insufficiency. Also important are possible hypotension caused by the rapid withdrawal of mineralocorticoids, electrolyte imbalances, and infection resulting from suppression of the immune system. The surgical hazards associated with adrenalectomy include possible injury to the spleen, liver, duodenum, and common bile duct as well as hemorrhage [54].

Postoperative nursing care of the patient following adrenalectomy includes frequent monitoring of the vital signs, including level of consciousness and blood pressure. Blood pressure is monitored every 15 minutes in the immediate postoperative period until it is stabilized. Any unexplained or significant fall in blood pressure should be reported immediately, because it may indicate immediate impending adrenal insufficiency. Complaints of chest pain should also be reported, because they may indicate cardiac involvement or a pulmonary embolism [54].

Patients should also be monitored for signs and symptoms of Addisonian crisis. Early signs of adrenal insufficiency may be subtle, including restlessness, dehydration, and tachycardia. Later signs (preceding overt shock) are increased weakness, hypotension, increased temperature, and vomiting. Addisonian crisis requires prompt intervention with increased corticosteroids, hypertonic saline solution, or both. In rare cases, peripheral vasoconstrictors may be used [54; 55].

If the tumor is removed but the gland remains, the gland may start to function again over time [29]. However, the patient may require supplemental cortisol until function returns [29]. Blood hormone levels should be checked at intervals after surgery to assess glandular function. In instances in which the gland is removed along with the tumor, lifelong cortisol replacement will be necessary. Surgery is often paired with radiation therapy and/or chemotherapy.

Pharmacotherapy

Three medication classes may be used in the treatment of Cushing syndrome: somatostatin analogs (central-acting inhibitors of ACTH), adrenal steroidogenesis inhibitors, and antiglucocorticoids [88]. Pasireotide, a somatostatin analog, is used to reduce ACTH to normal levels [88]. It is administered by subcutaneous or intramuscular injection and is effective in approximately 25% of patients; for others, it may decrease but not fully resolve symptoms [88]. It may take up to two months for the full effects of the agent to be seen [88]. Common side effects associated with pasireotide include fatigue, headache, hypertension, edema, alopecia, hyperglycemia, GI upset, anorexia, and injection-site reactions [75]. Ketoconazole, metyrapone, mitotane, and etomidate are adrenal steroidogenesis inhibitors that are used off-label to decrease cortisol levels in patients with Cushing syndrome [88]. For example, when administered at a dose of 400–1,200 mg per day, the antifungal ketoconazole effectively decreases cortisol produc-

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tion [58]. Mifepristone is a antiglucocorticoid commonly used to treat hypertension associated with Cushing syndrome [88]. A variety of side effects are associated with this medication, including but not limited to anxiety, headache, dizziness, fatigue, edema, hypothyroidism, hypocalcemia, GI upset, dry mouth, uterine bleeding, and dyspnea [75].

Radiation Therapy

Treatment of Cushing syndrome may also include targeted radiation therapy, known as stereotactic radiosurgery [88]. Stereotactic radiosurgery involves the application of x-ray beams to destroy the DNA of abnormal tissue [94]. This can reach small and/or difficult to reach areas in the body while decreasing the risk for damage to healthy tissue [94]. Stereotactic radiosurgery is associated with fewer side effects than other types of radiation therapy [94]. When side effects do develop, they may include fatigue, skin irritation at the site of treatment, hair loss at the site of treatment, headache, and GI upset [94].

Nursing Interventions

Standard nursing care for patients being treated for Cushing syndrome includes a medication review, vital signs, intake and output assessment, laboratory test monitoring, and infection prevention. Nurses should inquire about weight gain, paying particular attention to patient reports of the face becoming more "round" or a "hump on their back." Photographic comparison of the patient's previous appearance may be helpful. To assess for skin thinning, examine the skin on the back of the hand for striae, skin color, and skin texture [21]. The patient's muscle strength should be assessed by asking the patient to rise from sitting without using their hands or arms; the muscle wasting that occurs with Cushing syndrome tends to occur in the lower extremities [90]. The nurse should also examine the patient's extremities, noting if they appear thin or atrophied.

Electrolyte monitoring is important because potassium levels are often low and sodium levels are often high, requiring treatment and monitoring [42]. Patients may be encouraged to consume a high-potassium, low-sodium, and high-protein diet [16]. Patient education should include dietary recommendations and the importance of the various nutrients.

Patients with suspected Cushing syndrome should be asked about the use of steroids [90]. If Cushing syndrome is caused by long-term glucocorticoid use, the dose is usually decreased slowly over an extended period of time [28]. The nurse should also provide education to the patient about any medications and/or treatment ordered.

PRIMARY ALDOSTERONISM

Primary aldosteronism, also known as Conn syndrome or hyperaldosteronism, is a condition caused by excessive production of aldosterone by the adrenal cortex. It is characterized by hypertension, excessive urinary loss of potassium, and retention of sodium. Primary aldosteronism is thought to be the underlying cause in 1% to 2% of patients with diagnosed hypertension.

Primary aldosteronism originates from one of three sources: single adrenocortical tumor (generally a benign adenoma), bilateral hyperplasia of the adrenal cortices, or tumor of the juxtaglomerular cells of the kidney (which produce renin autonomously). A secondary form of aldosteronism occurs when increased renal secretion of renin leads to the increased production of aldosterone. The increase renin secretion results from other pathologic processes in the body, such as heart failure or cirrhosis. The production of aldosterone it triggers in turn initiates a cycle of pathologic changes, resulting in increased fluid retention, further compromising cardiac and hepatic function [95; 96].

SIGNS AND SYMPTOMS

What are the major clinical manifestations of primary aldosteronism?

The major clinical manifestations of primary aldosteronism are hypertension, excessive urinary loss of potassium resulting in hypokalemia, and retention of sodium (hypernatremia). The hypertension is usually a moderate elevation in diastolic blood pressure. Patients may complain of headaches, and on physical examination, early hypertensive retinopathy and cardiomegaly may be noted [95; 96].

Symptoms of hypokalemia range from mild fatigue to profound weakness. Patients may complain of paresthesia, loss of stamina, muscular weakness, and intermittent periods of paralysis. If hypokalemia alkalosis occurs, resulting in tetany, physical examination may elicit positive Trousseau and Chvostek signs [95; 96].

Because of the increased reabsorption of sodium and water, hypernatremia and hypervolemia occur. Generally, edema is not present. The hematocrit may appear abnormally low as a result of the hemodilution. In addition to these major clinical signs, the patient with primary aldosteronism may also have severe polydipsia, polyuria, and nocturia resulting from the renal tubules' inability to respond appropriately to ADH [95; 96].

Primary aldosteronism should be suspected in all patients with hypertension, particularly the young. Findings of comorbid hypertension, hypokalemia (potassium level less than 3.5 mEq/L), and excessive mineralocorticoid production (increased serum aldosterone levels) suggest the diagnosis. These findings become more significant if an excessive excretion of urinary potassium is found along with hypernatremia and decreased excretion of urinary sodium [95; 96].

DIAGNOSIS

For the diagnosis of primary aldosteronism, a spironolactone test may be used in conjunction with assessment of serum potassium levels. Spironolactone is an aldosterone antagonist and, when given orally for three to four days, will stop the urinary excretion of potassium and restore serum levels to normal. Serum potassium levels have been shown to drop again five to seven days after the drug is halted [95; 96].

To identify and localize an aldosterone-producing adenoma, various techniques may be used. Noninvasive procedures such as CT, MRI, and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET)/CT are the most commonly used imaging studies to assess potential adrenal masses. Invasive procedures, such as arteriography and retrograde adrenal venography, are rarely used for this purpose [95; 96].

TREATMENT

The two main approaches to the treatment of primary aldosteronism are surgery and pharmacotherapy. Surgery is indicated when there is a unilateral aldosterone-producing tumor. In cases of hyperplasia, a subtotal or total adrenalectomy may be performed. Postoperatively, the return of normal aldosterone secretion by the remaining adrenal tissue may take several months. Following resection of the tumor, blood pressure will return to normal in most patients, but in one-third it may be lowered only slightly [97; 98].

If surgery is not possible or declined by the patient, mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone) and lifestyle changes may be necessary to help control symptoms [99; 100]. Possible side effects of these medications include gynecomastia, hyperkalemia, and hyperglycemia. Lifestyle changes, including weight loss, exercise, and low-sodium diet, and smoking cessation, will also be necessary.

In patients with primary aldosteronism due to bilateral adrenal disease, the Endocrine Society recommends medical treatment with a mineralocorticoid receptor antagonist (e.g., spironolactone).

(https://academic.oup.com/jcem/article/101/5/1889/2804729. Last accessed August 5, 2021.)

Strength of Recommendation/Level of Evidence: 1 | ⊕⊕○○ (Strong recommendation based on low-quality evidence)

Nursing Interventions

The nursing care of patients with primary aldosteronism should include daily weights and measurement of intake and output to assess the degree of fluid retention and loss, as well as frequent assessment of blood pressure, pulse, and respiratory rate. Symptoms and signs of increased blood pressure (e.g., headaches, changes in visual acuity, hypertensive retinal changes) should also be noted. Patients should also be observed for symptoms and signs of cardiac decompensation and congestive heart failure (e.g., increasing shortness of breath, jugular venous distention, rales at lung bases, orthopnea, and paroxysmal nocturnal dyspnea), and irregularities in heart rate and rhythm [97; 98].

Symptoms and signs of hypokalemia, muscle weakness, cramping, fatigue, and skin breakdown should also be noted. Patients should be assessed for paresthesia and tetany. It is vital that these individuals take adequate rest. The recommended diet is low in sodium and high in protein and potassium. Calories may be restricted if weight reduction is desired [97; 98].

Patients with primary aldosteronism should receive instruction on the nature of the disorder (e.g., pathophysiology, symptoms and signs, prognosis) and the goals of the treatment plan. If pharmacotherapy is indicated, patients should be familiar with its purpose, action, dosage, administration, and side effects. Patient teaching on diet, physical activity, and regular medical follow-up should also be provided. If surgery is done, patients should be aware of the time frame for resumption of adrenal function, the potential need for postsurgical medication therapy, and signs of surgical complications [97; 98].

Patients who are able should take and record their blood pressure and pulse regularly. Nurses can provide instruction on how to interpret the findings and when to report issues. If patients are unable to self-monitor, a caregiver or family member may be engaged in the capacity [97; 98].

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PHEOCHROMOCYTOMA

Pheochromocytomas are tumors that arise from chromaffin cells in the adrenal medulla. While tumors originate in the adrenal medulla, they may rarely develop in the sympathetic ganglia of the abdomen, bladder, or chest; these are referred to as extra-adrenal pheochromocytomas or catecholamine-secreting paragangliomas. Pheochromocytomas characteristically produce both catecholamines (epinephrine and norepinephrine), although some tumors may release only one of the catecholamines. Hypersecretion of epinephrine elevates blood pressure by increasing the strength of contractions of the heart and increasing cardiac output. Norepinephrine causes arteriolar vasoconstriction, increasing peripheral vascular resistance to blood flow. Both of these effects result in marked elevation of both diastolic and systolic blood pressure, which is characteristic of pheochromocytoma [101; 102].

Pheochromocytomas are thought to occur more often than clinically recognized and are often diagnosed due to incidental findings when investigating other unrelated issues. Pheochromocytomas are also often asymptomatic or vaguely symptomatic for some time. Tumors that produce primarily epinephrine are typically associated with profuse diaphoresis, palpitations, tremors, anxiety, heat intolerance, and pallor followed by flushing. Tumors that produce primarily norepinephrine are associated with fewer symptoms; when symptoms are present, they are similar to those of essential hypertension [101; 102].

Most (70%) pheochromocytomas are benign, unilateral adrenal tumors; however, 10% are benign bilateral or multiple, 10% are extra-adrenal, and 10% are malignant. Men and women are equally affected, and the peak incidence is in the fourth and fifth decades of life, although they can occur at any age. Pheochromocytomas can also be found in association with certain familial neurofibromatosis disorders (e.g., neurofibromatosis, hemangioblastoma), hyperparathyroidism, and thyroid medullary carcinoma [101; 102].

SIGNS AND SYMPTOMS

Both epinephrine- and norepinephrine-producing tumors may secrete catecholamines paroxysmally, episodically, or continuously. The most severe symptoms are usually seen in patients with paroxysmally functioning tumors because of the rapid and marked changes in serum catecholamine levels. About 40% of patients with pheochromocytoma have paroxysmal hypertension, whereas the remainder experience either sustained or labile elevations in blood pressure [102].

Paroxysmal attacks vary in frequency, severity, and duration. Both the onset and resolution tend to be abrupt, with the average attack lasting a few minutes to a few hours. In many patients, these attacks may occur without warning, but others may be able to identify a prodrome of dermal paresthesia and increasing anxiety. Paroxysmal attacks may be precipitated by emotional changes (e.g., laughing, sexual activity, pain), postural changes (especially flexion or bending of the body), and/or physical exertion. Attacks may increase in frequency and duration over time and can result in pulmonary edema, cerebral hemorrhage, or ventricular fibrillation [102].

Symptoms of pheochromocytoma include headache, diaphoresis, and intense palpitations. The patient may also complain of extreme anxiety, tinnitus, excessive weakness, tremor, blurred vision, vertigo, dyspnea, and angina. After the attack, the patient may report a feeling of extreme weakness and exhaustion [97; 103; 104].

Signs of pheochromocytoma include marked elevation of the diastolic and systolic blood pressure (which may rise as high as 200 to 300/150 mm Hg), often with excessive diaphoresis, anxiety, dilation of the pupils, and tachycardia. Orthostatic hypotension and hypertensive retinopathy may occur in patients with persistently functioning tumors. Hyperglycemia and glycosuria are also frequently associated with pheochromocytoma because catecholamines can inhibit insulin production [97; 103; 104].

DIAGNOSIS

Pheochromocytoma should be suspected in patients with hypertension who have symptoms and signs of sympathetic hyperactivity, although only an estimated 0.2% of hypertension is related to pheochromocytoma. Diagnosis of pheochromocytoma is based on the presence of symptoms, laboratory confirmation, and imaging modalities. Biochemical testing of the serum and/or urine will reflect continuous production of catecholamines and their metabolites (metanephrines) [105]. In the past, pharmacologic tests (e.g., histamine test, phentolamine-blocking test) were used, but these have largely been replaced by more reliable and safer urinary assays [99].

After excessive catecholamine secretion has been determined, imaging studies are done to confirm the diagnosis and localize the tumor [97; 104]. PET is the preferred approach, coupled with CT. The American College of Radiology recommends FDG-PET/CT scan to detect metastatic disease [106].

TREATMENT

What interventions should be done to prevent perioperative cardiovascular complications in patients with hormonally functional pheochromocytoma?

The definitive treatment of pheochromocytoma is surgical excision of the tumor. In the 10% of patients who are not surgical candidates (because of malignant pheochromocytoma with metastases or serious medical problems), control of symptoms is attempted with cytoreductive techniques, radiopharmaceuticals, chemotherapy, radiotherapy, and experimental therapies.

Surgical resection of a pheochromocytoma is considered high-risk due to the potential impact on heart rate and blood pressure. The Endocrine Society recommends that all patients with hormonally functional pheochromocytoma undergo preoperative blockade to prevent perioperative cardiovascular complications. The recommended preoperative treatment of choice is alpha-adrenergic receptor blockers [107]. This treatment should continue for 7 to 14 days before surgery. During this period, patients should also be instructed to adhere to a high-sodium diet and to increase fluid intake. Adjustments should be made prior to surgery in response to blood pressure, heart rate, and blood glucose level monitoring.

The usual operative approach is minimally invasive (laparoscopic) adrenalectomy. Open resection is reserved for large (i.e., >6 cm) or invasive pheochromocytomas to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence [107]. Partial adrenalectomy may be appropriate for selected patients.

Because of the possibility of extreme fluctuations in the blood pressure in the immediate postoperative period, blood pressure should be monitored every 15 minutes until stabilized; the time to stabilization may be extended in patients with pheochromocytoma. Nurses should be alert for sudden elevation in blood pressure in the early postoperative period, which may reflect a release of epinephrine and norepinephrine from the tumor as it was being excised. An alpha-adrenergic blocking agent may be used intravenously if the blood pressure rises excessively [60].

Severe hypotension may also develop postoperatively and can lead to shock. Metaraminol or norepinephrine, usually administered via IV infusion, may be used to help stabilize the patient. The dosage and flow rate will depend on accurate blood pressure measurements [60]. All patients who have undergone resection of a pheochromocytoma should be advised to change positions slowly to avoid orthostatic hypotension.

Discharge planning should stress the need for lifelong medical supervision. Following successful resection, patients should undergo regular follow-up, including measuring plasma or urine levels of metanephrines, to diagnose persistent (recurrent or metastatic) disease. Pheochromocytomas recur in 10% to 13% of cases [55].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients who have undergone treatment for pheochromocytoma, the Endocrine Society suggests lifelong annual biochemical testing to assess for recurrent or metastatic disease.

(https://academic.oup.com/jcem/article/99/6/1915/2537399. Last accessed August 5, 2021.)

Strength of Recommendation/Level of Evidence: 2 | ⊕⊕○○ (Weak recommendation based on low-quality evidence)

PSYCHOSOCIAL/LIFESTYLE INFLUENCES AND EFFECTS

The pituitary and adrenal glands have far-reaching effects on both physiologic and psychological function, and dysfunction can contribute to major developmental and psychosocial crises. To provide comprehensive patient care, nurses should be aware of these potential crises and their manifestations [78; 79].

Patients with pituitary and/or adrenal dysfunction may have to face the reality of coping with chronic illness or an acute life-threatening situation. Anger, fear, guilt, and denial are common initial reactions. Individual responses to this challenge vary according to the patient's past experiences, attitudes toward health and illness, coping patterns, and support system strength. It is not unusual to find patients with several years' history of a disease still working through their anger and denial. In pediatric cases, parents' feelings of guilt and denial should also be considered as part of a holistic plan of care [78; 79].

In many patients, lifestyle changes are necessary to manage the disease, reduce symptoms, and perform activities of daily living and tolerate stress. However, these changes are often reminders to the patient and family that the illness is serious and that their lives will be affected [78; 79].

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SELF-CONCEPT AND SELF-ESTEEM

Patients with pituitary or adrenal dysfunction are often confronted with a change in self-concept and a loss of self-esteem arising from changes in body image, decreased functional abilities, sexual dysfunction, loss of autonomy, and limitations in the decision-making processes. Changes in self-concept and loss of self-esteem can interfere with the patient's ability to adhere with the treatment plan and accept the diagnosis and its implications. For example, patients with Cushing syndrome will often require time and support to adjust to the cosmetic implications of the "moon" face, upper back/neck fat deposits, and truncal obesity associated with that disorder. Some conditions will also affect patients' ability to participate in activities as they once had or wish to. Individuals with Addison disease are required to take steps to avoid stressful situations. These pathophysiologic changes affect the patient's ability to function in normal situations, causing further stress and anxiety [78; 79].

Certain disorders, including pituitary tumor and dysfunction of the adrenal cortex and medulla, cause emotional liability and personality changes. This presents serious concerns for the patient, who often feels out of control or unrecognizable. The nurse can help both the patient and family to understand the relationship between the physiologic condition problem and the psychological changes [78; 79].

SEXUAL EXPRESSION AND REPRODUCTION

How does hypercortisolism affect sexual function?

Often in disorders affecting the creation of the adrenocortical sex hormones, changes in libido and sexual potency concern patients and their sexual partner. Sensitive intervention by the nurse may relieve anxiety in the couple [79]. Unfortunately, sexual dysfunction is rarely addressed in the treatment plan for these patients. Research indicates that different domains of sexual health are affected by different disease processes, particularly in women. Specifically, hypercortisolism is associated with impaired lubrication, orgasm, sexual arousal, and satisfaction, while hyperprolactinemia and hypoandrogenism are associated with decreased sexual desire and arousal [108]. Treatment of the underlying condition may help, but if sexual dysfunction persists, it should be addressed by pharmacotherapy, adaptive practices, and psychotherapy. It is important to remember that pharmacotherapy cannot address important psychosocial factors of performance anxiety, poor self-confidence, partner sexual dysfunction, relationship conflict or poor communication, sexual factors in the relationship (e.g., sexual scripts, sexual satisfaction), and contextual factors (e.g., life stressors) [109]. Even when sexual dysfunction is primarily physiologic, virtually all patients experience negative psychologic and interpersonal effects. These include interpersonal conflict, depression, performance anxiety, and avoidance of sex.

OCCUPATIONAL AND ECONOMIC FACTORS

Occupational implications of pituitary/adrenal disorders include the possible need to change occupations or limitations in one's ability to work because of a physical disability. Patients with visual loss or changes in mentation often must make significant occupational adjustments. Patients may require adaptive equipment or may move to a different area to be closer to a source of health care or to access a special living environment. Economic factors may include the necessity for lifelong mediations and medical supervision along with the increasing costs of diagnostic tests and hospitalizations [101; 102].

DIETARY FACTORS

The adjustment to new dietary requirements is a major challenge for patients with pituitary/adrenal disease. Patients who previously gave little thought to nutrition or balanced meals are often introduced into a life of fluid restrictions, special diets, and dietary supplements. These changes add extra strain to an already stressful situation and can also be an economic burden. Nurses should acknowledge the importance of dietary challenges and understand how they affect the patient and family, with particular consideration of how food features in the patient's culture. Patient teaching should include an exploration of dietary customs and how changes will be linked to improved health and quality of life [101; 102].

CULTURAL CONSIDERATIONS

As society becomes increasingly diverse, nurses are encountering a wide variety of cultural values and perceptions that influence health behavior in individuals and families. Because culture can have a strong influence on a patient's response to nursing interventions, nurses should be continually aware of these influences.

Cultural competence means being sensitive to differences in the values and beliefs that are shared by the members of an ethnic, cultural, racial, religious, or lifestyle preference of a group. Components of effective transcultural nursing include communication style, use of personal space, eye contact, and understanding of biologic variations. It is important to keep in mind, however, that there can be great variation among individuals within cultures. Therefore, stereotyping and making assumptions about an individual patient's beliefs based solely upon ethnic identification should be avoided.

In most cases, it is not necessary to develop a thorough understanding of each and every culture encountered in diverse healthcare settings. However, a certain degree of cultural competence can and should be developed. The first step in doing this is to recognize that cultural differences do exist. How these variations impact self-management can be explored in the needs assessment. This may include a sensitive exploration of the person's healthcare practices and the role of family members. Other culturally impacted

areas may include beliefs about illness, diet, the role of the patient in self-care, gender roles, religious rituals, and communication styles.

Dietary preferences, meal preparation practices, and the symbolism of food represent an especially important area. When giving diet instructions, efforts should be made to consider the food preferences of the cultural group.

Cultural competence includes recognizing that cultural healthcare practices may differ from one's own beliefs about how an illness should be treated. Furthermore, cultural influences may not always be consistent with healthcare recommendations. This may be especially true for diseases that require significant behavioral adaptations. Americanized versions of traditional foods are high in salt, fat, and calories and are not recommended for people with restricted diets. Therefore, patients may experience a conflict between cultural values and those of the mainstream healthcare system.

CASE STUDIES

ACUTE ADRENAL INSUFFICIENCY (ADDISON DISEASE)

Present Illness

Patient A, a man 50 years of age, is admitted for diagnosis and initial management of suspected adrenal hypofunction with acute adrenal insufficiency. For the past five years, Patient A has been under considerable stress managing his failing contracting business. Initially, he dismissed his complaints of fatigue and weakness as job-related. Lately, the symptoms have been difficult to ignore and associated with anorexia, nausea, and vomiting. He has lost 30 pounds over the past three months without dieting. He complains of frequently feeling cold and has had two syncopal attacks in the month prior to admission. He reports that although he has spent essentially all this time indoors at the office, his skin has become as dark as his employees who work outdoors.

On the morning of admission, he did not wake at his usual early hour and told his wife that he felt gravely ill. His wife called the family physician, who instructed her to take Patient A to the emergency department. After evaluation in the emergency department, Patient A is admitted to the critical care unit (CCU).

Medical History

A medical history is obtained from Patient A's wife. She states that the patient has no allergies to medications but was very allergic to ragweed when they were first married. During the first 10 years of their marriage, Patient A had frequent asthma attacks requiring treatment with epinephrine injections. The asthma attacks diminished in frequency during his middle years, and his wife cannot remember when he last had an attack.

Patient A also has a history of coccidioidomycosis, which was active for several years late in adolescence and in early adulthood. Mrs. A has no recollection of being told of changes in the patient's routine chest x-rays for some time. Ten years previously, Patient A was diagnosed with hypertension, but his blood pressure has been well-controlled with daily exercise and dietary changes.

Patient A has been married to his wife for 35 years and has three grown children who live out of state. His contracting business had been successful until five years ago, when a decrease in housing starts resulted in a decline in business and increased financial stress.

Assessment and Diagnosis

Upon admittance to the CCU, a full physical exam is conducted (***Table 2***). A chest x-ray is done and shows normal lung fields and a smaller than expected heart. Several laboratory tests are ordered, with the following results:

- Serum chemistry results:
  - Sodium: 125 mEq/L
  - Potassium: 6.2 mEq/L
  - Chloride: 89 mEq/L
  - Carbon dioxide (CO_2): 19 mmol/L
  - Blood glucose: 45 mg/dL
  - BUN: 37 mg/dL
- Hematocrit: 50%
- White blood count: 3.5 x 10^9/L

Based on the results of the assessment, Patient A is diagnosed with possible acute adrenal insufficiency and possible Addison disease.

Management

Shortly after arriving in the CCU, Patient A vomits a large amount of bile-colored gastric contents and then develops coma and shock. His blood pressure is 60/10 mm Hg, his heart rate is 50 beats per minute, and his respiratory rate is 8 breaths per minute and gasping. He is quickly resuscitated with rapid IV infusion of normal saline, hydrocortisone sodium succinate (100 mg IV), tracheal intubation, and artificial ventilation. A double lumen nasogastric tube is inserted and connected to low constant suction. An indwelling urinary catheter is inserted and connected to a urine meter. Patient A's condition stabilizes as he becomes alert and orientated, has adequate spontaneous ventilation, and maintains adequate cardiac output and blood pressure. Efforts are made to confirm the diagnosis of Addison disease.

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PATIENT A'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	A thin, well-tanned man who seemed mildly confused Height: 6 feet 2 inches (188 cm) Weight: 190 pounds (86 kg)
Head and eyes	Normocephalic Numerous gray-brown freckles on forehead Pupils equal (4 mm), round, reactive to light and accommodation Normal fundoscopic exam Extraocular muscles full Nasal turbinates slightly reddened, with clear exudate Brown freckles on oral mucosa Pharynx clear
Ears	External ear canals clear Tympanic membranes clear and retracted
Neck	Supple, without masses or thyromegaly Nonpalpable cervical lymph nodes
Chest	Symmetrical excursion Areolas darkly pigmented Lungs clear to percussion and auscultation
Abdomen	Flat with active bowel sounds in all quadrants Normally unexposed skin appears tanned Soft, nontender, and without organomegaly or masses
Extremities	Pulses present, equal, and faint. Normal hair distribution
Genitourinary system	Within normal limits
Neurologic status	Oriented to person, place, and time but very slow to answer questions Cranial nerves II–XII grossly intact Deep tendon reflexes 1+ and symmetrical Bilateral plantar flexor responses
Cardiovascular system	Cardiac rhythm sinus bradycardia without ectopy Point of maximal impulse at sixth intercostal space 1 inch left of midclavicular line Heart sounds quiet with normal S1 and S2, without gallops, rubs, or murmurs
Vital Signs	
Blood pressure	100/60 mm Hg
Temperature	96.5° F
Heart rate	58 bpm
Respiratory rate	12 breaths per minute
Source: Author	*Table 2*

The physician orders diagnostic tests of adrenal, thyroid, and pituitary function. Results of the 24-hour urine collection assessed for 17-ketosteroids and 17-hydroxycorticosteroids indicates that adrenal secretion of cortisol, corticosterone, cortisone, and 11-hydroxycorticosternone is inadequate. The result of the plasma cortisol response to ACTH test confirms the diagnosis of Addison disease. The latest results of tests of thyroid and pituitary function are within normal limits.

Patient A is prescribed fludrocortisone acetate (0.1 mg daily) and hydrocortisone (20 mg daily) as replacement therapy. He responds well and is transferred out of the CCU four days after admission.

Study Questions

Consider the information that has been presented in this course regarding adrenal insufficiency and Addison disease.

1. What fluid and electrolyte imbalances are usually associated with adrenal insufficiency? How does the pathophysiology of adrenal insufficiently create these imbalances?
2. What are the expected results of the plasma cortisol response to ACTH test and 24-hour urine collection in adrenal insufficiency? How are the tests conducted?
3. What risks will subsequent critical illness pose for Patient A?
4. What nursing observation would be important in a critically ill patient with a history of adrenal insufficiency?
5. How might chronic adrenal insufficiency be managed during a critical illness?
6. What are the symptoms and signs of hypoadrenalism?
7. What is the most common type of hypoadrenalism?
8. What are the other causes of hypoadrenalism?
9. How is hypoadrenalism diagnosed?

DIABETES INSIPIDUS

Present Illness

Patient B, a man 26 years of age, is in the hospital recovering from surgical clipping of an aneurysm on the anterior communicating artery. Three days after surgery, he begins voiding large quantiles of very pale urine. His IV intake is 80 mL/hour, and his oral intake is minimal. The specific gravity of the urine is 1.002, and the patient's calculated urine output is more than 200 mL/hour for four consecutive hours. The nurse observes that during the past two hours Patient B's blood pressure has declined from 120/80 mm Hg to 110/70 mm Hg and that his heart rate has increased from 68 beats per minute to 110 beats per minute. The nurse notifies the neurosurgeon of the large unconcentrated urinary output and the changes in vital signs.

Medical History

Patient B has suffered chronic severe headaches, and the diagnosis of cerebral aneurysm led to the cerebrovascular procedure. The surgical procedure went well, and Patient B was recovering as expected.

Assessment and Diagnosis

Upon the onset of diuresis, a full physical exam is conducted (***Table 3***). Laboratory findings are:

- Plasma osmolality: 289 mOsm/L
- Urine osmolality: 108 mOsm/L
- Serum sodium level: 150 mEq/L

Based on the findings of the assessment, Patient B is diagnosed with diabetes insipidus secondary to manipulation of the pituitary.

Management

The neurosurgeon orders 2.5 units of aqueous vasopressin to be administered immediately intramuscularly. Following administration, urine output is reduced to 60 mL/hr in 30 minutes. The urine osmolality level two hours later is 760 mOsm/L. Patient B continues to be monitored to determine if the pituitary damage is permanent and if he requires long-term desmopressin therapy.

Study Questions

Consider the information that has been presented in this course regarding diabetes insipidus.

1. What are the key signs and symptoms of diabetes insipidus? How did it present in Patient B?
2. What is the action of vasopressin?
3. What are the main types of diabetes insipidus? What type does Patient B have?
4. What causes central diabetes insipidus? What causes nephrogenic diabetes insipidus?
5. What diagnostic test(s) can reveal whether diabetes insipidus is central or nephrogenic? How are these conditions treated?

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Present Illness

Patient C is a Hispanic man, 60 years of age. He is brought to the emergency department by his family because of acute mental confusion and combativeness. His wife and son report that he has been complaining of anorexia, a nonproductive cough, and unusual fatigue and weakness for the past seven months. During this time, he lost 40 pounds. In the past two weeks, Patient C has been unusually irritable and occasionally irrational. The day before admission, the patient's confusion and disorientation became so severe that he tried to hit his wife. Because she could not manage him alone, the patient's wife asked their son to come and stay with them.

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PATIENT B'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	A young African American man who appears his stated age and is alert and oriented Height: 5 feet 11 inches (180.5 cm) Weight: 190 pounds (86 kg)
Head and eyes	Normocephalic Dressing dry and intact No ecchymosis visible Pupils equal (4 mm), round, reactive to light and accommodation Normal fundoscopic exam Extraocular muscles full Nasal turbinates and oral mucosa pink and moist Pharynx clear
Ears	External ear canals clear Tympanic membranes clear
Neck	Supple, without masses or thyromegaly
Chest	Symmetrical excursion Lungs clear to percussion and auscultation
Abdomen	Flat with active bowel sounds in all quadrants Soft, nontender, and without organomegaly or masses
Extremities	Pulses present, equal, and moderate
Genitourinary system	Within normal limits
Neurologic status	Oriented to person, place, and time Cranial nerves II–XII grossly intact Deep tendon reflexes 1+ to 2+ and symmetrical Bilateral plantar flexor responses present
Cardiovascular system	Cardiac rhythm normal sinus without ectopy Point of maximal impulse at fifth intercostal space 2 cm left of midclavicular line Heart sounds normal S1 and S2, without gallops, rubs, or murmurs
Vital Signs	
Blood pressure	110/70 mm Hg
Temperature	98.4° F
Heart rate	69 bpm
Respiratory rate	11 breaths per minute
Source: Author	*Table 3*

The morning of the admission, Patient C has a seizure (with signs consistent with a tonic-clonic seizure), and the family transports the patient to the emergency department for evaluation.

Medical History

Patient C's wife reports that her husband drinks six 12-ounce beers daily and has smoked two to three packs of cigarettes per day for the 35 years of their marriage. She has no knowledge of Patient C's family medical history. In addition, Patient C has only rarely seen a physician for illnesses and has never had a routine physical examination.

PATIENT C'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	A thin, disoriented, and irritable man who appears older than his stated age and coughs frequently Height: 5 feet 8 inches (173 cm) Weight: 149 pounds (68 kg)
Head and eyes	Normocephalic All structures normal
Ears	External ear canals clear Tympanic membranes clear
Neck	Supple, without thyromegaly Firm 2 x 3 cm lymph node in right supraclavicular area Jugular vein distention to the angle of the jaw while sitting up 45 degrees
Chest	Increased anteroposterior diameter and increased curvature to thoracic spine curvature Dullness to percussion in right base Lungs have scattered rhonchi and diminished breath sounds in the right base
Abdomen	Flat with active bowel sounds in all quadrants Soft with mild tenderness in right upper quadrant Liver palpable 5 cm below right costal margin
Extremities	Peripheral pulses present, equal, and bounding Normal hair distribution
Genitourinary system	Within normal limits
Neurologic status	Confused, oriented to self only Unable to follow instructions for cranial nerve exam Deep tendon reflexes symmetrically diminished, with bilateral plantar flexion
Cardiovascular system	Heart sounds are normal S1 and S2 with S3 with a soft systolic murmur the base No pericardial friction rub
Vital Signs	
Blood pressure	140/80 mm Hg, supine and standing
Temperature	98.9° F
Heart rate	100 bpm
Respiratory rate	18 breaths per minute
Source: Author	*Table 4*

Assessment and Diagnosis

Upon presentation to the emergency department, a full physical exam is conducted (***Table 4***). An electrocardiogram (ECG) is normal with nonspecific ST-T wave changes. Skull imaging is normal, but a chest x-ray visualizes a mass in the lower right lobe. Laboratory studies find:

- Blood chemistry levels:
  - Sodium: 115 mEq/L
  - Potassium: 3.8 mEq/L
  - Chloride: 80 mEq/L
  - Calcium: 7.2 mg/dL
  - Total protein: 5.8 mg/dL
- CO_2: 25 mmol/L
- BUN: 15 mg/dL
- Blood glucose: 90 mg/dL
- Creatinine: 0.9 mg/dL
- Serum osmolality: 235 mOsm/L
- Urine osmolality: 260 mOsm/L

Based on the findings of the assessment, Patient C is diagnosed with severe hyponatremia secondary to water intoxication. A lack of history for excessive water intake suggests SIADH.

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Management

The physician suspects that Patient C has SIADH, and further diagnostic studies are planned and carried out. The supraclavicular lymph node is biopsied. The pathology report identifies the node as small-cell lung cancer.

Patient C's serum cortisol is 10 mcg/dL in the morning. A 24-hour urine collection is completed, and 17-ketosteroids excretion is 9 mg per day and sodium excretion is 150 mEq per day. Patient C's fluid intake is restricted, furosemide is administered, and hypertonic saline is carefully infused. As the patient undergoes diuresis, his serum sodium gradually returns to normal and his sensorium improves. His wife is relieved at the return of her normally gentle husband.

Extended management includes assessment of the underlying cause of the SIADH, assumed to be metastatic small-cell lung cancer. The patient is referred to an oncologist for further testing and treatment.

Study Questions

Consider the information that has been presented in this course regarding SIADH.

1. What are the key signs and symptoms of SIADH? What pathophysiology underlies these effects?
2. How do diabetes insipidus and SIADH present differently? How are they similar?
3. What studies assist in confirming the diagnosis of SIADH? What are the nursing responsibilities in conducting these tests?
4. What safety precautions should be implemented for Patient C because he is confused and oriented to self only?
5. What nursing observations and actions are required to compensate for patients who are not alert and/or do not have access to food and water and therefore cannot use normal physiologic mechanisms to achieve fluid and electrolyte balance?
6. What typically causes SIADH?
7. How is SIADH treated?

CONCLUSION

The pituitary and adrenal glands play a significant role in many functions in the body, and proper functioning is essential for the maintenance of health. Dysfunction in these glands can have detrimental effects and may lead to death if untreated. Although disorders of the pituitary or adrenal glands are not as easy to see or identify as many conditions, they are nonetheless relatively common among many patient populations.

This course has provided a brief overview of the anatomy and physiology of the pituitary and adrenal glands, assessment, common disorders, and care of the patient with pituitary/adrenal dysfunction. Nurses have a responsibility and duty to identify the signs and symptoms of these disorders and to care for patients appropriately and fully.

Customer Information/Evaluation insert located between pages 88–89.

Course Availability List

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PRESSURE ULCERS AND SKIN CARE

#34343 • 5 ANCC Hours

Book By Mail – $28 • **ONLINE – $20**

Purpose: The purpose of this course is to provide nurses with the information necessary to accurately identify, treat, and manage skin breakdown (pressure ulcers), thereby improving patient outcomes and quality of life.
Faculty: Maryam Mamou, BSN, RN, CRRN, CWOCN
Audience: This course is designed for nurses in all practice settings, particularly those caring for patients at high risk for developing pressure ulcers.
Additional Approval: AACN Synergy CERP Category A, CCMC

HYPERGLYCEMIA AND WOUND MANAGEMENT

#34373 • 5 ANCC Hours

Book By Mail – $28 • **ONLINE – $20**

Purpose: The impact of hyperglycemia as a comorbidity in delayed wound healing is well documented. The purpose of this course is to provide nurses with a working knowledge of preventative strategies of skin breakdown, identification of types of skin breakdown, and steps for appropriate care of wounds in patients with diabetes.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in all practice settings with a desire to better understand the relationship between diabetes/hyperglycemia and wound management.
Additional Approval: AACN Synergy CERP Category A, CCMC

ETHICAL DECISION MAKING

#37073 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: The purpose of this course is to assist healthcare professionals to define the predominant ethical theories and principles used in health care, determine any legal and regulatory implications, and in collaboration with their colleagues and patients/clients, make effective decisions that determine the appropriate course
of treatment, or refusal of such, for and with those for whom they care.
Faculty: Michele Nichols, RN, BSN, MA
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approval: AACN Synergy CERP Category B, CCMC

PANCREATIC CANCER

NEW!

#90240 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to recognize and appropriately manage pancreatic cancer in their patients.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for physicians, nurses, and other members of the interprofessional healthcare team involved in the care of patients with pancreatic cancer.
Additional Approval: AACN Synergy CERP Category A

ISCHEMIC STROKE

#90283 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

Purpose: The purpose of this course is to provide needed information about the roles of diagnosis and screening, evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.
Additional Approval: AACN Synergy CERP Category A, CCMC

WHAT HEALTHCARE PROFESSIONALS SHOULD KNOW ABOUT EXERCISE

#91723 • 5 ANCC Hours

Book By Mail – $28 • **ONLINE – $20**

Purpose: The purpose of this course is to supply the information necessary for physicians and other healthcare professionals to provide practical advice for patients beginning an exercise program.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for physicians and will be of interest to nurses and other healthcare professionals working with adult patients who are overweight or obese and should begin an exercise program.
Additional Approval: AACN Synergy CERP Category A

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Course Availability List *(Cont'd)*

CARE OF THE PEDIATRIC TRAUMA PATIENT

#92073 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

UPDATE

Purpose: As injury remains a leading cause of mortality and morbidity among children, the purpose of this course is to allow healthcare professionals to provide timely care to pediatric trauma patients and to assist parents and caregivers in recognizing measures that prevent this type of injury.

Faculty: Susan Engman Lazear, RN, MN

Audience: This course is designed for all healthcare professionals involved in the care of pediatric patients, especially those in trauma care centers.

Additional Approval: AACN Synergy CERP Category A

THE CORONAVIRUS DISEASE (COVID-19) PANDEMIC

#94150 • 2 ANCC Hours

Book By Mail – $8 • **ONLINE – FREE**

UPDATE

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals an overview of the 2019–2020 global outbreak of novel human coronavirus (SARS-CoV-2) infection, including background epidemiology, clinical features, mode of transmission, epidemic potential, and the clinical and public health measures recommended to limit the spread of infection and control the outbreak.

Faculty: John M. Leonard, MD

Audience: This course is designed for physicians, nurses, and other healthcare professionals who may identify or educate patients regarding coronavirus infection.

Additional Approval: AACN Synergy CERP Category A, CCMC

PNEUMONIA

#94673 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

UPDATE

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals who manage the care of patients with pneumonia a foundation for effective management strategies in order to improve outcomes and foster an interprofessional collaborative practice consistent with published guidelines.

Faculty: Carol Whelan, APRN; Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for all physicians, physician assistants, and nurses, especially those working in the emergency department, outpatient settings, pediatrics, nursing homes, and intensive care units.

Additional Approval: AACN Synergy CERP Category A, CCMC

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

#95151 • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

Opioid/ Controlled Substance & Pain Mgmt

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approval: AACN Synergy CERP Category A, CCMC

Special Approvals: This course is designed to meet the requirements for opioid/substance abuse education.

DIABETES PHARMACOLOGY

#95323 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

UPDATE

Purpose: The purpose of this course is to meet the needs of healthcare professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.

Faculty: Diane Thompson, RN, MSN, CDE, CLNC

Audience: This course is designed for pharmacy professionals and nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.

Additional Approval: AACN Synergy CERP Category A, CCMC

ALZHEIMER DISEASE

#96153 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

Faculty: Joan Needham, MSEd, RNC

Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

Additional Approval: AACN Synergy CERP Category A, CCMC

Prices are subject to change.
Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

SUICIDE ASSESSMENT AND PREVENTION

#96441 • 6 ANCC Hours

Book By Mail – $32 • **ONLINE – $24**

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

Additional Approval: AACN Synergy CERP Category A, CCMC

ALCOHOL AND ALCOHOL USE DISORDERS

#96563 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

Purpose: The purpose of this course is to address the ongoing alcohol competency educational needs of practicing physicians, nurses, and other healthcare providers. The material will include core competencies as well as knowledge, assessment, and treatment-based competencies.

Faculty: Mark S. Gold, MD, DFASAM, DLFAPA; William S. Jacobs, MD

Audience: This course is designed for physicians, nurses, and allied health professionals involved in the treatment or care of patients who consume alcohol.

Additional Approval: AACN Synergy CERP Category A, CCMC

PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE

#97383 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: The purpose of this course is to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and a discussion of the benefits and barriers to optimum palliative care at the end of life.

Faculty: Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for all members of the interdisciplinary team, including physicians, physician assistants, nurse practitioners, nurses, social workers, marriage and family therapists, and other members seeking to enhance their knowledge of palliative care.

Additional Approval: AACN Synergy CERP Category A, CCMC

HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW

#98393 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

Purpose: Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

Faculty: A. José Lança, MD, PhD

Audience: This course is primarily designed for physicians, pharmacists, and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

Additional Approval: AACN Synergy CERP Category A, CCMC

DIZZINESS AND VERTIGO

#98401 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

Purpose: The purpose of this course is to provide clinicians with the information necessary to appropriately diagnose and treat causes of dizziness and vertigo and improve patients' quality of life.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for physicians and nurses involved in the diagnosis, treatment, and care of patients with dizziness and/or vertigo.

Additional Approval: AACN Synergy CERP Category A, CCMC

AGING AND LONG-TERM CARE

#99353 • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

Purpose: The purpose of this course is to provide the tools necessary for social workers, counselors, mental health professionals, and allied health professionals to successfully assess and care for older adults, an increasingly large portion of the U.S. population.

Faculty: Alice Yick Flanagan, PhD, MSW

Audience: This course is designed for nurses, social workers, counselors, mental health professionals, and allied health professionals involved in the care of older adults.

Additional Approval: AACN Synergy CERP Category B, CCMC

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4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#90072 Migraine 5 Contact Hours	**#95230** Psychopharmacology 10 Contact Hours	**#30830** Pituitary and Adrenal Disorders 15 Contact Hours
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No
13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#90072 Migraine: Diagnostic and Therapeutic Advances — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

#95230 Psychopharmacology — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

#30830 Pituitary and Adrenal Disorders — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

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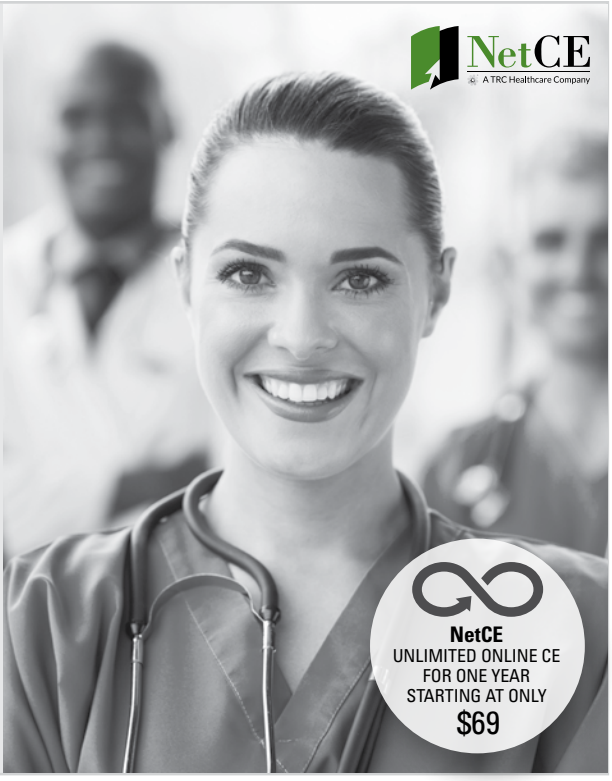

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