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Migraine: Diagnosis and Therapeutic Advances

This course meets the Michigan requirement for 2 hours of pain and symptom management education.

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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 updated 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 can be found at NetCE.com.)

Faculty Disclosure

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

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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 2021 Global Burden of Disease study, migraine was responsible for 43.4 million years of healthy life lost due to disability, or 4.7% of total years lost to disability in 2021. Migraine headache comprises 88.3% of the total burden of headache disorders [1]. 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 [2].

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% [3]. 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 [4; 5].

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 in emergency admissions in the United States?

Cephalalgias have a lifetime prevalence of more than 90% and an estimated prevalence of 50% in the adult population worldwide [4; 5]. Primary headaches are the sixth most common cause for patients to seek emergency care in the United States [6]. 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]) [7; 8].

According to the International Classification of Headache Disorders, published by the International Headache Society, there are four main types of primary headaches: migraine, tension-type headache, cluster headache/trigeminal autonomic cephalalgias (TACs), and a group that includes other primary headache disorders [7; 9]. Tension-type headache is the most common, with a prevalence of 30% to 78% [4; 7; 9; 10]. 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 [7; 9; 10].

Cluster headache/TACs are severe and uncommon headaches with a prevalence of 0.07% to 0.4% and occur more commonly in men than in women [11]. 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 to three hours. 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) [7; 9; 10].

The miscellaneous group of primary headaches is made up of a variety of conditions, including thunderclap headache and exertional headache [7]. 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" [12]. Thunderclap headache mimics the pain of a ruptured cerebral aneurysm [7]. 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 [13; 14]. Clinically, it is recommended that the diagnosis of thunderclap headache should apply only when no specific etiology is identified despite comprehensive diagnostic evaluation [9; 12; 13].

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 24, 2024.)

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 [7; 9; 10; 15].

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 frontotemporal 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 [7; 9; 10].

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%) [16]. 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 [17; 18]. The prevalence increases in adolescence (12%), affecting prepubertal boys and postmenarche girls [19]. The lifetime prevalence of migraine increases from age 12 to 40 years then declines thereafter in both sexes [20].

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 [2; 20]. 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% [20]. 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 [16].

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 [16]. 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 4.7% of years lived with disability, and the Global Burden of Disease study has ranked it among the top four most disabling medical conditions [2; 20; 21; 22; 23]. 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 [3; 24; 25]. 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 [26; 27].

CLASSIFICATION OF MIGRAINES

The International Classification of Headache Disorders categorizes migraines as acute or chronic [7; 9]. Acute or episodic migraine with aura is characterized by "transient focal neurologic symptoms that usually precede or sometimes accompany the headache" [9]. 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 [9]. 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 [10]. In 30% 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 [9; 10].

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 [7; 9].

The criteria of chronic migraine were updated and included in the revised ICHD-2R, and later confirmed in the ICHD-3 [9; 28]. 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 [9; 28]. Pain medication overuse is the most common reversible cause of headaches resembling chronic migraine [9; 29]. 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 [9].

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 [30]. 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 [31; 32].

Alternatively, the neurogenic theory views migraine as the combination of neuronal hyperactivity with a local process of neurogenic inflammation triggered by an increase in proinflammatory mediators such as CGRP, neurokinin, and substance P [31; 33]. 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 [34; 35].

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 [31; 34; 36; 37]. It is now known that the pathogenesis of migraine involves the trigeminal nerve and its axonal projections to the intracranial vasculature (the trigeminovascular system) [38]. 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 [38]. Progress in understanding these components of pathogenesis has enabled development of mechanism-based, targeted therapies with increased clinical efficacy and fewer adverse effects [39].

CORTICAL SPREADING DEPRESSION AND TRIGEMINAL NEUROPATHIES

What is cortical spreading depression?

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 [38; 40]. 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 [34; 41; 42]. However, the precise role of cortical spreading depression in migraine without aura remains elusive and somewhat controversial. Among the arguments against cortical spreading depression in migraine is that it is difficult to evoke in humans and that EEG readings are not flattened during migraine (as opposed to EEG during cortical spreading depression). Migraine can occur bilaterally, in contrast to cortical spreading depression, and is not accompanied by a disrupted blood-brain barrier, increased cerebral metabolism, or cerebral swelling. Additionally, cortical spreading depression does not explain the appearance of premonitory symptoms or allodynia, long before the actual onset of aura [43]. Animal models have shown that induction of cortical spreading depression causes meningeal vasodilation, a mechanism that requires participation of the trigeminal nerve [44; 45]. 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) [46; 47; 48; 49].

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 [34; 50; 51]. 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 [36; 52].

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 [53; 54; 55; 56; 57]. Guidelines for clinical evaluation and differential diagnosis will be discussed later in this course.

SIGNALING MOLECULES AND GENETIC MUTATIONS

Signaling molecules are the neurochemical messengers used by neurons and glial cells to transfer information among each other [58]. 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 [42; 58; 59].

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 [60]. Additional research and clinical studies are required to determine the efficacy of gap junction blockers for the treatment of migraine [60; 61; 62].

Voltage-gated calcium and sodium channels regulate neuronal excitability and intracellular signaling pathways [58]. 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 [63; 64; 65]. Accordingly, channel blockers such as valproate and topiramate used in the management of epilepsy are also effective in migraine prevention [39; 65; 66].

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 [39; 67; 68]. 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 [69; 70]. 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 [39; 67; 68]. 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 [69; 70]. 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 [69; 71].

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 [72]. Furthermore, antagonists of the glutamate NMDA receptor (e.g., memantine) are effective in the prevention of migraine [63; 64].

The role of dopamine in the pathophysiology of migraine 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 [73; 74]. 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 [51; 75].

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 [31; 40; 76; 77]. 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 [31; 34; 37; 40; 76; 78].

CGRP is a potent vasodilatory neuropeptide that increases blood flow in the meningeal arteries [77]. 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-HT1B/1D agonist (zolmitriptan) [77; 79; 80]. After success in several clinical trials, three novel CGRP antagonists were approved by the FDA in 2018 for migraine prophylaxis [81; 82; 83; 84]. Two additional CGRP antagonists received approval for an expanded indication for migraine prophylaxis in 2021 and 2023 [85; 86; 87].

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 [88]. 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 [70; 88; 89].

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) [70].

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 [90]. 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 [91; 92]. 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 [93; 94; 95].

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 [96]. 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 [63; 65; 97]. These findings provide the mechanistic explanation for the therapeutic efficacy of channel blockers such as valproate and topiramate in the prevention of migraine [51; 66; 98].

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 [99; 100; 101]. Genetic variants related to the excitatory neurotransmitter glutamate and its receptors have also been identified in non-familial migraine [72]. This evidence further supports the therapeutic value of memantine—a glutamate NMDA receptor antagonist—in the treatment of migraine [102; 103].

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 [104]. These results provide support for the role of antidopaminergic medications in the treatment of migraine with aura [105; 106].

MIGRAINE DIAGNOSIS

ACUTE MIGRAINE WITH AND WITHOUT AURA

What are the components of the clinically useful mnemonic POUND?

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 [107; 108].

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 [34; 41; 42]. 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 [75; 109]. 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 [109; 110]. In women, migraine with aura is associated with a twofold increased risk for cardiovascular events such as myocardial infarction and stroke [111].

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 [11; 112]. 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 [11; 20]. 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 [9; 109].

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 [75; 113]. 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 [75; 114]. 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 [75; 109; 114].

Potential complications of migraine include [9]:

- 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 [9; 75; 109; 114; 115].

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
- 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 [7; 9; 28; 75].

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 [75; 109]:

- 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 [116; 117]. 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) [31]. 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 [117; 118; 119]. Morphologic changes in brainstem regions involved in pain modulation (periaqueductal gray) and serotonin-producing neurons (dorsolateral pons) have also been reported [120]. 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 [121]. However, most patients with migraine with aura do not consistently present with these imaging alterations [40]. 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 [121].

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 [116; 122]. These studies are particularly important because they demonstrate that structural and functional changes occur during acute migraine and that changes in vascular function

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: [8] *Table 1*

do not represent the primary cause of migraine attacks, further validating the role of cortical spreading depression and the neural etiology of migraine [122].

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 [7; 8; 116; 123; 124; 125]. 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***) [8].

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 [109]. 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 [126; 127; 128].

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 [75; 111; 129; 130; 131; 132; 133; 134]. When compared with the rest of the population, patients with migraine with aura have a doubled risk of developing an ischemic stroke [135]. Migraine with aura in women using oral contraceptives has been identified as a risk factor for cardiovascular comorbidity [9]. 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 [136].

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 [9]. 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 [28; 29].

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 [24; 26; 137].

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 [9; 29]. Patient education regarding the judicious use of medications should begin before rather than after medication-overuse headache is established [109].

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 [138]. Chronic migraine should respond favorably to pharmacologic treatment with ergots or triptans [29].

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 [109]. This evaluation takes into account frequency, intensity, and impact of migraine on the patient's life [109]. 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

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

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 [109].

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 [109]. 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 [109].

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 [109].

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 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 [139].

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***) [140; 141].

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 [7; 11; 75].

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 [11].

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 [9; 11]. 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 [9]. 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 [11; 142]. 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 [7; 9; 10; 51; 142]. The standard treatment for cluster headache/TAC is high-flow oxygen (100% O2 at 7–10 L/min for 15 to 30 minutes).

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 24, 2024.)

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 galcanezumab-gnlm received FDA-approval in 2019 for cluster headache prophylaxis [81; 143]. 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 [11; 51; 75; 142; 144; 145].

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 [11; 146; 147]. Primary thunderclap headache should be a diagnosis of last resort, reached only when all organic causes have been demonstrably excluded [9].

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 [51; 146].

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 parenchy-

mal hemorrhage, cerebral vein thrombosis, cavernous sinus thrombosis, increased intracranial pressure, meningitis/encephalitis, hypertensive emergency, brain metastases, and HIV/AIDS [51; 124; 148]. 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 [149].

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 [51; 124; 148].

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 [150; 151; 152].

Approximately 20% of the population experiences orofacial pain more than once every six months [153]. Odontogenic pathology is the most common cause of orofacial pain, followed by nonodontogenic pain (e.g. temporomandibular disorders, neuropathies) and burning mouth syndrome [154; 155]. 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 [151; 156]. Sinusitis may also cause orofacial pain and headache, and a careful assessment of the patient is required to establish a differential diagnosis [9; 55; 154; 157].

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 [158]. 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 [158].

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 [158; 159]. 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 [158; 159; 160]. 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) [160].

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 [158].

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 [161]. 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 [162]. Onset can coincide with dental treatment, including denervation or dental extraction, a condition known as phantom tooth pain [163]. 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 [164]. 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 [165].

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 [154; 155]. 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 [154; 166; 167]. 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 [154; 157].

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 [154]. 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) [151; 154].

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 [168]. 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 [168; 169; 170].

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 [171; 172].

Patients suffering from daily migraines may be misdiagnosed with chronic sinusitis or rhinitis and repeatedly and unsuccessfully treated with broad-spectrum antibiotics [154; 157]. 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 [173].

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 [174]. 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 [175; 176; 177].

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 [178]. The International Headache Society defines burning mouth syndrome as "an intraoral burning or dysaesthetic sensation, recurring daily for more than two hours per day over more than three months, without clinically evident causative lesions" [7]. It is most commonly observed in postmenopausal women and is usually confined to the tip of the tongue. It may be associated with xerostomia and loss of taste (ageusia) [179; 180]. Burning mouth syndrome may develop as an adverse effect of angiotensin-converting enzyme inhibitors, with the condition subsiding after drug discontinuation [178]. If pharmacotherapy is required, clonazepam and gabapentin are the most commonly prescribed drugs for this condition [180].

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 [29; 109]. 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 [181].

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 [182; 183; 184; 185; 186]. 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 [187; 188]:

- 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 [187; 188]:

- 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 [109].

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 [181; 189]. 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) [190].

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 [105; 107; 191; 192; 193]. 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 [194]. 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 [195].

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 [188; 196].

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 [192]. 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 [6; 107; 197]. 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 [6; 51; 107; 197]. Ketorolac (30 mg IV or 60 mg IM) has also been shown to be effective and is recommended for acute treatment in emergency settings [106; 198; 199; 200].

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) [106; 194; 195; 198; 201]. 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 [196].

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 [107]. 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 [198; 200]. 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 [105; 198]. One study showed that granisetron is more beneficial than metoclopramide, because it also controls migraine-related emesis [202]. 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 [105]. 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 [203]. 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 [198; 200].

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 [105; 198]. Side effects are less common with prochlorperazine than with chlorpromazine, but both agents are recommended in the treatment of acute migraine in emergency settings [105; 198].

Antihistamine drugs (e.g., diphenhydramine, hydroxyzine) have been evaluated in combination with other medications for the treatment of acute migraine attack, with variable outcomes [105]. One trial showed benefits with diphenhydramine 12.5 mg IV plus prochlorperazine 10 mg IV, when compared with sumatriptan 6 mg subcutaneous [204]. 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 [205]. 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 [206]. However, its use as acute therapy is not recommended due to a lack of clear evidence of a favorable risk-benefit profile [198].

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 [105; 107; 207]. Intravenous lidocaine and propofol are not recommended, as serious side effects outweigh possible benefits [198].

Steroids—specifically dexamethasone (IV 6–24 mg) or prednisone (40 mg/day)—are used as adjuncts to the standard emergent treatment of migraine [208]. 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) [208]. Steroids should be used cautiously in diabetic patients. Repeated administration increases the risk of osteoporosis and well-known endocrine disorders [107; 192].

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 [191; 209]. Magnesium has an effect on a variety of neurotransmitters and receptors underlying acute migraine, including serotonin receptors, NMDA receptors, nitric oxide, and substance P [191; 209]. Research has shown that magnesium sulphate (1 g IV) is effective in 80% of patients 15 minutes postinfusion in emergency settings [191; 210]. 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 [198; 201].

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 [69; 71; 126; 211].

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 [195]. Adverse effects of ergots include nausea and vomiting, tingling of the extremities, muscle cramps, and chest discomfort [195]. 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 [195]. Ergots are contraindicated in patients with heart conditions or hypertension, and any chest or cardiac symptoms should be appropriately evaluated [69; 70; 81; 195]. Dihydroergotamine is oxytocic and should not be used during pregnancy or breastfeeding [81; 211]. 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 [81; 191].

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 [69; 70; 211]. As of 2024, 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 [81; 191; 195]. Failure or intolerance to one triptan warrants the trial of an alternative agent [191; 195]. It is advisable to switch from one oral triptan to another if three migraine attacks have been treated without success [38]. 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 [212]. A combination of sumatriptan 85 mg and naproxen 500 mg (Trexima) has been shown to provide better pain relief than either drug alone [107]. 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 [107; 213].

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 [81; 191; 195]. 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 [107; 126]. 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 [214]. 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 [214]. 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 [205].

In 2019, lasmiditan, a ditan, was approved for the treatment of migraine [81]. 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 [215]. Adverse events were mostly mild or moderate in intensity.

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 [9; 216].

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 [217]. Patients with migraine should be considered for preventive treatment in any of the following situations [218; 219; 220]:

- 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 [221; 222]. 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 [222].

Novel Preventive Treatment of Migraine

In 2018, the first medications in a novel class of drugs received FDA-approval for the prevention of migraine [81; 82; 83; 84]. As previously noted, CGRP is a potent vasodilatory neuropeptide that increases blood flow in the meningeal arteries [77]. 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 [31; 33]. 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 [82; 223; 224; 225].

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 [82; 223]. 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 [81]. There are no contraindications to erenumab-aaoe, and known side effects are limited to injection site reactions (less than 6%) and constipation (3%) [81]. Pregnancy and breastfeeding considerations are unknown; however, adverse events were not seen in animal reproduction studies [81].

The results of multiple phase II and phase III clinical trials resulted in additional CGRP antagonists receiving FDA approval in 2018, 2019, and 2020 [224; 226]. Like erenumad, fremanezumab-vfrm, galcanezumab, ubrogepant, and eptinezumab-jjmr are administered subcutaneously for prevention of migraine in adults [83; 84]. Fremanezumab-vfrm is administered either as a 225-mg monthly dose or 675 mg every three months [83]. The initial dose of galcanezumab is 240 mg, followed by 120-mg monthly doses [84]. Ubregepant is taken orally at a dose of 50–100 mg (maximum in 24 hours: 200 mg) [226]. 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 [227]. 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 [217].

Although preventive treatments do not completely prevent the occurrence of migraines, they do reduce the frequency by at least 50% [222; 228]. 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***) [95; 220; 227]. 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 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 [220]. 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) [220].

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 [222]. Although the Canadian Headache Society guideline for migraine prophylaxis recommends the use of the anticonvulsant gabapentin, this is not supported by a 2015 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

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: [227; 229]	*Table 2*

use of gabapentin [185; 230; 231]. 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) [81].

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 [95; 227; 232]. 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 [232].

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 24, 2024.)

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 [233]. 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 [60; 234; 235].

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 [236].

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 [237].

In 2014, the FDA approved the first transcutaneous electrical nerve stimulation (TENS) device as an alternative to medication for migraine prevention [237]. 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 [237]. 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 [238]. 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 [239]. 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 [239]. 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 [240].

In 2019, the AAN and the AHS published practice guidelines for treatment of acute migraine in children and adolescents [241]. 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 [239]. Ergots and naproxen for acute migraine have not been studied in children [240].

The FDA has certified a remote electrical neuromodulation (REN) device for the acute and/or preventive treatment of migraine in patients 12 years of age or older. The REN is a nonpharmacologic, prescribed, wearable device [241]. A group of 83 adolescents were analyzed to determine whether frequent use of the REN resulted in a reduction in monthly migraine treatment days. The participants used the REN on at least 10 days per month, following the REN migraine prevention guideline of an every-other-day pattern. Results demonstrated a substantial month-to-month reduction in the mean number of REN treatment days from 12.6 days in the first month, to 9.0 days in the second month, to 7.4 days in the third month. Additionally, 61.9% of users reported experiencing pain relief, 24.% reported freedom from pain, 67.4% reported relief in functional disability, and 41.3% reported complete freedom from functional disability [241].

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.

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

Migraine Research Foundation
https://migraineresearchfoundation.org

Customer Information and Evaluation are located on pages 87–88.

Medical Marijuana and Other Cannabinoids

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, physicians, physician assistants, pharmacists, social workers, therapists, and counselors in the primary care setting involved in the care of patients who use or who are candidates for the therapeutic use of marijuana or other cannabinoids.

Course Objective
The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.

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

1. Recall the history of therapeutic cannabis use.
2. Outline the function of the endocannabinoid system.
3. Analyze the pharmacology of exogenous cannabinoids in clinical or experimental use.
4. Discuss potential side effects and areas of safety concern when medicinal cannabis and other cannabinoids are used.
5. Describe the potential therapeutic benefit and appropriate indications for the medical use of marijuana and other cannabinoids.
6. Identify primary indications, side effects, chronic effects, and contraindications to therapeutic cannabinoid use.

Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Margo A. Halm, RN, PhD, ACNS-BC

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Division Planner/Director Disclosure
The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Designations of Credit
NetCE designates this continuing education activity for 5 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

A full Works Cited list is available online at www.NetCE.com.

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

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

Cannabis, or marijuana, was introduced to the United States as a medicinal product in the mid-1800s and was widely prescribed by physicians as a therapeutic until 1937, when sanctions were levied against medical or recreational use and physician prescribing. Prohibition culminated in 1970 with passage of the Controlled Substance Act, which formalized the criminalization of marijuana possession or use, regardless of quantity or context. Despite its illegal status, public demand for medical access led to the legalization of marijuana for medical use in California in 1996; as of 2023, voters in an additional 38 states and the District of Columbia have followed suit. In addition, 23 states have also legalized recreational cannabis use [1]. Popular demand and legal access to medical marijuana began despite the lack of well-designed randomized clinical trials (RCTs), the result of decades-long federal law enforcement obstruction. However, numerous RCTs have been published since 2000, markedly clarifying appropriate indications and contraindications.

In aggregate, the published clinical research strongly supports medical marijuana use in alleviating chronic neuropathic or cancer pain, spasticity, nausea and vomiting, weight loss and wasting syndrome associated with chronic debilitating conditions, and potential opioid dose reduction with analgesic enhancement as co-therapy in long-term opioid analgesic use [2; 3; 4]. Possible efficacy is suggested in fibromyalgia, post-traumatic stress disorder (PTSD), seizure disorders, and irritable bowel syndrome/Crohn disease. Contraindications include a personal or family history of psychoses; age younger than 18 years; and pregnancy or breastfeeding. Medical marijuana users are unlikely to develop negative immune effects, cognitive impairment persisting beyond the acute dose, or psychotic disorder when appropriately screened. Lifetime addiction prevalence is 1.5% to 9% in recreational users and unknown in medical users [5; 6]. However, about 11% of recreational marijuana users report daily use, compared with one-third of medical marijuana users [7]. In states with medical marijuana laws, 83% use cannabis recreationally and 17% use it for medical reasons.

The sociopolitical controversy surrounding nonmedical marijuana use frequently spills over into discussion of medical marijuana, obscuring objective discussion of the scientific basis. Value judgments play an even greater role in legal and regulatory decisions related to marijuana and other drugs that are used for recreational purposes [8]. Kalant offers two important suggestions to physicians weighing medical marijuana benefits/risks [2]. First, medical use and non-medical use are unrelated. For example, heroin can be legally prescribed in Canada to relieve suffering in patients terminally ill with cancer. No one has suggested heroin should therefore be available for non-medical use, and to think differently about marijuana lacks a rational basis. Second, marijuana is not

used as first-line therapy for any indication. Instead, its greatest therapeutic potential comes from treating patients with chronic conditions refractory to standard therapies [2]. The initial primary concerns of the Institute of Medicine (IOM) over medical marijuana were possible pulmonary harms and inability to control and replicate drug concentrations, but these are being resolved by availability of vaporization and, in Canada, Holland, and some U.S. states, by large-scale cannabis growing with quality, purity, and reliability consistent with pharmaceutical standards [8].

Despite substantial progress in the scientific understanding of cannabis mechanisms and the available outcomes of rigorously designed RCTs, this information is not reaching healthcare providers who practice in states legally permitting medical marijuana use [9]. This information transfer is essential to elevate the knowledge base of benefits, risks, and indications for medical marijuana and to improve patient interactions when this controversial topic is raised [9].

Provider demand for this information was captured by a survey of Colorado family practice physicians, of whom 82% endorsed including medical marijuana education in family practice residency training and 92% expressed interest in medical marijuana continuing education. However, only 19% agreed that physicians should recommend medical marijuana to their patients. One concerning finding was the significantly greater influence of news media in the decision to not recommend medical marijuana to patients. While these results were based on a 30% response rate to the surveys, they indicate that physicians are uncomfortable recommending medical marijuana but recognize the importance and unmet need of education and training on its clinical use [10]. In other words, lack of education is a fundamental cause of healthcare professionals' reluctance; more specifically, this results from knowledge deficits in the therapeutic value, appropriate indications, contraindications, dosing, and benefits/risks balance in medical marijuana, all of which can be addressed by continuing education [2; 11].

The urgent need for medical marijuana continuing education is underscored by findings that primary care providers refusing medical marijuana involvement has led to naturopathic doctors (NDs) filling this void by opening medical marijuana authorization practices in states granting NDs this function. Prescribers' discomfort is also influenced by fears over revocation of their license to prescribe controlled substances, with medical marijuana legally allowed in some states while remaining a violation of the federal Controlled Substance Act [12]. This concern is similar to the widespread fear over opioid analgesic prescribing, that doing so heightens risk of law enforcement or regulatory scrutiny and possible sanction or prosecution. This barrier to patient care is amenable to educational intervention by presentation of the potential benefits and factual reassurance that by authorizing medical marijuana consistent with state laws, the risks to one's licensure are essentially nonexistent. Unlike opioid prescribing, no U.S. physician has been successfully prosecuted or sanctioned for authorizing medical marijuana consistent with their state laws (as of 2020) [11]. In fact, a congressional spending bill (passed in 2017) prohibits the U.S. Drug Enforcement Administration (DEA) from spending any money to block states from "implementing their own laws that authorize the use, distribution, possession, or cultivation of medical marijuana," which, as affirmed by the Supreme Court in 2016, prevents the Department of Justice from prosecuting anyone in states with legal marijuana [13].

Botanical cannabis is the focus of this course, and while pharmaceutical cannabinoids are also discussed, the two should not be viewed as medicinally equivalent. Differences in pharmacologically active constituents and routes of administration result in distinct pharmacologic and clinical profiles [14]. This course will emphasize medical marijuana use in chronic pain because this is the most frequent condition for its use and because the highest proportion of well-designed clinical trials have evaluated efficacy in treating chronic pain [10; 15].

TERMS

The following terms are used often in discussions of medical marijuana use, and these definitions may help clarify the issues being described.

Cannabis: derived from *Cannabis sativa*, the proper name of the marijuana plant. Cannabis is a dioecious species, meaning it has male and female plants. Roughly half the plants grown from seed are female; when not fertilized by males to produce seeds, female plants bear flowering buds called sinsemilla, the part of the plant with highest Δ9-tetrahydrocannabinol (THC) concentration [16].

Marijuana: a synonym and slang term for cannabis, often used when discussing medical use.

Cannabinoid: a category that includes endogenous cannabinoid receptors, their endogenous ligands, and the plant-occurring or synthetic molecules that interact with cannabinoid receptors or their ligands [17].

Δ9-tetrahydrocannabinol: the primary active cannabis constituent. Referred to throughout this course as THC.

HISTORY OF MEDICINAL CANNABIS USE

USE IN ANCIENT CIVILIZATIONS

The evolution of *Cannabis sativa* has been traced to the Central Asian/Himalayan region roughly 36 million years ago [18]. Over time, cannabis spread to all regions with human habitation, reflecting the value placed on its medicinal, spiritual, and dietary utility [19].

The Chinese emperor Shen Nung is believed the first to formally describe the therapeutic properties and uses of cannabis in his 2737 B.C.E. compendium, in which it was recommended

for the treatment of malaria, constipation, rheumatic pains, and childbirth and mixed with wine as a surgical analgesic [20; 21]. Medicinal and religious use achieved great prominence in India around 1000 B.C.E. and was implicitly endorsed by the Hindu religion. Medicinal cannabis became widely used as an analgesic (for neuralgia, headache, toothache), anticonvulsant (for epilepsy, tetanus, rabies), sedative-hypnotic (for anxiety, mania, hysteria), anesthetic and anti-inflammatory (for rheumatism and other inflammatory diseases), antibiotic (for topical use on skin infections, erysipelas, tuberculosis), antiparasitic (for internal and external worms), antispasmodic (for colic, diarrhea), digestive, appetite stimulant, diuretic, aphrodisiac or anaphrodisiac, antitussive, and expectorant (for bronchitis, asthma). During the pre-Christian era, medical cannabis use remained widespread in India and areas of Assyria and Persia. Through the Christian era into the 18th century, it remained extensively used in India and spread throughout the Middle East, Africa, and the Arabian Peninsula, where prominent Arab physicians placed cannabis in their medical compendiums [20; 22].

INTRODUCTION AND WIDESPREAD USE IN WESTERN MEDICINE

Western medicine was introduced to cannabis by a 1839 publication of O'Shaughnessy, a physician who described its successful use in his patients as an analgesic, appetite stimulant, antiemetic, muscle relaxant, and anticonvulsant, and by the 1845 publication of Moreau, a psychiatrist who documented the results of cannabis use in his patients, his students, and himself [20; 21]. Support for medical cannabis use was disseminated by these publications from England and France throughout Europe and North America. Cannabis was entered in the U.S. Dispensatory in 1854, and the first medical conference on cannabis was held in 1860 by the Ohio State Medical Society. By 1900, more than 100 scientific articles on cannabis efficacy had been published in the United States and Europe. Cannabis was usually available as a tincture comprised of plant extract. Aware of the therapeutic potential, researchers worked to resolve its limitations, including lack of water solubility, delayed onset of action (when given orally), variable potency, difficulty in standardized dosing, and individual differences in response. The importance of dose titration was stressed [20; 22]. The late 19th to early 20th century was the pinnacle of cannabis use in Western medicine. Cannabis extracts were marketed by Merck, Burroughs-Wellcome, Bristol-Meyers Squibb, Parke-Davis, and Eli Lilly. The 1924 edition of the influential medical textbook *Sajous's Analytic Cyclopedia of Practical Medicine* listed numerous indications for cannabis, including [20; 22]:

- Sedative or hypnotic: Insomnia, melancholia, delirium tremens, chorea, tetanus, rabies, hay fever, bronchitis, pulmonary tuberculosis, coughs, spasm of the bladder
- Analgesic: Headaches, migraine, eye strain, menopause, brain tumors, neuralgia, gastric ulcer, indigestion, multiple neuritis, pain not due to lesions, dysmenorrhea, chronic inflammation, acute rheumatism, eczema and pruritus, tingling, numbness of gout, dental pain
- Other uses: To improve appetite and digestion associated with "pronounced anorexia following exhausting diseases," dyspepsia, diarrhea, dysentery, cholera, nephritis, diabetes mellitus, vertigo

Many indications are consistent with scientific confirmation, more than 90 years later, of analgesic, antispasmodic, antiemetic, sedative, anti-inflammatory, anticachexic, and antianorexic efficacy.

THE 20TH CENTURY

What was the first state to legally approve the use of cannabis for medical purposes?

The psychoactive properties of cannabis were recognized thousands of years ago but were valued mainly as religious adjuncts. Before the mid-20th century, recreational cannabis use was restricted to "fringe" or marginalized groups and the impoverished, for whom it was considered "the opium of the poor" [19]. Its use became increasingly popular in African American and immigrant Hispanic neighborhoods in the United States before 1950.

Cannabis prescribing in the United States significantly declined over the first three decades of the 20th century due to difficulty in developing reliable, standardized preparations; inability to isolate its active constituent; and introduction of effective medications in the areas of primary indication for cannabis. Medical cannabis use was burdened with severe taxation by the Federal Marihuana Tax Act of 1937, and cannabis was removed from the U.S. Pharmacopoeia in 1942 [8]. The American Medical Association (AMA) opposed both acts and testified before Congress that nearly 100 years of medical experience in the United States had demonstrated an irreplaceable therapeutic role for cannabis [23; 24]. Prohibition of medical marijuana culminated with the 1970 Controlled Substance Act (CSA) that categorized marijuana, along with heroin, as a Schedule I substance or CS-I. Drugs with CS-I listing are deemed highly addictive and devoid of medical value or safety. The CSA was a component of the "War on Drugs" launched in 1968, enforced and upheld by the newly established DEA. Possession of a CS-I substance potentially confers severe legal consequences, and possessing small amounts of cannabis has led to the lengthy incarceration of many. Black Americans have been disproportionately arrested and incarcerated for marijuana possession. Despite data showing that drug use is unaffected by severity (or leniency) in drug policy, harsh sentencing of marijuana possession has persisted in some jurisdictions [25]. Prominent groups have petitioned the government to review and reconsider its Schedule I status, including the IOM, the AMA, and the American College of Physicians [24].

Research and clinical interest in cannabis was re-ignited with identification of the chemical structure for THC in 1964, followed by discovery and cloning of cannabinoid receptors and isolation of the endogenous cannabinoid anandamide in the 1970s to early 1990s [24]. The first sporadic scientific reporting of medical marijuana benefit started in the 1970s, particularly

with nausea and vomiting from chemotherapy. As the acquired immune deficiency syndrome (AIDS) epidemic spread through the 1980s, patients increasingly found that marijuana relieved many of their symptoms, particularly wasting symptoms associated with AIDS. A landmark 1999 IOM report described the scientific and clinical basis for supporting medical marijuana use. There were increasing media reports of medical marijuana users subjected to criminal prosecution during this period [8]. These events stimulated media attention and growing public demand for medical access. Despite its illegal status at the federal level, cannabis was reintroduced into medical use in 1996 by popular vote and legislative acts in California. By 2023, 38 states and the District of Columbia had followed suit [1]. (For information on laws pertaining to medical marijuana in your state, visit https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc.) In addition, cannabis is used by millions of patients for medicinal purposes in jurisdictions where it remains illegal for medical use [11]. In opposition to federal law, state medical marijuana programs have received support by official federal statements of cooperative noninterference by the Veterans Health Administration and the U.S. Department of Justice in 2009 [24].

The DEA and National Institute on Drug Abuse (NIDA) are funded by the Office of National Drug Control Policy (ONDCP). Both agencies are guided by ONDCP's agenda and explicit policy goal of a drug-free America. The NIDAs research priority on cannabis harms reinforces its CS-I status by DEA. This long-standing federal obstruction of cannabis efficacy research perpetuated criticism that cannabis lacked scientific evidence of clinical benefit [11]. However, since 2000, advances in research design and evaluation have finally been applied to cannabis research. There are now numerous well-controlled clinical trials that fulfill the highest contemporary standards of scientific evidence. This clinical data, and the findings of preclinical and population-level studies, have greatly clarified the risk/benefit profiles of cannabis in a number of indications, addressed many long-standing safety concerns, defined patient contraindications, and identified the safety outcomes in recreational users that are inappropriate for generalization to medical users [11].

Contributing to this body of evidence was the 1999 founding of the Center for Medicinal Cannabis Research (CMCR) at the University of California, San Diego. The CMCR is the first comprehensive cannabis clinical research program in the United States and was launched with the goal of conducting randomized, placebo-controlled safety and efficacy trials of smoked cannabis in the treatment or management of the diseases and conditions identified by the IOM for which cannabis has highest therapeutic potential [26]. A similar process began in Canada in 2001, with the goal of systematically investigating cannabinoid safety and efficacy through preclinical and clinical trials. This was part of a larger effort by the Canadian government to better understand safe and effective medical cannabis use and was initiated in tandem with a centralized and controlled process of cannabis cultivation and distribution to appropriate medical patients [27; 28]. The Netherlands government established the Office of Medicinal Cannabis (OMC) in 2000 to grow cannabis according to pharmaceutical standards and to implement a supply chain to distribute and dispense cannabis to patients and researchers [29].

THE ENDOGENOUS CANNABINOID SYSTEM

What does the endogenous cannabinoid system (ECS) help to regulate?

The endogenous cannabinoid system (ECS) is a signaling system that includes cannabinoid receptors, endogenous receptor ligands (termed endocannabinoids), and their synthesizing and degrading enzymes [30]. Core functions of the ECS have been described as "relax, eat, sleep, forget, and protect," shorthand for the diversity of processes involving the ECS [31]. The ECS regulates neuronal excitability and inflammation in pain circuits and cascades and also helps regulate movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal (HPA) axis modulation, immunomodulation, mood, wake/sleep cycles, blood pressure, bone density, tumor surveillance, neuroprotection, and reproduction. The so-called "runner's high" and the effects of osteopathic manipulative therapy and electroacupuncture are mediated by the ECS [32; 33].

The ECS is a system common to all vertebrates and many invertebrates and has been present in living organisms as far back as 600 million years. In the invertebrate species *Hydra vulgaris*, a primitive evolutionary throw-back to several hundred million years, feeding is mediated by the ECS. This discovery underscores the essential pro-survival function of the ECS that long pre-dates mammalian evolution, where the more recently evolved hypothalamic system regulates the survival function of appetite [28; 34].

CANNABINOID RECEPTORS

CB1 Receptors

CB1 receptors are the most abundant G-protein-coupled receptors in the brain and are expressed at lower densities in many peripheral tissues. CB1 receptors solely mediate the psychotropic and behavioral effects of cannabinoids and regulate several peripheral processes, such as energy homeostasis, cardiovascular function, and reproduction [30; 35].

CB1 distribution in the brain matches the known pharmacodynamic effects of cannabinoids; CB1 activation prominently modulates cognition and memory, perception, control of motor function, and analgesia [36]. The location and relative density of CB1 receptors in the brain and function mediated by CB1 activation are outlined in ***Table 1*** [37; 38; 39; 40].

CB2 Receptors

CB2 receptors are sparsely expressed in the central nervous system (CNS) but highly expressed in immune cells, where they play an important role in regulating immune function and inflammation. Their activation modulates immune cell

CB1 RECEPTORS IN THE BRAIN	
Brain Region	**Function**
Highest CB1 density	
Substantia nigra	Reward, addiction, movement
Cerebellum	Motor control and coordination
Globus pallidus	Voluntary movements
Caudate nucleus	Learning and memory system
Moderate CB1 density	
Cerebral cortex	Decision-making, cognition, emotional behavior
Putamen	Movement, learning
Amygdala	Anxiety and stress, emotion and fear, pain
Hippocampus	Memory and learning
Lower CB1 density	
Hypothalamus	Body temperature, feeding, neuroendocrine function
Minimal or absent CB1 density	
Brain stem	--
Medulla	
Thalamus	
Source: [37; 38; 39; 40]	*Table 1*

migration and cytokine and chemokine release, and CB2 receptor expression on CNS microglia may explain cannabinoid efficacy in reducing cytokine-mediated neuroinflammation [30; 41; 42; 43].

Other Endocannabinoid Receptors

In addition to CB1 and CB2 receptors, endocannabinoids are thought to bind several other molecular targets. These include a third presumed cannabinoid receptor, GPR55 (sometimes termed CB3), the transient receptor potential cation channel subfamily V member 1 (TRPV1), and a class of nuclear receptors/transcription factors known as the peroxisome proliferator-activated receptors (PPARs) [30].

Endogenous Cannabinoids Receptor Ligands

Anandamide and 2-arachidonoyl glycerol (2-AG) are the two primary endogenous cannabinoid receptor ligands.

Anandamide (Arachidonoyl Ethanolamide, AEA)

Anandamide was the first endogenous cannabinoid identified by researchers and was assigned its name after *ananda*, the Sanskrit word for "bliss" [37]. Anandamide is derived from arachidonic acid following synthesis from membrane phospholipid precursors. At CB receptors, anandamide acts as a partial agonist, with slightly higher binding affinity at CB1 versus CB2 [36]. Anandamide is hydrolysed by the enzyme fatty-acid amide hydrolase (FAAH) as the primary metabolic pathway [44].

2-Arachidonoyl Glycerol (2-AG)

2-AG binds essentially equally to both CB receptors (with slightly higher CB1 affinity) and possesses greater overall potency and efficacy than anandamide at both CB receptors [36]. 2-AG is an arachidonic acid derivative synthesized by the same process as anandamide. The metabolic pathway of 2-AG predominantly involves monoacylglycerol lipase (MGL or MAGL) [36; 44].

Additional Endocannabinoids

Other endogenous molecules have been identified that mimic endocannabinoid effects. These include 2-AG ether (noladin ether), *N*-arachidonoyl dopamine (NADA), virodhamine, *N*-homo-γ-linolenoylethanolamine (HEA), and *N*-docosatetraenoylethanolamine. Although the molecules palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) bind to PPARs instead of cannabinoid receptors, their action potentiates anandamide effect by inhibiting FAAH (the enzyme that degrades anandamide) and by direct allosteric effects on other receptors. The sum of these effects is referred to as the "entourage effect" [45; 46; 47; 48]. Advocates of the term suggest the effect mechanism is the underlying reason that many patients claim to experience an overall better effect from full-spectrum *Cannabis* products. However, this suggestion relies mostly on anecdotal evidence from observational studies. Critics state that the "entourage effect" is unsupported by sound evidence and that the term is primarily used for marketing

purposes in the cannabis industry [49; 50; 51; 52]. PEA has become a research focus, with a growing number of clinical trials evaluating its pain-reducing efficacy in diverse chronic pain conditions [53; 54].

MECHANISMS OF ECS ACTION

Cannabinoid binding and activation of CB1/CB2 receptors produce many pharmacologic effects resulting from ECS modulation of other neurotransmitter systems [55].

Shared CB Mechanisms

The ECS facilitates rapid local response to pathologic states or disease. Increased intracellular calcium release from neuronal activation or cellular stress triggers membrane phospholipids to synthesize and immediately release anandamide or 2-AG, which binds and activates nearby CB receptors. This activation inhibits adenylyl cyclase activity, decreasing cyclic adenosine monophosphate (AMP) formation and protein kinase A activity, which in turn blocks Ca2+ influx through various calcium channels. CB receptor activation also stimulates inwardly rectifying potassium (K+) channels and the mitogen-activated protein kinase signaling cascades. Cellular uptake and enzymatic degradation rapidly clear the endocannabinoids [56].

The ECS alters CB1 or CB2 receptor expression during stress response, which is beneficial in some pathologic states (e.g., neuropathic pain, multiple sclerosis) because increased CB expression may curtail symptoms or disease progression and provide a protective role. Alteration in CB1 expression is maladaptive in other disease conditions, such as CB1 up-regulation in liver fibrosis and down-regulation in colorectal cancer [56; 57; 58].

CB1 Mechanisms

In CNS tissue, CB1 activation inhibits neuronal calcium channels and activates potassium channels, as described. Anandamide and 2-AG are synthesized and released from post-synaptic neuron terminals, travel "backwards" across the synaptic cleft to presynaptic neurons, and bind CB1 receptors on pre-synaptic terminals. This, in turn, inhibits release from excitatory and inhibitory synapses of serotonin, glutamate, acetylcholine, gamma-aminobutyric acid (GABA), noradrenaline, dopamine, D-aspartate, and cholecystokinin. This process of post-synaptic release, backwards diffusion across the synaptic cleft, and pre-synaptic CB1 binding is termed "retrograde signaling" [36; 59; 60].

CB2 Mechanisms

As noted, CB2 receptor expression is highest in immune cells. CB2 activation mediates immunosuppressive effects, including inhibition of proinflammatory cytokine production and cytokine and chemokine release, and blockade of neutrophil and macrophage migration [36; 59; 60].

ECS and Pain Pathways

Pain is the most frequent condition for which medical cannabis is used, and the antinociceptive (analgesic) actions of cannabinoids are distinct from mechanisms that mediate psychoactive effects [10; 15]. For instance, THC enhances analgesia produced by kappa opioid receptor agonist drugs, and administration of a kappa opioid receptor antagonist blocks this analgesic effect but has no effect on the psychoactive effects of THC. Cannabinoids interact with opioid, serotonin, and N-methyl-d-aspartate (NMDA) receptors, all of which are highly relevant in pain modulation [37].

The efficacy of cannabinoids in the management of chronic neuropathic pain is partially explained by ECS modulation of the descending supraspinal inhibitory pathway, an important pain pathway functionally compromised in patients with chronic pain. Via periaqueductal grey and rostral ventromedial medulla inputs, cannabinoid activation of CB1 and CB2 receptors stimulates the endogenous noradrenergic pathway, which activates peripheral adrenoreceptors to induce antinociception. Other mechanisms of cannabinoid analgesia include functional CB2 receptor expression in dorsal root ganglion sensory neurons, the spinal cord, and brain regions highly relevant to nociceptive integration and modulation [37; 61].

Serious gastrointestinal and cardiovascular adverse effects are associated with nonsteroidal anti-inflammatory drugs (NSAIDs), and their use is now recommended at the lowest effective dose over the shortest duration possible [62; 63; 64]. In theory, cannabis may have NSAID dose-sparing effects.

Cannabinoids and cyclo-oxygenase-2 (COX-2) have independent but interacting roles in pain. During inflammatory pain, prostanoids are produced, potentiating bradykinin to sensitize pain signal-transmitting C-fibers. COX-2 metabolizes anandamide and 2-AG to prostanoid compounds that potentiate this pain-inducing cascade, and COX-2 oxidizes 2-AG into the pro-nociceptive metabolic product prostaglandin E2 (PGE2)-G. Thus, inflammatory states with COX-2 up-regulation can nullify the antinociceptive effects of endogenous cannabinoids and produce pro-nociceptive byproducts from their metabolism. COX-2 inhibitors block this conversion, an effect shown in peripheral pain where anandamide release is the dominant analgesic mechanism, and in stress-induced CNS pain where 2-AG release is the dominant analgesic. Low-dose COX-2 inhibitors do not block COX-2 but block the conversion of 2-AG into pro-nociceptive PGE2-G. Acetaminophen prolongs the analgesic action of 2-AG by inhibiting its enzymatic degradation by FAAH [61]. These findings indicate that co-ingesting cannabinoids and COX-2 inhibitors synergistically inhibits prostaglandin and enhances endocannabinoid activity to produce greater analgesia than monotherapy with either agent [65]. Also, tolerance is a main unwanted development with all analgesic drugs, including cannabinoids, and COX-2 inhibition may prolong cannabinoid analgesia [66].

CANNABINOID PHARMACOLOGY

Cannabinoids are the molecular constituents of botanical cannabis (also termed phytocannabinoids) or pharmaceutical preparations that possess ECS activity.

BOTANICAL CANNABIS COMPOSITION

Cannabis possesses at least 489 distinct compounds from 18 different chemical classes that include terpenoids, flavonoids, phytosterols, and at least 100 cannabinoids. This does not mean there are 100 different cannabinoid effects or interactions; the cannabinoids fall into 10 groups of closely related cannabinoids, and most are not believed to contribute to cannabis's effects at their naturally occurring concentrations in the plant. THC is the primary psychoactive ingredient, and depending on the particular plant, THC or cannabidiol (CBD) is the most abundant cannabinoid. The relative concentration of THC, CBD, and other cannabinoids in a given plant is influenced by cannabis strain, soil and climate conditions, and cultivation techniques [8; 67].

Pyrolysis transforms hundreds of plant cannabinoid compounds into additional compounds. More than 2,000 compounds may be produced through pyrolysis of cannabis, many of which remain to be studied. As such, smoked cannabis produces many compounds not observed with vaporized or ingested cannabis [14; 68; 69]. Phytocannabinoids are discussed in detail later in this course.

Terpenoids

Terpenoids vary widely among *Cannabis* varieties, accounting for differences in fragrance among different strains and possibly contributing to the distinctive smoking qualities and character of the "high" from smoked cannabis. Preclinical studies suggest a broad spectrum of activity with terpenoids, including anti-oxidant, antianxiety, antibacterial, antineoplastic, and antimalarial action; however, these data await confirmation in clinical trials [70; 71]. Analgesic and anti-inflammatory activity have been found in several cannabis terpenoids [72]. Myrcene is an analgesic that inhibits inflammation via PGE2 activity. Naloxone blocks this activity, suggesting an opioid-mediated mechanism [73]. β-caryophyllene produces anti-inflammation via PGE1 inhibition comparable to phenylbutazone and also acts simultaneously as a gastric cytoprotective. It possesses selective CB2 agonist activity, and additional investigation has shown increasing promise with potentially broad clinical application [74]. Other possibly therapeutic terpenoids include the PGE1 inhibitor α-pinene and the local anesthetic linalool [71; 75]. One study examined six common terpenoids, alone and in combination with cannabinoid receptor agonists, on CB1 and CB2 signaling in vitro [76]. The terpenoids were tested both individually and in combination for periods of up to 30 minutes. None of the six terpenoids tested directly activated CB1 or CB2 or modulated the signaling of THC [76]. A study that included five common terpenoids from *Cannabis* also found that none had direct interactions with CB1 or CB2 [77].

Flavonoids

Cannabis flavonoids are natural plant constituents also found in whole cannabis extracts. Beneficial activities from flavonoids include inhibition of TNF-α by apigenin, a potentially therapeutic mechanism in multiple sclerosis and rheumatoid arthritis; and PGE2 inhibition by cannflavin A, an action 30 times greater than PGE2 inhibition by aspirin [78]. One study evaluated the neuroprotective and anti-aggregative properties of cannflavin A and found that it demonstrated a neuroprotective role against the amyloid β-mediated neurotoxicity associated with Alzheimer disease [79].

Phytosterols

A number of phytosterols are present in cannabis, with specific effects associated with each. For example, the cannabis phytosterol β-sitosterol was found to reduce topical inflammation by 65% and chronic edema by 41% in skin models [80]. Cannabis root contains significant amounts of β-sitosterol and other sterols that can be extracted by various methods [81]. Extracts of cannabis root have been used to treat pain and inflammation for millennia by various cultures, including the Romans as described by Pliny the Elder.

PHARMACEUTICAL CANNABINOID PREPARATIONS

Following identification of THC as the primary active constituent in cannabis, investigative focus primarily involved the therapeutic potential of isolated THC. Although efficacy was found across many pathologic conditions, the prominent psychotropic effects of THC limited its clinical appeal. Discovery of the ECS and characterization of additional phytocannabinoids prompted research evaluation of the therapeutic potential of other phytocannabinoids lacking the psychotropic effects of THC. Investigation of CBD, cannabigerol, Δ9-tetrahydrocannabivarin, and cannabidivarin led to promising results in preclinical models of CNS disease. This research also revealed the basis for expanded receptor targeting beyond CB receptors with these agents and the suggestion of clinical utility in epilepsy, neurodegenerative diseases, affective disorders, and central modulation of feeding and appetitive behavior [82]. These findings have influenced the direction of modern cannabinoid drug development and evaluation. Many novel cannabinoid therapeutics are in early-stage safety and efficacy evaluation, and the following cannabinoids are in current clinical or advanced-phase investigative use.

Dronabinol

Dronabinol (branded as Marinol) is an isomer of THC, and across a wide range of oral doses, it is shown to be chemically identical to plant-derived THC [37]. Dronabinol was initially approved by the U.S. Food and Drug Administration (FDA) in 1985 for the treatment of chemotherapy-induced nausea and vomiting in patients lacking adequate response to existing antiemetics, and then in 1992 for anorexia and cachexia in patients with AIDS. Dronabinol is a Schedule III substance and is available in 2.5–10 mg oral capsules and 5 mg/mL oral solution [83].

Nabilone

Nabilone (Cesamet) is a Schedule II THC analog that is chemically similar but not identical to THC [37]. Approved by the FDA in 1985 for the treatment of chemotherapy-induced refractory nausea and vomiting and used off-label for

analgesia, it is considered more potent than synthetic THC (e.g., dronabinol) [84]. It is administered (1 mg oral capsule) in doses of 1–2 mg twice daily for adults and 0.5–1 mg twice daily for pediatric patients [83].

Nabiximols

Nabiximols (Sativex) is a botanically derived cannabis extract with a defined 1:1 ratio of THC to CBD (27 mg/mL THC + 25 mg/mL CBD) delivered as a metered buccal spray. This drug has regulatory approval for select pain indications in 20 countries (including Canada) and is currently undergoing advanced phase III trials in the United States for treatment of cancer pain refractory to optimal opioid therapy and for treatment of multiple sclerosis spasticity [83; 85].

Cannador

Cannador is an orally administered cannabis extract containing a 2:1 ratio of THC to CBD. It is under investigation in Europe by the Institute for Clinical Research for the treatment of anorexia/cachexia in patients with cancer [86].

Pharmaceutical-Grade Smoked Cannabis

Smoked cannabis here applies to the medicinal cannabis produced in Canada and the Netherlands, because the exceptional quality, purity, and consistency controls are in line with pharmaceutical-level standards. In both countries, cannabis for medical or research use is grown by a single contractor, licensed by the government, under exceptionally strict, controlled, and documented conditions. From "seed to smoke," the seedlings are grown, packaged, and distributed via a centralized supply chain.

In the Netherlands, cannabis with the following THC and CBD concentrations are available [87]:

- 22%, 14%, or 13.5% THC with <1% CBD
- 6.3% THC/8% CBD
- <1% THC/7.5% CBD

In Canada, cannabis is available in potencies of [14]:

- 22% THC/<1% CBD
- 17% THC/<1% CBD
- 15% THC/5% CBD
- 12.5% THC/<0.5% CBD
- 9% THC/9.5% CBD
- 4% THC/10% CBD
- 0.7% THC/13% CBD

The cannabis used by the CMCR is of comparable pharmaceutical quality to the medical cannabis in the Netherlands and Canada [26]. In contrast, legal medicinal cannabis purchased from dispensaries in the United States lacks government-controlled standardization of cultivation, potency, and purity [88]. In the United States, cannabis grown for recreational or medical use has been bred to increase THC effects by increasingly reducing the CBD concentration. This also increases the side effect potential, and medical cannabis users may want to avoid this by seeking strains bred for higher CBD concentration [89].

PHYTOCANNABINOIDS

In contrast to pharmaceuticals that contain a single cannabinoid or a combination of two cannabinoids, the effects of inhaled cannabis are the result of pharmacologic activity from multiple agents. The psychoactive effects are largely the result of THC activity at the CB1 receptor. Therapeutic effects are influenced by THC and also by additional cannabinoids lacking psychoactive properties [8].

Δ-9-Tetrahydrocannabinol (THC)

THC is present in the living *Cannabis* plant as a mixture of monocarboxylic acids, and heating to greater than 120°C decarboxylates THC to promote biologic activity. THC decomposes from exposure to air, heat, or light, and oxidizes to cannabinol when exposed to acid [68; 69]. THC binds to CB1 and CB2 receptors as a partial agonist, with preferential binding at CB1. The mechanism of action, transmitter system interactivity, and demonstrated and theoretical therapeutic utility of THC are complex and vast, and the following summary is limited to the area of pain.

Among natural cannabinoids, THC possesses the greatest psychoactive potency and also exhibits the greatest analgesic activity. Epidural (i.e., intrathecal, intraventricular) administration of THC produces antinociception similar in magnitude to that of opioid analgesics [90].

Analgesic mechanisms of THC include interaction with serotonergic 5-hydroxytryptamine (5-HT) systems. THC inhibits 5-HT release from platelet cells, increases cerebral production of 5-HT, and decreases synaptosomal uptake. These effects involve multiple trigeminovascular system mechanisms associated with migraine headache. Dopaminergic inhibition by THC may also contribute to analgesic benefits [31; 91].

The glutamatergic system is foundational in chronic neuropathic pain and is causal in the development of secondary and tertiary hyperalgesia, via NMDA mechanisms, that characterize conditions such as migraine and fibromyalgia [92]. Cannabinoids inhibit pre-synaptic glutamate release, and THC reduces NMDA response by 30% to 40%. THC is also neuroprotective through antioxidant activity [93]. THC inhibits calcitonin gene-related peptide to reduce hyperalgesia, and preclinical studies show that THC blocks capsaicin-induced hyperalgesia at sub-psychoactive doses [94; 95].

THC stimulates beta-endorphin production, and this important opioid system interaction partially accounts for the repeated findings of the opioid sparing effects with cannabis in clinical trials and preventing development of opioid tolerance and withdrawal and the reinstatement of analgesia when a prior opioid dosage has worn off in other studies [96; 97; 98].

THC also produces extensive anti-inflammatory activity through mechanisms that include inhibition of PGE2 synthesis, suppression of platelet aggregation, and stimulation of lipoxygenase. Studies have confirmed that THC produces 20 times the anti-inflammatory potency of aspirin and twice the potency of hydrocortisone, but unlike NSAIDs, it has not demonstrated COX inhibition [31; 99].

11-Hydroxy-THC

11-hydroxy-THC is the primary metabolic product of THC. It is four times more potent in producing psychoactive and immunosuppressive effects than the parent compound [68; 69].

Δ 8-THC

Δ8-THC is a Δ9-THC isomer found in smaller amounts in the cannabis plant and has activity as a partial CB1 and CB2 agonist. In vitro assays have shown comparable efficacy and potency with Δ9-THC, and preliminary clinical results suggest greater antiemetic potency with Δ8-THC compared with Δ9-THC [100; 101]. Δ8-THC is psychoactive, but the effect is very weak and substantially overshadowed by THC due to its low concentration [8].

In 2022, the FDA issued a warning letter and consumer update regarding products containing Δ8-THC [102]. These products contain concentrated amounts of Δ8-THC, typically manufactured from CBD. At the levels found in these products, the isomer induces significant psychoactive effects, and adverse effects have been reported, including hallucinations, vomiting, tremor, anxiety, dizziness, confusion, and loss of consciousness [102].

Cannabidiol

CBD has shown exceptional therapeutic promise as a single molecular entity. It is already in clinical use as a combination product with THC and in certain cannabis strains developed to overexpress CBD.

CBD produces pharmacologic actions different from, and often the opposite of, those of THC, and an increasing number of publications suggest broad therapeutic potential [103]. CBD is non-psychoactive but modulates ion channel, receptor, and enzyme targets. Preclinical studies suggest beneficial anti-inflammatory, analgesic, antiemetic, antipsychotic, anti-ischemic, anxiolytic, and antiepileptiform effects; human studies suggest anxiolytic efficacy [103; 104; 105]. CB2 receptor activity accounts for some anti-inflammatory and antinociceptive effects. CBD does not affect memory and probably curtails negative THC side effects by CB1 inverse agonist activity. The anxiolytic effects of CBD probably result from 5HT1-A receptor agonist activity [37].

Other mechanisms of therapeutic activity have been found. The neuroprotective properties of CBD are produced by inhibition of glutamate neurotoxicity and by antioxidant activity that surpasses ascorbic acid (vitamin C) and tocopherol (vitamin E) [93]. CBD modulates endocannabinoid activity as a TRPV1 agonist and an FAAH inhibitor, and through inhibition of THC first pass hepatic metabolism into the more highly psychoactive metabolite 11-hydroxy-THC, which prolongs THC half-life and reduces the unwanted THC side effects of intoxication, panic, anxiety, and tachycardia [106]. CBD inhibits tumor necrosis factor-alpha (TNF-α) in an animal model of rheumatoid arthritis and produces anti-inflammation and analgesia unrelated to COX-1 or COX-2 inhibition that involves promotion of adenosine receptor A2A signaling through adenosine transporter inhibition [31; 107]. Many effects of CBD follow a bell-shaped dose-response curve, suggesting that dose is a key factor in CBD pharmacology [104].

Outside the United States, CBD is available in equal ratio to THC in the oromucosal spray nabiximols. In Canada and the Netherlands, some cannabis strains available for medicinal use have been bred to overexpress CBD, for a 1:1 ratio of CBD to THC. Pure (>99%) isolated CBD crystals, oils, waxes, and other extracts are available from many dispensaries.

In 2018, the FDA approved the first drug that contains purified CBD—a CBD oral solution for the treatment of seizures associated with Lennox-Gastuat syndrome and Dravet syndrome in patients 2 years of age and older [108].

Cannabinol

Cannabinol is produced by THC oxidation and is most often found in aged cannabis products. Cannabinol shares some characteristics with CBD, such as anti-convulsant and anti-inflammatory activity. Adding cannabinol to THC does not significantly increase THC effect. It is a weak CB1 and CB2 partial agonist with approximately 10% of the activity of THC and appears to possess immunosuppressive properties. Potential therapeutic applications of cannabinol include diseases characterized by cannabinoid receptor up-regulation [72; 104; 109].

Cannabigerol

Cannabigerol possesses a broad mechanistic range, with activity as a partial CB1 and CB2 receptor agonist, a potent TRPM8 antagonist, an agonist at TRPV1and TRPA1, and also as an anandamide reuptake inhibitor in the low micromolar range. Other mechanisms of cannabigerol include 5-HT1A receptor antagonism and α2-adrenoceptor agonism [104; 109]. Cannabigerol possesses anti-inflammatory and analgesic properties and also demonstrates anti-proliferative and antibacterial activity [104].

Tetrahydrocannabivarin

Tetrahydrocannabivarin is a CB1 receptor antagonist and CB2 receptor partial agonist. This effect is dose-dependent, as it shows THC antagonist activity at low doses while higher doses act as a CB1 agonist. Tetrahydrocannabivarin has shown anticonvulsant properties in in vitro and in vivo studies [110; 111]. Other potential benefits of tetrahydrocannabivarin include its increase of central inhibitory neurotransmission, giving it therapeutic potential in epilepsy, and CB1 antagonism suggesting clinical benefit by decreasing food intake [104].

Cannabichromene

Cannabichromene, together with THC, is a major cannabinoid constituent in freshly harvested cannabis. It has activity as a potent TRPA1 agonist and weak anandamide reuptake inhibitor, and it is shown to exert anti-inflammatory, antimicrobial and modest analgesic activity. In preclinical animal studies, cannabichromene showed greater propensity than THC in producing adverse events, including hypothermia, sedation, and hypoactivity [104].

PHARMACOKINETICS

Cannabis is inhaled or orally ingested, with substantial differences between routes in the time course of absorption, distribution, and duration of action that explain the overwhelming preference of medical users for inhaled over orally ingested cannabis products [59]. In one study, more than 4,000 Californian medical patients expressed a preference for inhaling their medication, stating the therapeutic effects from oral dronabinol or nabilone were more difficult to achieve and more likely to be unpleasant or excessively prolonged [112]. In contrast, inhaling cannabis provides more rapid onset of symptom relief and rapid feedback informing the patient whether titration with additional dose is needed or not [68; 113].

Absorption and Distribution

The rate of drug absorption is determined by the route of administration and drug formulation. Inhalation is the primary route of cannabis administration and provides rapid and efficient drug delivery from the lungs to the brain [68].

Smoked Cannabis

With smoking, the onset of effect occurs within seconds to minutes. Maximal effect is experienced after 30 minutes, and the duration of effect is 2 to 3 hours [59]. Peak plasma THC occurs within 10 minutes and decreases to roughly 60% of peak by 15 minutes and to 20% of peak by 30 minutes. This rapid onset and predictable decay allows for effective dose titration not possible with oral cannabinoids [88]. The THC dose absorbed systemically is 25% to 27% of the total available THC content in a marijuana cigarette ("joint") [68; 114].

Vaporized Cannabis

A study comparing smoked and vaporized administration found higher serum THC at 30 and 60 minutes post-inhalation with vaporization and comparable serum THC levels over the remaining six-hour period [115]. Vaporization was preferred by 80% of subjects, and as with smoking, vaporization was highly conducive to self-titration. The amount of THC delivery is influenced by the amount and type of cannabis, vaporizing temperature, duration of vaporization, and the balloon volume [116; 117].

Oral Ingestion

The CNS and physiologic effects with oral ingestion are substantially delayed relative to inhalation, including slower onset of action, lower peak plasma levels, and longer duration of effect. With pharmaceutical cannabinoids such as dronabinol, 10% to 20% of ingested THC enters systemic circulation due to extensive first-pass metabolism. In healthy volunteers, a single 2.5-mg dose of dronabinol produces mean peak plasma THC at two hours, with a range of 30 minutes to four hours; these absorption and distribution kinetics are similar following a single 10-mg dose of dronabinol [118].

Plant cannabis can be mixed into brownies, cookies, or tea prepared from the flowering tops, but all result in unreliable absorption. In one study, oral ingestion of 20 mg THC in chocolate cookies resulted in only 4% to 12% of THC entering systemic absorption and peak plasma THC at one to two hours in most subjects and six hours in others, with some subjects showing multiple plasma peaks [68]. The bioavailability of THC from tea made of plant cannabis is lower than with smoking due to the poor water solubility of THC and the effect of hepatic first-pass metabolism [14].

Distribution

THC distribution is time-dependent and begins rapidly after absorption. In plasma, THC is 95% to 99% plasma protein bound, primarily lipoproteins. The tissue distribution of lipophilic THC and its metabolites mostly involves uptake in fatty tissues and highly perfused organs such as the brain, heart, lung, and liver [59; 68]. Whether THC accumulates in the brain with long-term use is unknown, due to limits in THC access and accumulation imposed by the blood-brain barrier [119].

Metabolism

Most cannabinoid metabolism occurs in the liver, with different metabolic byproducts predominating by route of administration. THC metabolism is complex and involves allylic oxidation, epoxidation, decarboxylation, and conjugation. THC is oxidized by the cytochrome P450 (CYP450) oxidases 2C9, 2C19, and 3A4 to produce the active metabolite 11-hydroxy THC and the inactive metabolite 11-nor-9-carboxy THC [120]. The 11-hydroxy THC plasma level parallels observable drug action [68]. Relative to inhalation, first-pass hepatic metabolism with oral ingestion yields a greater proportion of 11-hydroxy THC [59].

Elimination

What is the major long-term storage site of THC and its biometabolites?

Body fat is the major long-term storage site of THC and its biometabolites. Elimination occurs over several days due to the slow rediffusion of THC from body fat and other tissues. Roughly 20% to 35% of THC is eliminated in urine and 65% to 80% in feces, and by five days, 80% to 90% of THC is eliminated, although THC from a single dose can be detected in plasma up to 13 days later in chronic smokers as a result of extensive storage and release from body fat [59; 121].

Adverse Drug-Drug Interactions

Most patients in the RCTs discussed in this course were maintained on their pre-study medications for neuropathic pain, cancer pain, fibromyalgia, or multiple sclerosis. In these and other RCTs, patients smoked or ingested cannabis while taking their prescribed opioids, NSAIDs, muscle relaxants, ketamine, anticonvulsants, antidepressants, and benzodiazepines. Cannabis use with these other agents was well tolerated, and observed side effects did not differ from those expected with cannabis [14].

In theory, ingesting cannabis with drugs that alter its metabolic pathway should increase the risk of side effect enhancement or efficacy failure, but adverse drug-drug interactions of clinical relevance have not been reported to date. Cannabis should be used with caution by patients also using sedating substances such as alcohol or benzodiazepines [59].

Tolerance

Tolerance is defined as tissue adaptation resulting from repeated drug exposure, such that one or more drug effects diminish over time. Cannabis tolerance primarily results from pharmacodynamic mechanisms, including changes in CB1 signaling ability due to receptor desensitization and down-regulation. THC tolerance varies across different brain regions, possibly explaining why tolerance develops to some cannabis effects but not to others [122]. Tolerance to most THC effects develops after a few doses and then disappears rapidly following cessation, and pharmacodynamic tolerance can be minimized by combining a low dose of cannabinoid with one or more additional therapeutic drugs [123].

SIDE EFFECTS AND SAFETY

Information on medical cannabis safety and side effects should ideally come from RCTs that control for confounding factors that may otherwise account for the results. Such studies are increasingly being published, but similar to other drug efficacy trials, safety information is available with short-term (less than three months) use while long-term safety data remains sparse. In contrast to studies with medicinal users, many studies of long-term heavy recreational users have been published. Generalizing safety outcomes from chronic recreational users to medicinal users is cautioned against because of numerous confounding factors, including differences in age of first regular use; duration, quantity, and THC content of cannabis use; concurrent alcohol or other drug use; drug delivery approaches; and past or current psychiatric, neurologic, and comorbid medical histories [124; 125; 126]. Raphael Mechoulam, who in 1964 co-discovered THC, concluded that most cannabis safety data from "street users" are "useless" (his words) for extrapolation to medicinal cannabis safety, based on the before-mentioned factors and the widely variable THC and unknown CBD content of illicitly obtained cannabis in contrast to cannabis now cultivated under tightly controlled environmental conditions to ensure reliability [127; 128]. In the following sections, the available evidence on medical cannabis and pharmaceutical cannabinoids is presented.

RISK/BENEFIT CONSIDERATIONS

Importantly, the potential acute and long-term adverse effects with medical cannabis should be weighed against the known side effect profiles of standard therapeutic agents for the same indication [88]. For example, in standard therapies for chronic pain or spasticity, opioids often produce sedation, nausea, constipation, physiologic dependence, and with abrupt cessation of long-term use, a more severe withdrawal syndrome than cannabis withdrawal. Tricyclic antidepressants and antiepileptic drugs are frequently prescribed for chronic neuropathic pain and may produce sedation, constipation, dizziness, palpitations, visual disturbance, urinary retention, and neuromuscular effects. Antispasmodic drugs may produce sedation (e.g., baclofen), hypotension (e.g., tizanidine), and potentially serious interactions with antibiotics (as with tizanidine and ciprofloxacin). Benzodiazepines prescribed for spasticity may produce sedation, psychomotor incoordination, memory impairment, paradoxical reactions, dependence, and with daily long-term use, a severe protracted withdrawal syndrome. Opioids and benzodiazepines are also drugs with potential for abuse, addiction, diversion, and fatal overdose exceeding cannabis. This comparison helps put consideration of the relative benefits and risks of medical cannabis in the proper context [88].

As with any drug therapy, important considerations include the dose-response relationship and margin of safety that separates beneficial dose from dosage producing adverse effects [2]. Safety concerns can be addressed, as with any drug, by appropriate patient screening and monitoring, adherence to known contraindications, and administration with alternative delivery systems (as in patients with lung disease). In many (non-cannabis) contexts, clinical medicine involves balancing risk and benefit even when limited evidence is available to base a decision, and the needs and wishes of patients should be considered while the merits of medical cannabis use are debated [15].

Cannabinoid-drug interactions should be considered in all patients. CBD and possibly THC are known to increase the levels of direct-acting oral anticoagulants and clopidogrel. In patients using cannabis or products containing CBD or THC, other agents should be considered [129]. THC and CBD also inhibit metabolism of warfarin, which can lead to elevated INRs. There is also some evidence that cannabis or cannabinoid use can effect postoperative outcomes. As such, the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends universal screening for cannabinoids prior to surgery, including type of cannabis or cannabinoid product, time of last consumption, route of administration, amount, and frequency of use [129]. Further, the ASRA recommends delaying or postponing elective surgery in patients who are acutely intoxicated or who have recently smoked cannabis.

PHARMACOLOGIC MANAGEMENT OF CANNABIS SIDE EFFECTS	
Symptom	**Therapeutic Agent**
Palpitations and tachycardia	Propranolol
Arrhythmia, atrial fibrillation	Flecainide, propafenone, digoxin
Acute psychotic state	Olanzapine, haloperidol
Acute intoxication	Propranolol
Acute anxious psychotic symptoms from very high-dose THC	Cannabidiol
Acute panic anxiety state	Lorazepam, alprazolam
Acute manic and depressive syndromes during intoxication	Benzodiazepines, antipsychotics
Cognitive impairment with repeated use	COX-2 inhibitors[a]
[a]Based on preclinical studies of primates.	
Source: [135; 136]	*Table 2*

DATA FROM PHARMACEUTICAL CANNABINOID TRIALS

Cannabinoid safety and side effect data from 23 RCTs and 8 observational studies involving 1,932 participants with medical conditions such as cancer and multiple sclerosis were reviewed [124]. The cannabinoids included dronabinol and nabiximols spray. In the RCTs, median cannabinoid exposure was two weeks (range: 8 hours to 12 months). Serious adverse events occurred in 164 cannabinoid subjects and 60 control subjects; the most frequent by category were respiratory (16.5%), gastrointestinal (16.5%), and nervous system disorders (15.2%) with cannabinoids, and nervous system disorders (30%) with placebo. The difference in incidence between cannabinoid and placebo subjects was not statistically significant. Non-serious adverse events were significantly more prevalent with cannabinoids, with the most common being blurred vision, dry mouth, weakness, dizziness, somnolence, sedation, confusion, hypotension, and altered mood [124]. Data from two recent high-quality systematic reviews found sufficient evidence that cannabinoids (e.g., nabiximols, nabilone, dronabinol) may be effective for reducing the symptoms of patient-reported pain and spasticity in multiple sclerosis [130; 131]. A systematic review conducted by the American Academy of Neurology found that oral cannabis extract is effective for symptoms of spasticity in patients with multiple sclerosis and that nabiximols and THC are probably effective for reducing patient-centered measures [132].

DATA FROM MEDICINAL CANNABIS TRIALS

Results from RCTs of smoked cannabis found that side effects were generally dose-related, mild-to-moderate in severity, time-limited, and less common in experienced cannabis users. Most frequent were dizziness or lightheadedness (30% to 60% of subjects), dry mouth (10% to 25%), fatigue (5% to 40%), muscle weakness (10% to 25%), myalgia (25%), and palpitations (20%). Cough and throat irritation occurred initially in a few participants. Euphoria was reported in some but not all subjects, with the low incidence attributed to plasma THC concentrations less than 25% of the levels generally found with recreational cannabis use. Infrequently, tachycardia and postural hypotension were noted, a potential concern in patients with cardiovascular disease. Tachycardia was a frequent acute physiologic effect, with it and other acute cardiovascular effects rapidly resolving due to the brief period of THC occupancy and then distribution out of the circulatory system [14].

A dose-effect relationship was found, with higher rates of sedation, ataxia, and loss of balance following higher dose levels [133; 134]. Tolerance to cardiovascular, autonomic, and other subjective and cognitive side effects developed rapidly over the initial 2 to 12 days of therapy [88]. As with other therapeutics, large inter-individual differences in side effects were observed, and severely ill patients, elderly persons, and patients taking multiple concurrent medications may be especially prone [14]. Anxiety or psychotic symptoms were uncommon, dose-related, occurred primarily during acute administration of high doses, and in most cases could be avoided by dose titration [60]. Successful resolution or management of cannabis side effects has been described with several agents (***Table 2***) [135].

AREAS OF SAFETY CONCERN

Contaminants in the Cannabis Plant

Cannabis may be contaminated by a variety of organisms, such as *Aspergillus* fungus and bacteria, that can result in fulminant pneumonia, especially in immunocompromised persons. Nonbiologic contaminants can include heavy metals such as aluminum and cadmium from the soil, with cadmium readily absorbed into the plant at high concentrations. Organophosphate pesticides are found less often in cannabis grown outdoors versus indoor cultivation [137]. Concerns over inorganic and biologic contaminant ingestion prompted Health Canada and the OMC to carefully control all aspects of cultivation, test the product for the presence of mold spores and 28 different metals including heavy metals, and pre-emptively irradiate all

cannabis products before distribution to medical or research users [14; 27]. This is not currently done to most cannabis available in the United States.

Pulmonary Function

Physician and patient concerns over pulmonary harm from cannabis smoking have been based on the known hazards from smoking tobacco, findings of carcinogenic compounds in cannabis smoke, and earlier epidemiologic studies associating long-term cannabis use with respiratory dysfunction [138]. This has contributed to reluctance over medical smoked cannabis use.

Although many carcinogens and tumor promoters are common to tobacco and cannabis smoke, differences in the active constituents result in different biologic outcomes. Molecules in tobacco smoke enhance carcinogenic pathways through several mechanisms, including circumvention of normal cellular checkpoint protective mechanisms; activation of respiratory epithelial cell nicotine receptors; promotion of tumor angiogenesis; stimulation of enzymes that convert polycyclic aromatic hydrocarbons found in smoke into carcinogens; and prevention of apoptotic cascades (cell death) in cells accumulating sufficient genetic damage. In contrast, molecules in cannabis smoke inhibit carcinogenic pathways through down-regulation of immunologically generated free radical production (the innate response to inhaled smoke and particulate); THC blockade of enzymatic conversion of smoke constituents into carcinogens; the absence of cannabinoid receptors in respiratory epithelial cells (which maintains DNA damage checkpoint mechanism integrity with prolonged cannabis smoke exposure); and the anti-angiogenic, tumor-retardant, and anti-inflammatory activity of many cannabinoid smoke constituents [139; 140; 141].

These factors appear in the results of a 20-year longitudinal study of pulmonary health in 5,115 participants who smoked cannabis [142]. The authors stated that pulmonary risks from cannabis smoking had been overstated and found that, unlike tobacco smoking, cannabis smoking had no effect on measures of pulmonary function. Medicinal use of smoked cannabis was also found to be very unlikely to produce adverse effects on pulmonary function [142]. In 878 Canadians 40 years of age and older, history of tobacco smoking or tobacco and marijuana smoking, but not marijuana-only smoking, significantly elevated the risk of respiratory problems or chronic obstructive pulmonary disease (COPD) relative to non-smokers [143]. In a 2022 study comparing 56 cannabis smokers and 33 tobacco-only smokers, the cannabis smokers showed higher rates of emphysema and airway inflammation than nonsmokers or tobacco-only smokers [144]. However, the researchers were careful to point out that high rates of concomitant tobacco smoking in the cannabis group made drawing firm conclusions difficult.

Vaporizing systems have been developed to further minimize pulmonary risks from smoked cannabis. These involve heating the plant material short of combustion and then inhaling the mist (instead of smoke). Vaporization may produce smaller quantities of the toxic smoking byproducts carbon monoxide, polycyclic aromatic hydrocarbons and tar, and compared with smoked cannabis, vaporization was found to significantly reduce carbon monoxide levels [115; 116]. One study evaluated the subjective and physiologic effects and expired carbon monoxide in frequent and occasional cannabis users following placebo, smoked, vaporized, and oral cannabis [145]. Participants' subjective ratings were significantly elevated compared with placebo after smoking and vaporization; only occasional smokers' ratings were significantly elevated compared with placebo following oral dosing. Smoking produced significantly increased expired carbon monoxide concentrations post-dose compared with vaporization [145].

Immunosuppression

Concern was raised in the 1990s over the potential negative effects of cannabinoids on immune function in immunosuppressed patients, particularly those with HIV. Data from several studies have alleviated these concerns. In HIV patients randomized to placebo, dronabinol, or smoked cannabis for 21 days, both cannabinoid groups failed to show increased viral load or reductions in protease inhibitor levels or CD4 or CD8 cell counts. Both cannabinoid groups showed statistically significant weight increases, and the smoked cannabis group showed significantly increased CD4 and CD8 counts [146]. Supportive data include a study of primates injected daily with THC before and after infection with simian immunodeficiency virus (SIV). Contrary to expectations, chronic cannabinoid exposure did not increase viral load or diminish immune function. Instead, the primates given THC showed significantly decreased rates of early mortality from SIV infection, associated with attenuation of plasma and cerebrospinal fluid viral load and retention of body mass [147]. Other conformational findings include a 10-year follow study of HIV patients, which found that regular cannabis smoking had no effect on viral load or CD4 and CD8 cell percentages [148]. An exception comes from preclinical trial results suggesting that increased CB2 activity may impose risks in immunocompromised patients with specific infection, such as *Legionella* [59]. Further, results of a 2022 study found that THC, used for the treatment of chemotherapy-induced nausea, reduced the therapeutic effect of PD-1 blockade that impeded antitumor immunity, indicating an immunosuppressive role of the ECS [149].

Neurocognitive Impairment

There is abundant evidence from studies in adult subjects that smoking cannabis has an acute effect on motor coordination and impairs verbal and working memory for several hours after ingestion, an effect mitigated by several factors, including the degree of previous exposure to cannabis, the dose of THC, the ratio of THC to CBD, and genetic susceptibility [150]. These effects on cognition, mediated by THC, appear to resolve within hours to days after cessation of cannabis exposure.

The long-term effects of chronic cannabis use are more subtle and complex and involve multiple domains of cognitive function, as evidenced by psychologic testing and brain imaging

studies. A growing body of evidence indicates that while significant neuropsychologic deficits may develop following chronic cannabis use, these deficits are largely reversible if chronic use did not commence until after one achieves adulthood (i.e., after full anatomic maturation of the brain). Early-onset (in adolescence) and long-term use of cannabis causes the greatest morphologic and functional impairments in the still-developing brain, and these deficits may not resolve completely after cessation of usage [150; 151].

Results from the 2012 Dunedin study provide the most definitive data on neurocognitive effects from cannabis use [152]. This prospective study followed 1,037 individuals from birth in 1972/1973, assessed their cannabis use at ages 18, 21, 26, 32, and 38 years. Neuropsychologic testing was administered at 13 years of age, before cannabis use was initiated, and at 38 years of age, after persistent cannabis use patterns were established. Family member informants provided corroborating input. Among adolescent-onset, heavy cannabis users, there was an average decline in IQ of 8 points from 13 years of age to 38 years of age (impairment that was global and detectable across five domains of neuropsychologic functioning) and attention and memory problems observable by informants. Following cessation or infrequent use (median past-year use: 14 days) for one year, the IQ decline remained significant. In contrast, adult-onset heavy cannabis users did not exhibit IQ decline as a function of persistent cannabis use. The authors concluded that these findings suggest a neurotoxic effect of cannabis on the developing adolescent brain [152].

Observational studies suggest that THC may have psychotogenic effects while CBD may have antipsychotic effects. However, whether these effects on brain function are consistent with their opposing behavioral effects is unclear. One systematic review sought to identify the key brain substrates where these opposing effects can be observed [153]. Evidence suggests that the opposing effects may be present in the striatum, parahippocampus, anterior cingulate/medial prefrontal cortex, and amygdala, with opposite effects less consistently identified in other regions. Broadly, THC seems to increase brain activation and blood flow, while CBD seems to decrease brain activation and blood flow [153].

While cognitive function in long-term medical cannabis users has not been evaluated, a review of the published research on short- and long-term cognitive function in recreational users suggests that cognitive impairment is unlikely to persist beyond the acute intoxication state, even with high-THC cannabis, in late-onset users, short-term users, and occasional users [150].

Amotivational Syndrome

Amotivational syndrome is not a medical diagnosis but a term used to describe adolescents and young adults who lose interest in and drop out from school, work, socializing, and other goal-directed activities. Cannabis has been cited as the cause when its heavy use accompanies these symptoms, but evidence of causality is lacking [8; 126].

Schizophrenia and Psychoses

An acute psychotic reaction to cannabis has been described and is more likely to occur in young adults who are under stress and have a pre-existing vulnerability to psychoses or schizophrenia. An association has been found between cannabis use history and schizophrenia, but the causal direction of this link has not been established, with many studies suggesting causality showing instead a non-specific association between the most severe levels of cannabis use and a wide range of adverse psychosocial outcomes [126; 154]. Furthermore, cannabis use in the general population soared between 1949 and 1995, while the population rates of schizophrenia remained stable [155].

However, a subgroup of patients who are genetically vulnerable to cannabis-induced acute psychoses, and possibly cannabis-initiated schizophrenia, carry a functional polymorphism in the catechol-O-methyltransferase gene and a polymorphism in the brain-derived neurotrophic factor gene. Considering the potentially substantial risks, cannabis should be avoided in adolescents and adults with current, past, or family history of any psychotic disorder [59; 156].

Toxicity and Overdose

There are no cases in the literature of death due to toxicity following the maximum oral THC dose in dogs (up to 3,000 mg/kg THC) and monkeys (up to 9,000 mg/kg THC). In animals and humans, it is virtually impossible to induce fatal toxicity, and no human fatalities resulting from cannabis ingestion have been documented to date [37].

The side effect profile of medical cannabis is comparable to those produced by other medications tolerated by patients and approved for clinical use by the FDA [126; 157]. The rare acute complications resulting in emergency department presentation, such as panic attacks, psychosis, or convulsions, can be managed with conservative measures such as reassurance in a quiet environment and IV administration of benzodiazepines if needed [14; 158].

The greatest risk for toxicity and potential overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently [159; 160]. A concern with toxic reactions is self-harm. In 2014, a young man (19 years of age) from Colorado died after consuming an edible marijuana product (a cookie). The decedent initially ate only a single serving (one-sixth of the cookie), as directed by the salesclerk. Each serving contained approximately 10 mg of THC. Approximately 30 to 60 minutes later, after not feeling any effects, the decedent consumed the remainder of the cookie. For the next two hours, the young man exhibited erratic speech and hostile behaviors. About 3.5 hours following initial ingestion, he jumped off a fourth floor balcony and died from trauma [161]. In adults, most toxic reactions are mild, but in children, overdose can result in significant respiratory depression [160]. Signs can include somnolence, hallucinations, dyspnea, CNS depression, and even coma. Healthcare professionals should assess for

availability of cannabis in the household if these signs present with no known explanation. If necessary, airway management and ventilation may be administered.

As "Gateway Drug"

The sensationalized 1980s theory of marijuana as the gateway to hard drug use lacks empirical support. While heavy adolescent use is associated with risk of other drug abuse, there is no good evidence of causality or directionality, and the large majority of cannabis users do not progress to "hard" drug use [19; 162]. Alcohol and nicotine use are more significant primers for hard drug use in many individuals [162]. Further research is necessary to clarify these points.

Cannabis Withdrawal Syndrome

What are the symptoms of cannabis withdrawal syndrome?

Until recently, considerable doubt surrounded the possibility of a cannabis withdrawal syndrome; however, cannabis withdrawal syndrome has now been unequivocally demonstrated in heavy chronic recreational users [163]. With abrupt cessation, withdrawal symptoms emerge within one to two days, reach peak intensity after two to six days, and generally resolve within one to two weeks. Common symptoms include irritability or anger, nervousness, tension, restlessness, reduced appetite, insomnia and sleep difficulties, dysphoria, and craving. Less frequent symptoms are chills, stomach pain, shakiness, and sweating [164]. Cannabis withdrawal can resemble a low-grade opioid withdrawal but usually lacks the severe aches and pains, piloerection, diarrhea, sweating, stuffy nose, and muscle spasms common to opioid withdrawal [28; 126].

The severity of cannabis withdrawal, and whether it develops at all in strictly medical users, is unknown. With cessation of regular medical use, the pharmacokinetics and possibly pharmacodynamics of THC, such as slow elimination, may diminish withdrawal symptom manifestation into the subclinical level of severity [28].

Cannabis Addiction

Roughly 9%, or 1 out of 11, who use recreational marijuana will develop an addiction syndrome; the figure increases to 17%, or 1 out of 6, who begin use in their early teens [19; 165]. This compares with lifetime prevalence rates of 32% for nicotine, 23% for heroin, 17% for cocaine, and 15% for alcohol [19; 166; 167].

Addiction risk among medical cannabis users is unknown. Data on cannabis addiction and risk factors come primarily from recreational users who began during adolescence or early adulthood and used high-potency cannabis with great frequency and intensity in the absence of medical supervision. Whether these data apply to the typically older adult patient using smaller doses of medical marijuana for symptom control is not known [168].

According to the Hartford Institute for Geriatric Nursing, little research on effective intervention for psychologic dependence on marijuana is available. Some guidance can be found in smoking cessation and self-help approaches.

(https://hign.org/consultgeri/resources/protocols/substance-misuse-and-alcohol-use-disorders. Last accessed November 21, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

The psychoactive effects and potential abuse liability of recreationally used cannabis are well known, but little is known of this potential with nabiximols spray (equal-ratio THC and CBD). A safety analysis using all published and unpublished nabiximols RCTs found that intoxication scores were low [166]. Euphoria was reported by only 2.2% of subjects, development of tolerance was not documented, abrupt cessation did not result in a withdrawal syndrome, and no cases of abuse or diversion were reported. An abuse liability study of nabiximols in experienced recreational cannabis smokers found some abuse potential at higher doses relative to placebo, but consistently lower abuse liability than equivalent doses of pure THC [166].

Although medical marijuana laws in some states have been anecdotally linked to increased recreational use among adolescents, a 2013 evaluation of the effects of these laws on adolescent marijuana use from 2003 through 2011 found that they had no measurable effect [169].

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) is characterized by severe cyclic nausea and vomiting in chronic (usually heavy) cannabis users [170]. It is a relatively rare adverse effect, but increasing case reports have been noted with the liberalization of cannabis in several states [171]. Individuals with CHS experience temporary relief of symptoms with hot baths or showers, and compulsive bathing is often an identifying feature (differentiating the condition from other causes of cyclic vomiting) [172; 173]. Typically, patients begin with recurrent nausea and progress to intense, persistent vomiting with continued use of cannabis.

The underlying pathogenesis of CHS is unclear, although several theories have been presented. One theory is that the enteric emetic effects of cannabis (e.g., decreased gastrointestinal motility) may promote emesis by over-riding the antiemetic effects mediated by the CNS [172]. Symptoms resolve with cessation of cannabis use; relapse to use often results in a recurrence of the syndrome. Early recognition of CHS is essential to prevent complications related to severe volume depletion [173].

TREATMENT EFFICACY

Neurologists in the 1970s began identifying two distinct patient groups self-medicating with cannabis for symptom alleviation: wounded Vietnam War veterans with traumatic spinal injury and female patients with multiple sclerosis, migraine, or menstrual pain. Although these observations led to several small clinical trials supporting the claims of individual patients, regulatory hurdles in conducting clinical research resulted in relatively few efficacy studies [157]. Since 2000, there has been a significant increase in the quantity and quality of cannabis efficacy studies.

For some clinical conditions, most of the published research involves oral cannabinoids, and there are questions over the extent this efficacy can be extrapolated to cannabis. Some reports indicate that patients benefiting from oral cannabinoids are likely to benefit from smoked cannabis, but the reverse is not always true [165]. For example, inhaled cannabis trials for the management of nausea and vomiting are sparse. Although RCTs of dronabinol or nabilone predominate and have consistently shown efficacy, patients tend to prefer smoked over oral delivery due to the rapid alleviation of nausea and vomiting, ease of titration, and greater tolerability. Thus, for indications for which cannabis RCTs are few or absent, it seems reasonable to extrapolate non-cannabis cannabinoid efficacy to smoked cannabis.

CHRONIC PAIN

As noted, cannabis and other cannabinoids are seldom considered first-choice therapeutic options but are used instead in patients for whom standard therapies are ineffective or intolerable either as sole therapy or more typically as an add-on to the current regimen [2]. Cannabis has been safely co-administered with a wide range of other drug agents (as discussed) and acts synergistically with opioids to enhance analgesia and allow opioid dose reduction. Chronic pain treatment often requires multiple drug agents that target different pain mechanisms, and the novel mechanism and superior safety profile of cannabis versus opioids suggests that it can be a valuable addition to therapeutic options for chronic pain [174; 175].

Chronic pain is a highly prevalent, heterogeneous group of disorders that in many patients is refractory or only partially responsive to treatment [174]. Many cannabis analgesia studies use a benchmark of more than 30% reduction in pain intensity, because a 30% decrease in pain has been validated as the threshold necessary for meaningful improvements in quality of life [26]. The following studies on chronic pain are presented in greater detail because their results and the scientifically rigorous conditions under which they were conducted are now regarded as providing the most definitive evidence of efficacy [88].

Neuropathic Pain

More than 2 million Americans currently suffer chronic and debilitating neuropathic pain from trauma or disease affecting the peripheral or central nervous system. These conditions include diabetic neuropathy, nerve compression syndromes, postherpetic or trigeminal neuralgia, stroke, multiple sclerosis, and spinal cord injury. Neuropathic pain is comprised of a sensory component of allodynia (pain response to benign stimuli) and hyperalgesia (exaggerated pain to mild provocation), and an affective component of prominent anxiety or depression, diminished motivation, and changes in motor control. Neuropathic pain is difficult to treat, and while the sensory and affective components may respond to opioid therapy, this drug class often produces intolerable side effects or fails to provide meaningful pain reduction. Earlier trials suggested effective analgesia with cannabis, and priorities in finding therapeutic alternatives to high-potency opioids prompted investigation of cannabis efficacy in neuropathic pain [176; 177]. Finding even modest clinical benefit is important given the limited treatment options for these patients, and the RCTs uniformly found the number needed to treat to achieve 30% pain reduction was 3.5 for cannabis [178]. In one study, use of nabiximols was found to be the most effective cannabinoid for multiple sclerosis-associated central pain [177]. Unless otherwise noted, the RCT methods in the following sections were double-blinded and placebo-controlled with inert, non-active cannabis and/or pills.

The National Institute for Health and Care Excellence recommends against starting *Cannabis sativa* extract to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so.

(https://www.nice.org.uk/guidance/cg173. Last accessed November 21, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

HIV-Associated Distal Sensory Polyneuropathy

In a five-day trial of 55 patients with HIV-associated distal sensory polyneuropathy, overall daily pain levels were reduced by 34% with active cannabis vs. 17% with placebo, and pain reduction of more than 30% was attained by 52% with active cannabis vs. 24% with placebo; both differences in pain reduction were statistically significant. Cannabis was well tolerated and no safety concerns were raised. Cannabis produced more side effects than placebo, the most common being sedation, anxiety, and dizziness, all rated as "mild" in severity [179].

Another study titrated 34 patients with HIV-associated distal sensory polyneuropathy to individualized effective and tolerated inhaled cannabis doses. Titration started with 4% THC or placebo, with downward or upward adjustment for problematic side effects or incomplete pain relief, respectively. In five study phases over seven weeks, >30% pain reduction was attained by 46% with cannabis vs. 18% with placebo (statistically significant). Side effects were more frequent with cannabis, the most common being sleepiness or sedation, fatigue, and difficulty concentrating. Aside from acute psychotic symptoms develop-

ing early in the only cannabis-naïve subject, all side effects were "mild" and no safety concerns emerged [180].

Both of these studies restricted enrollment to patients with refractory pain despite optimal pharmacologic management, and all patients remained on their pre-study analgesic therapies. Of note, the significant magnitude of pain reduction in HIV neuropathy with cannabis therapy represents an important medical finding, because this type of pain has been notoriously resistant to standard treatment approaches [60].

Neuropathic Pain of Heterogeneous Origin

A trial of 38 patients with complex regional pain syndrome (Type I), physical trauma to nerve bundles, spinal cord injury, multiple sclerosis, or diabetes smoked a single high-(7%), low-(3.5%), or 0% THC (placebo) cannabis cigarette in three six-hour sessions [181]. Previous cannabis exposure was required. Low-and high-THC cannabis produced effective analgesia with comparability, suggesting a dose ceiling. Unpleasant side effects were more frequent with high-dose THC. Side effects were comparable between low-dose and placebo, and no subject terminated their involvement from side effects. Negative mood changes (e.g., sadness, anxiety, fearfulness) were not found. The authors stated the effects produced by cannabis were comparable to those observed with opioid analgesics, with pain relief resulting from equal alleviation of the affective and sensory component of pain but not resulting from a relaxing or tranquilizing effect [181].

Chronic Post-Traumatic or Postsurgical Neuropathic Pain

In an RCT with crossover, 23 subjects with chronic post-traumatic neuropathic pain smoked a single 25-mg dose of 0%, 2.5%, 6%, or 9.4% THC cannabis, three times daily over four 14-day periods alternating with 9-day washout [134]. The average daily pain intensity score was significantly lower with high-dose (9.4%) THC than with placebo. Intermediate potencies showed reduced but non-significant pain reduction vs. placebo. In addition, the 9.4% THC dose significantly improved ability to fall asleep and sleep quality compared with placebo. Side effects were more frequent with 9.4% THC cannabis and included headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness, and cough. Most side effects were mild, and no serious or unexpected adverse events occurred. The authors concluded that single-inhalation 9.4% THC cannabis reduced pain intensity, improved sleep, and was well tolerated in these patients [134].

Vaporized Cannabis in Chronic Neuropathic Pain

In an RCT with crossover, patients with central or peripheral neuropathic pain resistant to conventional drug therapies received single-dose 3.53% THC, 1.29% THC, or 0% THC (placebo) cannabis [182]. Significant analgesic response was found with active but not placebo cannabis. Analgesia was equivalent with medium- vs. low-dose cannabis. Psychoactive effects were minimal and well tolerated, and neuropsychologic effects reversed within one to two hours. The authors state their findings of analgesic efficacy with low-dose cannabis in treatment-refractory neuropathic pain have large clinical value and that a negative impact on daily functioning is unlikely based on the observed side effects [182].

Experimental Neuropathic Pain

To examine the dose-by-time analgesic effect of cannabis, 19 healthy volunteers received capsaicin injection under the skin to simulate neuropathic pain and were administered in random sequence low-, medium-, and high-dose cannabis (2%, 4%, and 8% THC) or placebo cigarettes [183]. No effect on capsaicin-induced pain was found at any dose five minutes after smoking. At the 45-minute time point, there was a significant pain decrease with 4% THC, a significant pain increase with 8% THC, and no differences with 2% THC or placebo. A significant inverse relationship between pain perception and plasma THC was also found. The authors conclude a "therapeutic window" (or optimal dose) may exist for smoked cannabis with acute neuropathic pain, with low doses ineffective, medium doses efficacious, and higher doses pain-enhancing [183]. This biphasic dose-response effect of cannabinoids in acute neuropathic pain is consistent with the previous body of research [60].

Nociceptive Pain

Cannabis has not been found effective in acute nociceptive pain and has shown a biphasic dose-response effect with acute neuropathic pain [60]. However, chronic pain results from the development of abnormal sensory processing and other alterations in peripheral and CNS pain pathways [184]. The endocannabinoid receptor complex interacts with signaling pathways and pain circuitries expressing abnormal function in chronic pain, accounting for therapeutic effect not seen in acute pain [61].

Clinical trials of cannabinoids in patients with chronic pain due to rheumatoid arthritis, fibromyalgia syndrome, or cancer pain found statistically significant pain relief consistently around 30% in magnitude [185]. When considered alone, changes in pain scores understate the extent of overall relief in these patients, because improved mood, sleep, coping, and quality-of-life scores have been consistently reported with cannabis and cannabinoids. Patients with fibromyalgia and clinically relevant depression showed greater benefit from cannabinoids than non-depressed patients with fibromyalgia [60].

Reducing Opioid Requirements

Studies of chronic non-malignant pain have found significant pain relief, reduced bother from pain, and prevention or reduction of opioid tolerance with cannabinoid addition to opioid therapy [186; 187]. An RCT with patients with severe cancer pain found cannabinoid addition to opioid therapy led to pain level reduction of 30% to 50% in 43% of patients [60; 188]. In patients with pain from chronic progressive multiple sclerosis, HIV-related neuropathy, or spinal trauma pain poorly controlled with high-dose opioids, one study found adding smoked cannabis led to opioid dose decreases of 60% to 100%

and improvements in pain relief and function [189]. Abrams studied the effect on pain from giving four days of vaporized cannabis to 21 patients with mixed persistent chronic pain despite stable long-term use of morphine sustained-release (SR) or oxycodone SR (mean dose: 62 mg and 53 mg, respectively) [117]. Cannabis slightly reduced morphine levels, had no effect on oxycodone levels, and reduced pain by roughly 30%. A survey of 29 medicinal cannabis patients with chronic pain found that of the eight using cannabis as their sole analgesic, all had been prescribed but abandoned opioids for cannabis due to the greater perceived pain relief, fewer side effects, or absence of problematic opioid use risk [190].

Combining opioids and cannabis in pain therapy offers the added potential advantage of synergistic analgesic action that decreases the dosage requirements and side effects of both agents. Such an approach exploits the considerable functional interaction between endogenous opioid and cannabinoid systems and may also reduce the development of tolerance with both agents [176].

NEUROPSYCHIATRIC DISORDERS

Multiple Sclerosis and Spasticity

Spasticity is a core symptom of multiple sclerosis, is common after stroke and with other neurologic conditions, and greatly limits movement, activities of daily living, and participation in life by those afflicted. Oral antispasmodic agents are of limited effectiveness, and beneficial treatment options for spasticity have not significantly expanded since the late 1990s [191]. Consequently, many patients with multiple sclerosis have sought relief through cannabis use. The oromucosal cannabinoid spray nabiximols appears efficacious in multiple sclerosis but is not yet approved for clinical use in the United States [192]. Several clinical trials of cannabis in multiple sclerosis have been performed, and these studies have demonstrated cannabis efficacy in reducing spasticity and pain [193; 194]. Cannabis-based medicine was effective in reducing pain and sleep disturbance in patients with multiple sclerosis and central neuropathic pain in one trial, while other RCTs demonstrated significant improvements in spasticity, disability, cognition, mood, sleep, and fatigue [195; 196; 197]. A 2004 study also found that cannabis helped alleviate bladder dysfunction, a problematic multiple sclerosis symptom [198]. A double-blind, placebo-controlled crossover study randomized patients with multiple sclerosis to smoke 4% THC or placebo cannabis cigarettes once daily for three days [194]. The findings of significant objective improvement in pain and spasticity differed from earlier trials showing significant improvement in patient perceptions but not objective measurements of spasticity [194]. Side effects have been acceptable to patients, and no serious safety concerns have emerged. Preclinical studies suggest a positive effect on the underlying disease processes in multiple sclerosis, evidence of an anti-inflammatory effect, and facilitation of remyelination and neuroprotection [199].

The American Academy of Neurology asserts that clinicians might offer oral cannabis extract to patients with multiple sclerosis to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain).

(https://www.aan.com/Guidelines/home/GuidelineDetail/641. Last accessed November 21, 2023.)

Level of Evidence: A (Established as effective for the given condition in the specified population.)

Post-Traumatic Stress Disorder

Numerous case reports describe substantial reduction in PTSD symptoms with cannabis use [200]. An open-label study of nabilone in 47 patients with treatment-refractory PTSD-associated nightmares found cessation or significantly reduced nightmare intensity in 72% of participants and diminished daytime flashbacks and night sweats and/or improved sleep duration and quality for some [201]. More robust research supporting the safety and efficacy of this use is lacking [202].

Seizure Disorders

As noted, cannabis can be bred to overexpress CBD in order to avoid psychoactive effects. In one study, CBD-enriched cannabis was administered to 19 children with treatment-refractory epilepsy (after an average of 12 pre-study antiepileptic drugs) and their parents were interviewed to assess efficacy. Of the 19 patients, 84% showed reduced seizure frequency, 11% became completely seizure-free, 42% showed greater than 80% seizure reduction, and 32% showed a 25% to 60% seizure reduction. Other beneficial effects included increased alertness, elevated mood, and improved sleep, and side effects included drowsiness and fatigue. In 2018, the FDA approved purified cannabidiol for use in patients with Lennox-Gastaut and Dravet syndromes, but until recently, most published studies were relatively short-term (12 to 16 weeks) [83; 203; 204]. The objective of a 2019 study was to evaluate the long-term safety, tolerability, and efficacy of cannabidiol in children with epilepsy [204]. This open-label prospective study enrolled 26 children 1 to 17 years of age with refractory epilepsy, most with genetic epilepsies with daily or weekly seizures and multiple seizure types. All of the children were refractory to prior antiepileptic drugs and were, on average, taking two antiepileptic drugs. The duration of therapy ranged from 4 to 53 months (mean: 21 months). Adverse events were reported in 21 patients (80.8%) and included reduced appetite, diarrhea, and weight loss. Serious adverse events were reported in six patients (23.1%) and included status epilepticus, catatonia, and hypoalbuminemia. Fifteen patients (57.7%) discontinued cannabidiol for lack of efficacy. At 24 months, 9 of the original 26 patients (34.6%) remained on cannabidiol as adjunctive therapy. Of these, seven reported a more than 50% reduction in motor seizures and three remained seizure free [204].

Fibromyalgia

A matched case control study of medicinal cannabis use for symptom control in fibromyalgia found patient accounts of cannabis efficacy in alleviating pain, sleep disturbance, stiffness, problematic mood and anxiety, and headache, and objectively measured significant improvements in pain, stiffness, relaxation, and well-being [205]. An estimated 68% of participants experienced a reduction in standard therapies following cannabis initiation. Frequent side effects were somnolence, dry mouth, sedation, and dizziness. Significantly higher mental health-related quality of life scores were found in medicinal cannabis users compared with non-users [205].

GASTROINTESTINAL DISORDERS/DYSFUNCTION

Irritable Bowel Syndrome and Crohn Disease

In one study of patients with chronic irritable bowel syndrome, inhaled cannabis for three months led to improvements in quality of life, disease activity, and weight gain [206]. Observational study data in patients with Crohn disease suggest that cannabis helps alleviate disease symptom severity and reduces the requirements for other medications and/or the need for surgery [207].

Nausea and Vomiting

How does cannabis act to prevent chemotherapy-induced nausea and vomiting?

Chemotherapy-induced nausea and vomiting was very difficult to manage before the introduction of 5-HT3 receptor antagonists. However, 5-HT3 antagonists are not very effective in blocking acute nausea and are ineffective in reducing delayed (24 hours or more) and anticipatory (conditioned) nausea and vomiting. The drugs of the NK1 receptor antagonist class are more effective with delayed as well as acute vomiting, although they are much less effective in reducing nausea. Nausea is the most distressing symptom experienced by chemotherapy patients because it is a continuous sensation, and as many as 20% of patients with cancer discontinue chemotherapy because current standard agents fail to control nausea [105; 208]. A vast body of anecdotal evidence from the past 150 years as well as preclinical and clinical trial results strongly indicate a valuable role for cannabis in controlling nausea and vomiting caused by cytotoxic drug administration or secondary to another primary medical condition [105].

Most studies showing cannabinoid efficacy have used oral synthetics. The synthetic THC analogue nabilone and the synthetic THC dronabinol received initial regulatory approval for chemotherapy-induced nausea and vomiting based on improved outcomes over standard antiemetics used in the 1980s [105]. An older study of Δ8-THC, a close but less psychoactive relative of Δ9-THC, in pediatric patients with chemotherapy-induced nausea and vomiting found effective suppression of nausea and vomiting with negligible side effects [101]. More recently, an RCT with adults experiencing chemotherapy-induced nausea and vomiting found dronabinol comparable to the 5-HT3 antagonist ondansetron and superior to placebo [105; 209].

An additional rationale for cannabis use in chemotherapy-induced nausea and vomiting involves the principle of optimizing treatment by combining agents that inhibit multiple neurotransmitter pathways that mediate nausea and vomiting reflexes. Cannabinoids have known activity in many of these systems and can effectively compensate for the deficiencies of 5-HT3 antagonists and NK1 receptor inhibitors in preventing nausea and delayed and breakthrough chemotherapy-induced vomiting. Because cannabidiol does not induce psychotropic effects, its potential role as an antiemetic for patients undergoing chemotherapy is being investigated [210]. An RCT with patients with gynecologic cancer found that a cannabinoid extract (THC:CBD 1:1) was an appropriate adjuvant to reduce chemotherapy-induced nausea and vomiting in patients receiving high-emetogenic chemotherapy [211].

The potential role of smoked cannabis in rapidly alleviating breakthrough nausea and vomiting is especially promising given the findings of strong patient preference for smoked cannabis over oral therapies in a number of comparative clinical trials [3]. A study comparing 748 patients with cancer who smoked cannabis before and after chemotherapy with 345 patients using dronabinol found a reduction in nausea and vomiting of 70% to 100% with cannabis compared with 76% to 88% with dronabinol [212]. Oral cannabinoids may be less effective than sublingual or inhaled cannabis in chemotherapy-induced nausea and vomiting, and most patients prefer smoked marijuana over oral synthetic cannabinoids [213]. Several reasons account for this preference:

- The advantages and ease of self-titration with smoked cannabis
- Difficulty in swallowing pills when experiencing emesis
- Rapid speed of onset compared with oral delivery
- The combined therapeutic effects of additional cannabinoids in smoked cannabis

A meta-analysis of cannabinoid efficacy in chemotherapy-induced nausea and vomiting found superior antiemetic efficacy of dronabinol, nabilone, levonantradol (not approved for use in the United States), and smoked cannabis compared with conventional drugs and placebo [214].

Smoked cannabis has also been shown to improve non-chemotherapy medication adherence in which nausea and vomiting are common side effects. In a study of 258 patients receiving antiretroviral therapy for HIV infection, the subgroup of patients experiencing moderate-to-severe nausea who used marijuana were significantly more adherent to their regimen than non-marijuana users (75% vs. 48%). Alcohol use, the use of other illicit drugs, and marijuana use in those without nausea were associated with lower adherence [215].

HEPATITIS C THERAPY

Until 2014, interferon/ribavirin combination therapy was the sole treatment for hepatitis C virus infection, and it remains widely used. However, patient intolerability of side effects has been a substantial barrier to treatment success. Most patients experience significant side effects that can include debilitating fatigue, headaches, nausea, anorexia, clinical depression, and insomnia. Patients usually require adjunctive pharmacotherapy for side-effect management, but relief is often incomplete, leading to dose reduction or termination. Illicit cannabis is used by some patients to lessen side effects.

A prospective study compared 71 patients with hepatitis C receiving interferon/ribavirin who either used cannabis (31%) or did not use cannabis (69%) for side effect relief [216]. Several statistically significant differences were found between the cannabis-and non-cannabis using patients. Five percent of cannabis users vs. 33% of non-users discontinued therapy. Compared with 18% of non-users, 54% of cannabis users had a sustained virologic response, with post-treatment virologic relapse rates of 14% in cannabis users vs. 61% in non-users. Finally, 86% of cannabis users were treatment-adherent, while 59% of non-users adhered to treatment. Occasional and regular cannabis users did not differ in adherence or sustained virologic response. The authors conclude that moderate cannabis use may offer significant benefit to some patients enduring the frequently debilitating medication regimen for hepatitis C and that an additional biologic benefit beyond adherence promotion cannot be ruled out [216].

SLEEP DISORDERS

Sleep disturbances contribute to greater pain, disease activity, mood disturbance, and disability in patients with chronic pain, and restoring normal sleep improves pain and mood disorders associated with uncontrolled pain and sleep impairment [60]. However, drugs used for sleep induction (such as benzodiazepines) increase rates of sleep-disordered breathing and elevate the risk of respiratory depression and fatal respiratory arrest when combined with opioids, antihistamines, or alcohol. Unlike sedative-hypnotics, cannabinoids suppress sleep-related apnea and do not enhance opioid-induced respiratory depression [37]. Research in chronic pain patients has consistently shown beneficial cannabinoid effects on sleep quality [60].

CANCER- AND HIV-ASSOCIATED ANOREXIA AND WEIGHT LOSS

Anorexia, early satiety, weight loss, and cachexia are prevalent in late-stage cancer and advanced HIV disease. Most standard treatments are ineffective, but many patients show favorable response with marijuana and cannabinoids [88]. A 2005 survey of HIV-positive medical marijuana users found decreased nausea and other burdensome symptoms in 93% of participants and substantial improvement of nausea in 56% [4]. A double-blind clinical trial of HIV-positive patients found smoked cannabis increased daily caloric intake and body weight, with few adverse effects [217]. Benefits from smoked cannabis reported by 252 patients with HIV/AIDS included relief of anxiety and/or depression (57%), improved appetite (53%), increased pleasure (33%), and pain relief (28%). However, recent use of marijuana was strongly associated with severe nausea [218]. Long-term data on the sustained effect of cannabis and cannabinoids for the treatment of HIV/AIDS-associated anorexia are lacking [219].

A review of cannabinoid use in patients with cancer found a beneficial effect in stimulating appetite in patients who were receiving chemotherapy or experiencing pain [220]. Interestingly, the results of several preclinical and preliminary clinical testing studies have suggested that cannabinoids inhibit tumor and/or malignant cell growth in pancreatic, lung, leukemic, melanoma, oral, and lymphoma cancers and other malignant tumors [220; 222].

GLAUCOMA

High intraocular pressure is a risk factor for glaucoma, and smoked cannabis has been found to reduce pupil constriction, conjunctival hyperemia, and intraocular pressure by approximately 25% in those with normal range intraocular pressure with visual field changes, healthy adults, and patients with glaucoma [223]. However, the short duration of effect (three to four hours), side effect profile (including potentially lowering blood supply to the optic nerve by lowering systemic blood pressure), and lack of evidence regarding impact on the course of the disease limit the potential positive impact of cannabis for the treatment of treatment-resistant glaucoma [223; 224]. The American Glaucoma Society recommends against the use of smoked cannabis for the treatment of glaucoma, and the IOM and the American Academy of Ophthalmology concluded that smoked cannabis is neither a safer alternative nor offers increased benefits compared with conventional pharmaceutical agents [224]. More research is necessary to determine if topical administration may confer greater benefits.

NATURALISTIC STUDIES OF MEDICAL CANNABIS USE

Naturalistic studies have been performed in persons illicitly using medicinal cannabis for symptom relief over diverse diseases and conditions. These studies provide important background information on medicinal cannabis users and improved understanding of limitations with standard therapeutics [15]. Diverse backgrounds have been found in medical user members of Cannabis Buyer's Cooperatives. A 1998 study of 1,500 cooperative members in Oakland and Los Angeles found illicit cannabis was used for HIV/AIDS in 62% to 70% of members and cancer in 4% to 10%. In the remaining Oakland members, another 10% reported using cannabis for pain or arthritis, 8% for mood disorders, 6% for neurologic symptoms, 4% for glaucoma, and 6% for "other" conditions; in remaining Los Angeles members, 20% used cannabis for "other" diagnoses, including neurologic diseases, glaucoma, hepatitis, cardiovascular disease, and renal failure [225].

These patients differed from those in a UK study of 2,969 adults who used cannabis for symptom relief in chronic pain (25%), multiple sclerosis (22%), depression (22%), arthritis

(21%), and neuropathy (19%) [226]. In another study of 209 Canadians using cannabis to control chronic (median: eight years) non-cancer pain, the most frequent pain type was trauma or postsurgical pain (51%), with the most frequent pain sites being neck/upper body pain (68%) and myofascial pain (65%) [227]. Frequency of cannabis analgesic use was evenly distributed over the intervals of more than once daily, once daily, weekly, and rarely. Greatest symptom improvement was in pain, sleep, and mood [227]. In a report involving 220 Canadian patients with multiple sclerosis, 36% had used cannabis prior to legalization and 14% continued its use for symptom relief; the greatest improvements were in pain, stress, sleep difficulties, mood, and muscle spasm/stiffness [228]. Another study found that 80% of patients with limitations in activity or function from chronic illness attained consistent pain reduction, on a 1–10 scale, ranging from 7 to 10 [32].

ALTERNATIVES TO CANNABIS

Opponents of medicinal cannabis often state that dronabinol provides the alleged benefits of smoked cannabis and fewer risks, essentially arguing that any benefit is the result of Δ9-THC. However, dronabinol is not a realistic substitute for inhaled cannabis for a number of reasons. Many patients describe dronabinol's effect as unpleasant, due to excessive sedation and an overwhelming psychoactive effect. This is likely from its 100% THC content versus the 10% to 20% THC (and variable CBD) content in natural cannabis [229]. Also, dronabinol is often poorly absorbed as an oral agent, and the dosage is difficult to monitor and control. Patients with severe nausea and vomiting, or who otherwise cannot swallow, are unable to ingest oral medication (or keep it down). Cannabis possesses therapeutic constituents in addition to Δ9-THC, and the rapid onset of effect attained by inhalation can provide quick relief and allow dose titration unable to be achieved with slower-onset oral agents [88].

INDICATIONS AND PRACTITIONER CONSIDERATIONS

INDICATIONS

As noted, cannabis is generally recommended for patients in whom standard therapies have been ineffective or intolerable. Appropriate indications for medical cannabis have most recently been formalized by the State of New York, the OMC in the Netherlands, and Health Canada and include [230; 231; 232]:

- Disorders of pain and spasticity, including intractable spasticity, multiple sclerosis, and spinal cord damage or injury
- Chronic neuropathic pain, including nerve damage, phantom limb pain, facial neuralgia, and postherpetic neuralgia
- Pain from cancer and HIV/AIDS
- Nausea and vomiting from chemotherapy, radiotherapy, and/or medication for HIV and hepatitis C
- Neuropsychiatric disorders, including tics associated with Tourette syndrome, epilepsy, neuropathy, Parkinson disease, and PTSD
- Autoimmune conditions, including arthritis, lupus, and Crohn disease
- Palliative treatment of cancer and AIDS to stimulate appetite, avoid weight loss, and reduce debilitation and wasting syndrome
- Treatment-resistant glaucoma
- A debilitating symptom associated with a medical condition or the medical treatment of that condition, other than those described above

DOSE AND ADMINISTRATION GUIDANCE

The ideal dosage of cannabis or THC varies by condition and patient characteristics. Inhaled cannabis is not a preferred route of administration due to difficulty with dosing, risk of respiratory damage, and multi-component composition [232]. For the treatment of refractory pain, nabiximols spray is preferred over smoked cannabis. The initial recommended dose is one spray sublingually at bedtime and not more than 12 sprays daily [232]. For the treatment of chemotherapy-induced nausea and vomiting, nabilone is preferred over cannabis [232]. The recommended initial oral dose is 0.25–0.5 mg at bedtime and not more than 6 mg/day [232]. Studies conducted in Israel and the Netherlands found the average dose for patients in their medical cannabis programs was 1.5 g/day and 0.68 g/day, respectively [27; 233].

The recommended initial dose of dronabinol is 2.5 mg twice daily, but this may be reduced to 2.5 mg once daily at bedtime if the patient is unable to tolerate twice-daily dosing [83; 232]. This may be titrated up to effect to a maximum of 20 mg per day. Nabilone for chemotherapy-induced nausea and vomiting is started at 1–2 mg twice daily and may be increased to a maximum of 6 mg/day in three divided doses [83; 232].

In all cases, it is important to begin with the lower dose in the range and increase if needed. If the starting dose is tolerated but the desired effects are not achieved, slowly increase the dose [14; 232]. One should keep in mind that the therapeutic dose is usually lower than the recreational dose. For medicinal purposes, the OMC recommends vaporized or oral ingestion; smoking is not recommended [14]. Patients orally ingesting cannabis or cannabinoids should be advised of the slow onset and the need to ingest small amounts spaced several hours apart [14].

Vaporizing

Though it is often recommended in discussions of medical marijuana use, many healthcare professionals are not familiar with the process of administering cannabis through vaporizing. In essence, active cannabis ingredients can be vaporized if cannabis is heated and inhaled without combustion. The right

temperature is reached when vapor is just visible as a light mist, but no smoke has formed, usually at a temperature of 180°C to 195°C. Using this method, the same cannabis can be used two to three times. In most cases, the recommended initial dosing is one to two times per day, with a minimum of 5 to 15 minutes between inhalations. Patients may need to inhale a few times, until the desired effect is reached or side effects occur. It may take up to two weeks to achieve steady-state THC concentrations and full therapeutic effect.

Tea

As discussed, a cannabis tea may be used to ingest medical marijuana, though the limited THC bioavailability and lack of water solubility make this a less attractive option in most cases. To brew the cannabis tea, 0.5 g cannabis is boiled in a pint of water for 15 minutes. The plant material is then strained out of the tea and sweeteners are added. The addition of a substance containing fat (e.g., milk powder) can improve the availability of THC in the tea. The tea may be kept refrigerated for up to five days. The usual initial dose is one cup in the evening, though if the effects are insufficient after two weeks, an additional cup (usually in the morning) may be added.

CONTRAINDICATIONS AND PRECAUTIONS

What are contraindications to the use of medical marijuana?

At this time, experts recommend limiting medical cannabis use to adults older than 18 years of age [14; 231]. There are several other contraindications to the use of medical marijuana, including [14; 231]:

- Current, past, or family history of schizophrenia or other psychotic disorders
- History of hypersensitivity to cannabinoids or smoke
- Severe cardiopulmonary disease
- Severe liver or renal disease
- Pregnancy or planned pregnancy
- Breastfeeding

Cannabis may be considered with caution for patients with the following factors when alternatives have been ineffective/poorly tolerated, the benefit/risk ratio closely evaluated, and with sufficient monitoring [14; 231]:

- Smoked cannabis in patients with asthma or COPD
- History of substance abuse
- Non-psychotic psychiatric condition (e.g., anxiety, panic attacks)
- Current CNS depressant therapy

PATIENT EDUCATION

If a patient is prescribed a cannabinoid or medical cannabis, he or she should be advised of possible memory impairment and instructed to report any mental or behavioral changes. In addition, operating a vehicle or heavy machinery is not recommended after having taken the drug, and patients should limit or abstain from alcohol.

All patients should be monitored for outcomes, similar to the processes used for opioid follow-up monitoring. Any concomitant medications and drug interactions should also be monitored. For example, there is little evidence of clinically significant CYP450 interactions, but co-administration may potentiate somnolence [123; 177; 221]. Side effects should be noted and reported; however, it is important to note that tolerance may develop over time to side effects of mild-to-moderate severity. Smoking or vaporization should cease if a patient begins experiencing disorientation, dizziness, ataxia, agitation, anxiety, tachycardia and orthostatic hypotension, depression, hallucinations, or psychosis [14].

For patients who are not proficient in English, it is important that information regarding the benefits and risks associated with the use of medical marijuana and other cannabinoids be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between 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 treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

CONCLUSION

Medical marijuana has become a hot topic in health care. Initiatives to either legalize or prohibit marijuana use for medical purposes are being legislated by politicians or presented to voters in numerous municipalities. The preponderance of information on this subject seems to come from highly visible individuals or groups who either vehemently oppose or passionately advocate legal access to medical cannabis. What is most needed is a comprehensive presentation of the scientific facts from a dispassionate, evidence-based perspective. This course has reviewed the body of research on medical cannabis to provide the most current information on potential indications, pharmacology and mechanism of action, acute and chronic side effects, and contraindications for medicinal cannabis. A clear understanding of the potential uses of cannabinoids in the treatment of various medical conditions will benefit patients and healthcare providers alike.

Customer Information and Evaluation are located on pages 87–88.

Pathophysiology: The Hepatobiliary System

Includes 3 Pharmacotherapeutic/Pharmacology Hours

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 illness.

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

1. Identify and describe the anatomical structure of the liver.
2. Explain the liver's functions, integrating how these processes inter-relate with the hepatic and biliary systems.
3. Describe the anatomical location and structure and regulatory mechanisms of the gallbladder.
4. Discuss the pathophysiologic effects of hepatobiliary dysfunction, including how these conditions impact overall health and clinical management.
5. Review the impact of hepatobiliary dysfunction on the integumentary, cardiovascular, and neurologic systems.
6. Analyze how psychosocial and lifestyle factors influence the risk and progression of hepatobiliary disorders.
7. Conduct a comprehensive nursing assessment by effectively gathering and analyzing subjective and objective data related to hepatobiliary function.
8. Outline and interpret various diagnostic studies for hepatobiliary disorders, including the purpose, procedure, and nursing implications for advanced diagnostic tests.
9. Identify and formulate nursing diagnoses for patients with hepatic or biliary dysfunction based on comprehensive assessments.
10. Outline a comprehensive nursing care plan for patients with hepatobiliary dysfunction.
11. Differentiate between congenital disorders of the hepatic and biliary systems, specifically Gilbert syndrome and Alagille syndrome.
12. Discuss cirrhosis, including demonstrating an ability to apply appropriate therapeutic measures for managing complications and execute specific nursing interventions.
13. Differentiate between various forms of alcohol-induced liver disease.
14. Evaluate the role of metabolic dysfunction in the development of metabolic dysfunction-associated steatotic liver disease (MASLD).
15. Compare and contrast primary and secondary biliary cholangitis, including approaches to management.
16. Identify and differentiate between various infectious and inflammatory disorders of the hepatobiliary system.
17. Describe the various neoplastic and obstructive disorders affecting the hepatobiliary system.
18. Outline the key criteria for liver transplantation candidacy and the processes involved in donor organ selection and transplantation.

Faculty
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. (A complete biography can be found at NetCE.com.)

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

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

The liver, the gallbladder, and the exocrine pancreas are classified as accessory organs of the gastrointestinal tract and digestion. They introduce digestive hormones and enzymes into the alimentary canal, ensuring that the nutrients critical to life can be absorbed selectively by the small intestines into the bloodstream. In addition to producing digestive secretions, the liver and the pancreas have other important functions. The exocrine pancreas, for example, supplies the insulin and glucagon needed in cell metabolism, whereas the liver synthesizes glucose, plasma proteins, and blood clotting factors and is responsible for the degradation and elimination of drugs and hormones, among other functions. The liver and gallbladder perform several regulatory functions essential to the maintenance of homeostasis. The liver synthesizes a number of substances, including coagulation factors that are vital to life. The gallbladder plays an important role in the digestive process, in particular the digestion of fats. Although the human body can survive the loss of the gallbladder, survival without a liver is not possible [1; 2]. This course focuses on functions and disorders of the liver, the biliary tract, and the gallbladder.

STRUCTURAL AND FUNCTIONAL INTER-RELATIONSHIPS

The hepatic and biliary systems are both structurally and functionally inter-related. The liver, the largest of the internal organs, performs the following functions [3]:

- Storage and filtration of blood (a vascular function)
- Production of bile (a regulatory function)
- Removal of bilirubin from the body (an excretory function)
- Metabolism of carbohydrates, fats, and protein (a metabolic function)
- Storage of vitamins A, D, and B12
- Synthesis of coagulation factors
- Detoxification of chemicals

The principal function of the gallbladder is to store and release bile [3].

STRUCTURE OF THE LIVER

What are the major regions of the liver?

The normal liver of an adult weights about 1,500 g. The wedge-shaped organ lies in the upper right quadrant of the abdominal cavity, where it is protected by the rib cage. The superior surface underlies the diaphragm. The posterior and inferior surfaces together are generally referred to as the visceral surface. The right visceral surface is in contact with portions of the colon, the kidneys, the adrenal glands, and the duodenum; the left visceral surface is bordered by the stomach and spleen [3; 4].

The liver is divided into two major regions, the right and left lobes, separated by fissures on the inferior surface on the liver. On the posterior and inferior surfaces of the right lobe are two smaller lobes: the caudate and quadrate lobes. The gallbladder and the inferior vena cava lie in two shallow fossae that parallel the fissures. Veins, arteries, nerves, and lymphatic vessels enter and leave the liver through a space between the caudate and quadrate lobes [3; 4].

Except for the so-called bare area, which rests against the diaphragm, the liver is covered by visceral peritoneum. A thin layer of connective tissue extends into each lobe to divide the liver into 50,000–100,000 liver lobules. These tiny structures, a few millimeters in length and 1–2 mm in diameter, are the functional units of the liver [3; 4].

The Functional Liver Lobule

Each liver lobule is composed of plate like "spokes" of hepatic cells that radiate from a "hub" or central vein that passes through the connective tissue between lobules. The central veins are branches of the portal vein that, together with the portal artery, furnish the blood supply of the liver. Bile is manufactured in the hepatic plates, each of which is generally two cells thick. Tiny bile canaliculi, or bile channels, lying between the hepatic plates carry the bile to bile ducts. Like tributaries forming ever larger streams, the bile ducts merge to form larger ducts. Eventually, they form two hepatic ducts, one from the right lobe and one from the left. These in turn join to form a single hepatic duct that merges with the cystic duct to form the common bile duct. Bile manufactured by the liver, together with bile stored and later secreted by the gallbladder, leaves the hepatic-biliary system via the common bile duct [5].

The septa between lobules contain venules and arterioles, both of which drain into the hepatic sinusoids, where venous and arterial blood mingle. This mingling is related to the detoxifying and metabolic functions of the hepatic system. Plasma, including proteins, can diffuse out of the blood. For example, nutritive or toxic substances carried from the intestine in the blood diffuse through the epithelial lining of the sinusoids into the hepatic cells, where they are metabolized, stored, or altered. The sinusoids are also lined by Kupffer cells, phagocytic cells that remove bacteria and other foreign substances from blood that passes through the liver [5].

Hepatic Circulation

The liver is richly supplied with both arterial and venous blood. Each minute, approximately 1,100 mL arrives from the hepatic portal vein and 400 mL from the hepatic artery to mix in the sinusoids before returning to the heart via the inferior vena cava. Portal venous blood coming from the intestines has a low concentration of oxygen but a high concentration of substances absorbed by the intestine during digestion. Blood coming from the hepatic artery is high in oxygen but low in nutrients. The pressure of blood in the portal and haptic veins is low, allowing easy diffusion of nutrients and other substances along the concentration gradients. Oxygen-rich blood from the

hepatic artery maintains the integrity of the liver; if perfusion is absent or diminished, necrosis of hepatic cells will occur [5].

Arterial and venous vessels, bile ducts, and lymphatic vessels travel together through the liver in so-called portal tracts. The direction of flow is from the portal tracts through the sinusoids and into the central veins of the liver lobules. Thus, oxygen and nutrient supply is richest in the hepatic cells nearest the portal tracts and poorest near the central veins. The cells adjacent to the central veins, due to their relatively poor nutritional state, are more susceptible to damage from circulatory disturbances (e.g., shock, heart failure) and more vulnerable to toxins than the outermost cells [5].

FUNCTIONS OF THE LIVER

What are the functions of the liver?

As discussed, the hepatic system has vascular, secretory, and metabolic functions. It stores some vitamins and iron, detoxifies chemicals, and forms substances necessary for the coagulation of blood [5; 6].

Vascular Functions

The liver is capable of storing a considerable quantity of blood, the amount depending on the pressure relationships in the arteries and veins. If pressure in the hepatic veins increases by a few millimeters of mercury (e.g., in the presence of congestive heart failure, cirrhosis, or hepatic congestion), as much as 300–400 mL of blood may be stored. If hemorrhage occurs anywhere in the body, the liver releases this stored blood into the circulatory system to maintain circulatory volume [6].

The phagocytic Kupffer cells lining the sinusoids normally remove 99% to 100% of bacteria from blood entering the liver. Kupffer cells multiply in response to increased levels of foreign particles in the blood. Because blood entering the liver through the portal vein contains intestinal bacteria, the Kupffer cells play an important role in the body's defense against infection. Any condition that damages these cells or inhibits their replication increases the body's susceptibility to infection [6].

Secretory Functions

The hepatic cells of each liver lobule continually secrete small amounts of bile, a thick, greenish-yellow, slightly alkaline fluid. When first secreted from the liver through the canaliculi, bile is composed of water, bile salts, bilirubin, cholesterol, fatty acids, and lecithin as well as sodium, potassium, calcium, chloride, and bicarbonate ions [5; 6].

Bile is concentrated in the gallbladder, which contracts during digestion to send it into the duodenum, where it functions as kind of "biological detergent" to emulsify fat particles. The bile salts decrease the surface tension of fat particles so the agitation of the intestinal tract can break them into small globules easily acted upon by digestive enzymes. Lecithin acts similarly. Fat is digested much more slowly if bile is not present [5; 6].

Bile salts also improve absorption of lipids. The salts combine with fatty acids and monoglycerides to form small complexes called micelles. The ion charges provided by the bile salts enhance diffusion of the micelles across the intestinal mucosa into the bloodstream [5; 6].

If absorption of fats is diminished because of absence of bile, vitamins A, D, E, and K, which are fat-soluble, cannot be absorbed. Bile salts are "recycled" from 15 to 20 times in a process known as enterohepatic circulation. An estimated 90% to 95% of bile salts secreted are reabsorbed in the distal ileum and carried in the portal vein back to the hepatic cells, which reabsorb and then resecrete them [5; 6].

Excretory Functions

Bilirubin (bile pigment), a major waste product of hemoglobin metabolism, is excreted by the liver. Normally, erythrocytes have a lifespan of about 120 days. They are then broken down by the reticuloendothelial cells, and the iron (heme) from the worn-out red cells is conserved for reuse in the synthesis of fresh hemoglobin. The remaining iron-free pigment is free (unconjugated) bilirubin, which is continually present in the bloodstream in small quantities. As blood passes through the liver, unconjugated bilirubin is removed. It is then combined (conjugated) with other substances and excreted via the bile ducts; a small amount of conjugated bilirubin returns to the blood [1; 7].

Conjugated bilirubin is more soluble and less toxic than unconjugated bilirubin. In the intestines, conjugated bilirubin is converted into a highly soluble substance called urobilinogen, which is excreted primarily in the feces in an oxidized form known as stercobilin. About 5% of urobilinogen is absorbed into the bloodstream and excreted via the kidneys in an oxidized form called urobilin. Because stercobilin gives feces their brownish color, clay-colored stools are a classic sign of biliary tract abnormalities [1; 7].

Metabolic Functions

Carbohydrate Metabolism

The liver plays a major role in carbohydrate metabolism. One aspect of this role is a glucose buffer function that contributes to the maintenance of normal blood sugar levels. The liver can remove excess glucose from the blood, store it as glycogen, and reconvert and release it as glucose in response to hypoglycemia. If blood glucose concentrations fall and glycogen is not available, the liver can convert proteins or amino acids to glucose, a process known as gluconeogenesis. The liver is also capable of converting galactose to glucose [1; 2].

Fat (Lipid) Metabolism

Synthesis of fat from carbohydrates and proteins occurs primarily in the liver. The lipoprotein produced in this process is transported in the bloodstream to the body's adipose tissue or storage. The liver is also capable of rapid metabolism of

ingested fat in response to energy requirements. The liver can also synthesize lipoproteins, cholesterol, and other phospholipids [1; 2].

Protein Metabolism

Before amino acids can be converted into carbohydrates or fat or used to supply caloric needs, a process known as deamination (liberation of ammonia) must occur. The liver is the principal site of deamination and the only site where ammonia is detoxified by conversion into urea. In addition, nearly all the plasma proteins are synthesized in the liver, as are several nonessential amino acids. Serum protein determination measures the liver's ability to maintain a normal level of serum albumin [1; 2].

Storage Functions

Vitamin Storage

The liver is capable of storing up to a four-month supply of vitamins B_{12} and D and up to a 10-year supply of vitamin A for release as needed. Because of this storage capacity, excessive ingestion of vitamin A can have toxic effects on liver function [3; 4].

Iron Storage

Except for the iron stored in hemoglobin, most of the body's iron is stored in the liver as ferritin. Stored iron is released when blood levels of iron fall, a process known as iron buffering [3; 4].

Synthesis of Coagulation Factors

Prothrombin and factors VIII, IX, and X, necessary for effective blood coagulation, are synthesized in the liver. Vitamin K is necessary to promote synthesis for these clotting factors, but if bile secretion is inadequate, absorption of this fat-soluble vitamin cannot occur. The liver also synthesizes fibrinogen, another clotting factor [3; 4].

Detoxification

Many chemicals are detoxified in the liver, including such medications as barbiturates, antidiuretic hormone (ADH), amphetamines, aldosterone, and estrogen. If these substances were not detoxified, they could be fatally toxic to body tissues or organs, or could have other adverse effects (e.g., feminization of men or masculinization of women) [4; 5].

STRUCTURE OF THE GALLBLADDER

The gallbladder is a pear-shaped, hollow, saclike organ about 7–10 cm long that lies in a fossa on the inferior surface of the liver. The cystic duct, which drains the gallbladder, joins with the hepatic duct of the liver to form the common bile duct. Pancreatic secretions also enter this duct via the pancreatic duct. Bile in the common duct enters the duodenum through the sphincter of Oddi. When the sphincter is relaxed, bile can enter the duodenum; when the sphincter is contracted, bile manufactured by the liver is stored in the gallbladder [6].

FUNCTIONS OF THE GALLBLADDER

What are the major regulatory processes of the biliary system?

The major regulatory processes of the biliary system involve the concentration and storage of bile and the regulation of bile secretion [4; 5].

Concentration and Storage of Bile

The hepatic cells can produce from 600–1,000 mL of bile in 24 hours, more than 10 times the 50–75 mL storage capacity of the gallbladder. The mucosa of the gallbladder concentrates bile by absorbing water and electrolytes. This leaves a solution of bile salts, cholesterol, lecithin, and bilirubin that is 5 to 10 times as concentrated as bile secreted by the liver [4; 5].

Regulation of Bile Secretion

When ingested fat enters the small intestine, a hormone called cholecystokinin is released from the intestinal mucosa. Cholecystokinin travels to the gallbladder via the bloodstream, initiating contraction of the smooth muscle in the wall of the gallbladder and relaxation of the sphincter of Oddi. Vagal stimulation also contributes to contraction of the gallbladder. While the hormone secretin, produced by the jejunal and duodenal mucosa, weakly stimulates bile secretion by the liver, peristalsis stimulated by food further relaxes the sphincter of Oddi. These factors combine to produce the sending of bile into the duodenum with each gallbladder contraction and peristaltic wave. The gallbladder empties poorly in the absence of ingested fat but empties completely within an hour if fat is present. Approximately 94% of the bile salts released into the duodenum are reabsorbed and returned to the liver via the bloodstream [5; 6].

PATHOPHYSIOLOGIC INFLUENCES AND EFFECTS

ENLARGEMENT OF THE LIVER

Under normal circumstances, the liver is capable of regeneration following alleviation of an acute condition (e.g., drug toxicity, abscess, inflammation). If the pathogenic influence persists, however, regeneration will be of fibrotic origin [7].

When dead or diseased cells are replaced by fibrous tissue, the liver becomes enlarged (hepatomegaly). Fibrotic scar tissue may impede emptying of blood from the hepatic veins, causing the liver lobules to become engorged. This engorgement leads to further enlargement. Pressure exerted on abdominal nerves by the enlarged liver or displacement of other abdominal organs may cause discomfort or pain. Hepatomegaly may also be related to invasion and multiplication of neoplastic cells [7].

ATROPHY OF THE LIVER

Although the liver may be enlarged during the early stages of hepatic pathology, it eventually atrophies if the pathogenic influence is not removed. In patients with alcohol use disorder, for example, continued ingestion of alcohol combined with malnutrition causes scar tissue to replace the dead cells. In time, the scar tissue shrinks, and the liver becomes smaller than normal. Adjacent organs tend to encroach on the space formerly occupied by the liver. For this reason, a liver from a donor smaller than the recipient is best for transplant purposes [7; 8].

PORTAL HYPERTENSION

Portal hypertension contributes to the development of what serious complication?

As hepatic tissue becomes increasingly fibrotic, the portal veins become compressed. This compression increases back-pressure as portal venous blood volume rises. Portal hypertension results, with pressures in the portal vein as high as 20 mm Hg. This contributes to the development of ascites, the accumulation of protein-rich serum in the peritoneal cavity [7; 8].

Collateral pathways develop between the portal and systemic circulation in areas where tributaries of portal and systemic veins are in close approximation. As portal pressure increases, all collateral pathways between the portal and systemic circulation enlarge [8].

Collateral vessels in the lower esophagus dilate because they are not anatomically structured to carry the extra blood shunted via the azygous system. These dilated veins, called esophageal varices, may rupture, causing massive hemorrhage. Hemorrhoids (rectal varices) can result from the increased pressure in hemorrhoid veins. Splenomegaly can develop secondary to engorgement of the splenic veins [8].

When esophageal varices hemorrhage, treatment is complicated by abnormalities in blood coagulation related to impaired hepatic function. As bile production becomes impaired, absorption of vitamin K is also impaired. Insufficiency or lack of vitamin K leads to decreased production of prothrombin and coagulation factors VIII, IX, and X. Insufficient clotting factors, in turn, is related to increased clotting times. This pathogenic sequence may be signaled by ecchymosis all over the body, bleeding of the gums, or blood in the stool [8].

IMPAIRMENT OF GAS EXCHANGE

Although the vascular dehydration seen in hepatic failure may mask erythrocytopenia, red blood cell deficiency does occur in relation to several factors. For example, the impaired liver cannot store sufficient B_{12} and iron for erythrocyte synthesis. In alcohol-related pathologic states, ingestion of large quantities of alcohol inhibits renal synthesis of erythropoietin; the blood contains a higher proportion of immature erythrocytes and fewer mature red cells. This deficit may manifest as dyspnea, increased cardiac output, cardiomegaly, and clubbing of the fingers [7; 8].

INCREASED SUSCEPTIBILITY TO INFECTION

Injury to the liver is accompanied by damage to or destruction of the Kupffer cells. Phagocytosis is impaired. Micro-organisms enter the general circulation and may form abscesses in the liver tissue itself. Whereas the normal liver accounts of 25% of the body's production of lymphocytes, the diseased liver is incapable of lymphocyte production. Lymphocytopenia increases the body's susceptibility to infection [7; 8].

IMPAIRMENT OF BILIRUBIN EXCRETION

In a compromised liver, absorption and conjugation of bilirubin are impaired. Increased levels of unconjugated bilirubin in the blood and body fluids leads to jaundice, or icterus. The skin becomes yellowish and pruritic, renal excretion of unconjugated bilirubin causes the urine to become mahogany colored, and the stools are clay colored (acholic) due to the absence of stercobilin [7; 8].

Not all cases of jaundice are related to impairment of bilirubin conjugation. For example, if the common bile duct is obstructed by gallstone (choledocholithiasis) or a neoplasm, bilirubin that has been conjugated by the liver cannot be excreted into the duodenum. Levels of bilirubin rise, and the symptoms of jaundice occur. Jaundice may also be related to cholecystitis (inflammation of the gallbladders) or to spasms of the sphincter of Oddi, often associated with cholelithiasis [8].

Inability of the liver to remove the overproduction of bilirubin related to hemolytic states is another cause of jaundice. For example, reaction to a blood transfusion can induce a hemolytic state. The production of unconjugated bilirubin exceeds the conjugation capacity of the liver and levels of circulating unconjugated bilirubin rise. In newborn infants, a deficiency of glucuronyl transferase, the enzyme necessary for bilirubin conjugation, may lead to development of jaundice. This type of jaundice may usually be corrected by exposing the infant to ultraviolet light therapy [8].

Some hereditary disorders sere also associated with jaundice, including Gilbert syndrome and Dubin-Johnson syndrome. Gilbert syndrome is associated with deficiency of glucuronyl transferase, while Dubin-Johnson syndrome is associated with impaired hepatic excretion of bilirubin [8].

BILIARY INFECTIONS

In the presence of inflammation or obstruction, the gallbladder may become swollen by accumulated mucus secretions or purulent drainage. Staphylococcal, streptococcal, or enteric organisms may infect the gallbladder, or it may become gangrenous [9].

AMMONIA TOXICITY

As the functional capacity of the liver diminishes, the ability to convert ammonia to urea for excretion by the kidney is impaired. Moreover, the collateral circulation caused by portal hypertension allows ammonia formed in the intestines to bypass the liver and enter the general circulation. The

combined effect of these phenomena is ammonia toxicity. This toxicity manifests itself in hepatic encephalopathy, an altered mental state that begins with confusion and progresses to combative states and ultimately to hepatic coma. Another characteristic symptom of ammonia toxicity is asterixis, a flapping tremor of the hands [9].

ALTERNATION IN NUTRITION-RELATED FUNCTIONS

Injury to hepatic cells compromises bile production and interferes with other nutrition-related hepatic functions, such as synthesis of glycogen. The decrease in appetite that often occurs in liver disease is followed by weight loss, subnormal body temperature, fatigue, and the metabolism of body fat and muscle to meet caloric requirements. Impairment of bile secretion leads to fat intolerance and deceased fat absorption. The use of muscle mass as an energy source combined with decreased capacity for urea formation leads to a negative nitrogen balance. The limbs become emaciated while the abdomen swells with ascites. Skin breakdown is common. Inability to metabolize the amino acid methionine adequately produces fetor hepaticus, a sweet breath odor resembling acetone or old wine [9; 10].

Deficiencies of folic acid and the B complex vitamins often occur in patients with alcoholic liver disease. Alcohol increases the demand for B vitamins, impairs absorption of folate and the B vitamins, and generally contributes to an inadequate consumption of all nutrients. Folic acid deficiency is manifested by a macrocytic anemia, glossitis, and diarrhea. Lesions of the oral mucosa and tongue, fissures at the corners of the mouth (cheilosis), and peripheral neuropathies result from lack of B complex vitamins. Patients with bleeding tendencies require additional vitamin K [9; 10].

Diminished fat absorption leads to deficiencies of the fat-soluble vitamins A, D, E, and K. Night blindness is associated with deficiency of vitamin A. Osteoporosis may occur in relation to vitamin D deficiency, putting the patient at risk for fractures. Vitamin E deficiency can cause impaired red blood cell survival in adults [9; 10].

ALTERATIONS IN FLUID VOLUME

Among the substances synthesized by the normal liver is the plasma protein albumin, which is necessary for maintaining the colloidal osmotic pressure of the plasma. If plasma albumin is insufficient or absent the normal colloidal osmotic pressure of the blood is not maintained. Plasma seeps into the interstitial spaces, causing peripheral and dependent edema. Pulmonary edema may lead to right-sided congestive heart failure. Ascites may be related to hypoalbuminemia and failure of the liver to detoxify aldosterone, as well as to portal hypertension. Accumulations exceeding 2 L may lead to difficulty breathing from pressure on the diaphragm, decrease in appetite, increased feeling of fullness, constipation, flatulence, and umbilical hernia. The weight and bulk of the fluid may also restrict activity [9; 10].

IMPAIRMENT OF DETOXIFICATION

The diminished detoxification capacity of the compromised liver may compound problems related to hypoalbuminemia. Increased levels of circulating aldosterone and ADH increase retention of sodium and water, respectively, further complicating the patient's edema. Intravascular dehydration (lack of plasma in the blood vessels) related to hypoalbuminuria, may mask erythrocytopenia, because the dilution state of the blood has been altered [10; 11].

Alteration in detoxification may also induce other problems related to excessive levels of hormones, chemicals, or drugs. Changes associated with an excess of estrogen may occur, including loss of axillary, pubic, and body hair; soft skin; and gynecomastia and testicular atrophy in men. Decreased libido, impotence, spider angiomas, and palmar erythema are also associated with increased estrogen levels. Alcohol, antibiotics, psychotropic drugs, and some antihypertensive medications may also accumulate in toxic levels when liver function is impaired [10; 11].

RELATED SYSTEMS INFLUENCES AND EFFECTS

Because the hepatobiliary system performs multiple functions related to several other body systems, impairment of hepatobiliary function can affect these systems to varying degrees.

INTEGUMENTARY SYSTEM

Where are xanthomas and xanthelasmas most commonly seen?

Yellowing of the skin is characteristic of jaundice. Pruritus (itching) associated with jaundice may become so severe that patients scratch until they bleed. The break in skin integrity increases the patient's susceptibility to infection [11].

Xanthomas and xanthelasmas may occur in patients with biliary problems in whom serum cholesterol levels are high. These foamy, cholesterol-filled cells may appear anywhere on the body but are commonly seen on the hands and around the eyes [11].

Edema and poor nutritional status also may make the skin susceptible to breakdown. Pressure injuries may form within hours in patients who are not frequently repositioned. White nails, in which 80% of the proximal nail bed is white leaving a distal band of normal pink, are often associated with cirrhosis. In hepatolenticular degeneration (Wilson disease), the lunulae (half-moons in nail beds) are colored light blue instead of the normal white [11].

CARDIOVASCULAR SYSTEM

Fluid overload or congestive heart failure may occur in response to excessive levels of aldosterone and ADH. Reduced oxygen-carrying capacity from erythrocytopenia may lead to increased cardiac output, as the heart labors to deliver oxygen to starved tissues. Increased portal vein pressure related to hepatic fibrosis

increases pressure within adjacent vessels and thereby leads to esophageal varices, splenomegaly, and periumbilical dilatation. Hemorrhage of esophageal varices may further reduce the erythrocyte count. Increased clotting time because of efficiency in coagulation factors may produce hemorrhage and hypovolemic shock [11].

NEUROLOGIC SYSTEM

Ammonia toxicity is related to alteration in mental states ranging from confusion to hepatic coma. A patient who is confused or combative has a high potential for injury [11].

PSYCHOSOCIAL/LIFESTYLE INFLUENCES AND EFFECTS

Like all body systems, the hepatobiliary system both influences and is influenced by psychosocial factors.

SEX AND AGE

What groups are at increased risk for contracting viral hepatitis?

Cholelithiasis (gallstones) occurs in women four to five times as often as it does in men. This increased incidence is thought to be related to the action of estrogen and progesterone, which increase the cholesterol saturation of bile. The higher the cholesterol saturation, the greater the risk that gallstones will form. Pregnant women and those taking oral contraceptives are at even higher risk of developing cholelithiasis, especially those who have had several pregnancies or who have been on oral contraceptives for several years [12].

Cholelithiasis is more common in individuals older than 40 years of age; however, it can occur at any age, especially in association with risk factors such as high fat intake, obesity, diabetes, multiple pregnancies, or oral contraceptive use [12].

Young adults and older individuals are at greater risk of contracting viral hepatitis. This increased risk may be associated with poor nutrition or with crowded or unsanitary living conditions [13].

Older adult persons are susceptible to problems of drug toxicity, in part because renal and hepatic function declines with age. At 70 years of age, renal and hepatic efficiency may be half what it was at 20 years of age, yet the prescription of medications for elderly patients often do not reflect this fact. If dosage adjustments are not made, a drug may be prescribed at twice the dosage actually needed. If the patient misunderstands dosage instructions or increases the dosage in the supposition that "more is better," toxic reactions can occur. Older adults often have multiple health problems, and several different healthcare providers may inadvertently prescribe medications that interact unfavorably. Self-medication with over-the-counter remedies (especially laxatives) may compound the overdosage [14].

ALCOHOL AND DRUG ABUSE

Abuse of alcohol is a factor in many, though by no means all, conditions that damage the liver. In addition, drug abuse, especially of injected substances, is associated with an increased risk of contracting hepatitis [15].

LACK OF SANITATION

Drinking water or water used in preparation of foods (e.g., washing fresh fruit or salad greens) may become contaminated by secretions or fecal material from persons with viral hepatitis (A or B). Shellfish caught in waters contaminated by untreated or inadequately treated sewage may also transmit hepatitis A virus. As such, sanitation is an important factor in the control of hepatitis. Nurses, especially those working in community settings, can help inform their patients of the importance of washing hands before handling food and after using toilet facilities [15; 16].

DIETARY HABITS

High-fat diets can contribute to the development of cirrhosis of the liver as well as to gallbladder disease, and biliary diseases are more common in cultures in which food is prepared mostly by frying or large amounts of fat are used in cooking. Conversely, the incidence of gallbladder disease is low in African and South American countries in which fat consumption is low. Due in part to the popularity of fast-food chains and fried snack products, the typical American diet is high in fat. A high intake of alcohol and associated malnutrition also contribute to the development of hepatic and biliary disease [17].

ECONOMIC FACTORS

Although malnutrition is usually associated with poverty, a high income does not ensure a balanced diet. Reliance on fast foods and snack foods and consumption of a fat-laden diet occur in all socioeconomic classes. Poor sanitation and high alcohol consumption may also occur at any income level [17].

OCCUPATION AND AVOCATION

Exposure to all types of hepatitis is a special risk for healthcare professionals, who may be exposed to virus-contaminated blood or secretions. Laboratory and operating room personnel and those who work in hemodialysis units are at particular risk of contact through exposure to body fluids. Nurses administering intravenous therapy or disposing of secretions may be exposed to hepatitis if strict asepsis and isolation principles are not followed. In addition, dentists may be exposed to the hepatitis virus in the saliva of a hepatitis carrier or a person with active disease [18].

Exposure to toxic chemicals may be related to occupation, leisure-time hobbies, or a pharmaceutical regimen. Halothane and chloroform, to which operating room personnel are exposed, are hepatotoxic. Carbon tetrachloride, used in dry cleaning and in various industrial processes, is hepatotoxic, as are toluene and other chemicals used in paint thinners and other compounds used by both professionals and hobbyists.

Gold, used in the jewelry trade and in the fabrication of some electronic components, is also hepatotoxic. Among the medications that may have a toxic effect on the liver are a number of antibiotics (including erythromycin, oxacillin, and clindamycin), some psychotropic medications, and oral contraceptives. Highly stressful occupations or those that require a great deal of socialization may contribute to alcohol use disorder.

In taking the health history, nurses should be alert to these psychosocial factors that can help identify patients who appear to be at risk and refer them for detection of early pathological conditions affecting the hepatobiliary system [18].

NURSING ASSESSMENT: ESTABLISHING THE DATA BASE

SUBJECTIVE DATA

In assessing a patient's health status, the health history furnishes valuable clues to past and present problems, as well as to risk factors that can help predict the risk for future problems. Usually, the patient is the chief source of information, but family members also may be able to contribute useful data [19; 20; 21].

The patient should be questioned about any recent loss of weight, change in appetite, or changes in bowel patterns. What color are the patient's stools? What color is the urine? Clay-colored stools or mahogany-colored urine suggests obstruction of the common, hepatic, or cystic ducts or an abnormality of bilirubin excretion. Is a change in color of stool or urine accompanied by yellowing of the sclera or the skin? Did pruritus occur when these changes were noticed? Associating these symptoms may help the patient recall when they began [19; 20; 21].

Has the patient lost weight or lost interest in food? A positive reply might suggest the development of hepatitis or hepatic cancer, depending on other symptoms and signs elicited during the assessment. What does the patient usually eat? High fat intake might suggest cholelithiasis. Does the patient bruise easily or bleed for a long time after a minor cut? Decreased absorption of vitamin K may be associated with hyperbilirubinemia, which can affect blood coagulation and the clotting cascade [20; 21; 22].

Edema of the ankles, difficulty breathing, and collection of fluid in the abdomen could indicate right-sided heart failure, hypoalbuminemia, portal hypertension, or inadequate detoxification of ADH and aldosterone. The patient may not remember when such changes began, but asking when clothing became tight around the waist or shoes no longer fit can help to pinpoint onset [20].

Has the patient had frequent infections? Increased incidence of infection may be related to destruction of Kupffer cells. Has the patient been exposed to hepatitis or mononucleosis? Has the patient had any recent blood transfusion? A positive answer may be correlated with the evidence suggesting hepatitis. Impotence or loss of libido may be related to impaired estrogen detoxification. Determining whether alcohol use might be related to liver dysfunction also requires discretion and tact. One should not presuppose that the patient has alcohol use disorder, even if the suspected disorder is commonly associated with consumption of alcohol. The patient who does have an alcohol problem may be reluctant to answer, may evade questions, or may deny any drinking problems. In some cases, family members will verify unexplained changes in behavior that may suggest alcohol use disorder [20].

Specific, nonjudgmental questions are most likely to yield useful data about drinking habits. Possible questions include:

- What do you like to drink?
- How often do you drink? Every day? Several times each day? Week? Month? Such specifics are more useful than generalities such as "rarely" or "often."
- How much do you drink? One drink? Three or four?
- Does wine with dinner mean a glass or a carafe? By "a few beers" do you mean couple of cans? A six pack?
- When you drink, how much do you consume in 24 hours?
- What is the most you've drunk in 24 hours?
- Do you drink in the morning? At or after work? With friends? Alone?
- Have you ever blacked out?
- Does drinking make you sick or does it make you feel better?

Remember that alcohol in any form (wine, beer, or hard liquor) has the same effect. A 12-oz. bottle of beer, a 4-oz. glass of wine, and a 1-oz. shot of Scotch contain the same amount of alcohol. It is also important not to concentrate on alcohol while ignoring other clues. What is the patient's occupation? Does it involve exposure to solvents, dry-cleaning solutions, anesthetic agents, or other hepatotoxic substances? Does the patient have hobbies that might have hepatotoxic side effects (e.g., furniture refinishing) [20]?

OBJECTIVE DATA

Physical Assessment

What physical findings are suggestive of cirrhosis?

Physical assessment of the patient with hepatobiliary dysfunction involves careful inspection of the skin, nails, and hair. Physical findings that suggest cirrhosis include:

- Ascites
- Ankle edema
- Muscle wasting
- Dilated periumbilical veins (caput medusa)
- Ecchymosis
- Spider angiomas
- Loss of body hair

- Gynecomastia (breast enlargement in males)
- Jaundice (yellow coloration to skin and sclera)
- Clubbing of the fingers

If the patient is in a late stage of liver dysfunction, asterixis related to ammonia toxicity and impending coma will be observed; in these patients, the hands rapidly clench and unclench. Inflating a blood pressure cuff on the arm will worsen the tremor. Asterixis may also be seen in patients with cancer of the liver. In patients with hepatitis, however, only ecchymosis and jaundice will be apparent, unless the condition is long standing. Bruising and jaundice may sometimes accompany hepatic abscess; however, diminished appetite is often the only sign of this disorder. As mentioned previously, jaundice may also be secondary to an obstructive condition or an abnormality affecting bilirubin conjugation [20].

The abdomen should be auscultated before it is palpated. Diminished bowel sounds are common in patients with ascites. At the same time, auscultation of the lungs may elicit evidence of rales or rhonchi related to pulmonary edema. Listen for hepatic bruits, which may be heard with hepatic carcinoma [20].

Hepatomegaly and splenomegaly can be present in patients with hepatitis, cholecystitis, hepatic abscess, mononucleosis, cirrhosis, or liver cancer. Because of the danger of damaging or rupturing these organs, the one should generally avoid palpating the liver or spleen unless they are experienced in this type of examination. If enlargement is severe, these organs may be felt by very light palpation of the abdomen. Swollen lymph nodes may be palpable in the neck or in the groin with an infectious disorder such as mononucleosis [20].

If possible, percussion for measurement of liver size and the usual area of splenic dullness helps determine whether either organ is enlarged. The normal liver span at the midclavicular line (MCL) is 6–12 cm. When percussing liver size, begin low in the abdomen, below the umbilicus, and percuss up the right MCL. The percussion note heard initially is tympany, reflecting air in the bowel. The lower border of the liver is identified when the percussion note changes to dullness. To identify the upper liver border, begin above the nipple, percussing downward along the right MCL. When the percussion note changes from resonance to dullness, the upper liver border has been located. Measure the distance between these two points to determine liver size. Abnormal findings include feeling the liver more than 1 cm below the costal margin [20].

The normal adult spleen lies behind the ninth and eleventh ribs, at or slightly posterior to the left midaxillary line (MAL). The spleen can be located by percussing downward in the intercostal space (ICS) at the left MAL, beginning in the eighth left ICS. The percussion note should change from resonance to splenic dullness at about the tenth left ICS. A large area of dullness may indicate feces in the splenic flexure of the colon, a full stomach, or splenomegaly. Note that patients who have had organ transplants may have undergone splenectomy [20].

Three assessment techniques can be used to determine whether fluid is present in the abdomen:

- With the patient supine, both flanks may be percussed for dullness, which indicates the presence of fluid.
- When the patient assumes a side-laying position, fluid will fall toward the sides on which the patient is lying, where it may be percussed for dullness.
- The presence of a fluid wave may be determined by having the patient lie flat and place his or her hand, ulnar side down, along the abdominal midline and apply pressure to anchor the fat in the mesentery. (If the patient is too ill to participate, an assistant can do this.) Place one hand on one flank to detect signs of a fluid wave while tapping the opposite flank with the other hand. There will be a short time lag between the tap and receipt of the impulse.

Abdominal girth should be measured daily. Measurements taken at the same location (at the level of the umbilicus) assist in evaluating progression and/or treatment of ascites [20].

DIAGNOSTIC STUDIES

Hematologic Studies

Blood samples for determination of white blood cell count (WBC), prothrombin time (PT), hemoglobin level (Hb), and hematocrit (Hct) may be drawn at any time. Hemoglobin and hematocrit values are unaffected by early stages of hepatic disease but may drop if there is hemorrhage from esophageal varices and in response to malnourishment. Prothrombin time will increase with vitamin K deficiency, as may occur with cirrhosis, hepatitis, cholecystitis, cholelithiasis, mononucleosis, or liver cancer. Leukocyte levels increase in patients with mononucleosis, hepatitis, and abscesses [23; 24; 25].

Serum Enzyme Studies

What specific values are likely to be elevated with liver or gallbladder disease?

Elevated serum enzyme levels occur when hepatic cells are damaged and enzymes are released into the blood. Specific values that are likely to be elevated with liver or gallbladder disease include:

- Lactic dehydrogenase (LDH)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)

LDH, AST, and ALT values are significantly increased in obstructive jaundice and mononucleosis; they are also markedly elevated in acute and toxic hepatitis, cirrhosis, and hepatic neoplasia. Alkaline phosphatase levels, important in measuring biliary obstruction, are extremely elevated in obstructive jaundice, significantly elevated in liver cancer and mononucleosis, and slightly elevated in hepatitis (viral or toxic) and cirrhosis.

Elevation of GGT is the most accurate enzymatic indicator of hepatic disease. Enzyme levels will rise as the disease progresses, peaking at the time of maximum cell death, and then begin to fall [23; 24].

Serum Lipid Values

Changes in serum lipid values are related to the type of disorder. Serum lipids are elevated in obstructive disorders of the biliary system, such as cholelithiasis or neoplasia. They are decreased in disorders causing the destruction of hepatic cells (e.g., cirrhosis, hepatitis) [23; 24].

Bilirubin Values

Studies of bilirubin values are important in determining the cause of jaundice and hyperbilirubinemia. Direct or conjugated bilirubin levels will be elevated if biliary ducts are obstructed and conjugated bilirubin cannot be excreted. Indirect or unconjugated bilirubin levels will be high if parenchymal (liver lobule) cells have been damaged [23; 24].

Elevated levels of urobilinogen in the urine indicate parenchymal liver disease, such as cirrhosis, toxic or infectious hepatitis, or infectious mononucleosis, or they may indicate cholelithiasis. By impairing the excretion of bilirubin in the stool, these conditions lead to increased excretion by the kidneys. Urine that contains bilirubin develops a yellow foam when shaken. Fecal levels of urobilinogen are decreased if the bile ducts are obstructed, but this test is rarely performed because of the difficulty in obtaining accurate values. A 24-hour urine collection would be done to determine the presence and level of urobilinogen [23; 24].

Blood Ammonia Values

Blood ammonia values rise when cirrhosis is present, because the disease impairs the conversion of ammonia to urea for renal excretion. Bleeding esophageal varices exacerbate ammonia toxicity, because the ammonia produced by the action of intestinal bacteria on the protein in blood adds rapidly to already elevated serum ammonia levels. Hepatic coma can result [23; 24].

Other Laboratory Test Values

Changes in serum protein levels are common in hepatic and biliary disorders. Serum albumin levels drop (hypoalbuminemia) and gamma globulin levels rise when parenchymal cell damage occurs. Serum antigen-antibody levels help identify and type hepatitis. For example, hepatitis B surface antigen (HBsAg) is present in the blood of persons who have hepatitis B and also in those who are carriers of the disease. Patients with hepatitis B surface antibodies (anti-HBs) in their blood have immunity to hepatitis B [23; 24].

Ultrasound

For some patients, especially those for whom oral cholecystography or cholangiography are contraindicated, ultrasound offers a noninvasive alternative. This technique is being used with increasing frequency to investigate ambiguous findings obtained by other techniques. It is useful in differentiating benign cysts and tumors from malignancies. Liver abscesses and dilation of intrahepatic ducts can be identified by ultrasound, as can gallstones, biliary tumors, and tumors of the extrahepatic ducts. In a patient with jaundice, dilation of the extrahepatic ducts suggests extrahepatic obstruction. If the ducts appear normal, jaundice is likely to be related to extrahepatic or prehepatic conditions. Hepatic icterus is related to abnormalities of bilirubin conjugation or excretion. Extrahepatic icterus is related to obstruction of the hepatic, common, or cystic bile ducts. Prehepatic icterus is associated with an abnormality that takes effect before circulating bilirubin reaches the liver (e.g., hemolysis of neonatal icterus) [23].

Nursing Implications

To ensure that the gallbladder is a maximum size for the test, the patient must be kept NPO after midnight on the day of testing. Were the patient to eat, contraction and emptying of the gallbladder would reduce its size, making it more difficult to visualize. NPO orders are not necessary for visualization of the liver. If barium contrast studies have been performed prior to the ultrasonography, a laxative will be ordered to cleanse the bowel of residual contrast medium [23].

In explaining the procedure to the patient, the nurse can offer reassurance that the study is not painful. The patient should be prepared for the copious amount of lubricant that will be applied to the skin to enhance the transmission of the sound waves. The rationale for any NPO order should be explained. The procedure will take about 20 minutes [26; 27].

Liver Scan

For the liver scan, a radionuclide is administered intravenously. Thirty minutes later, a detecting device is passed over the patient's abdomen to record the distribution of radioactive particles in the liver. Although this technique exposes the patient to far less radiation than x-rays, it can only demonstrate filling defects greater than 2 cm in diameter. It is contraindicated for pregnant patients and those who might have difficulty lying still during the scan, which takes about one hour [23; 28; 29].

No special preparation is required for this study. The procedure should be fully explained to the patient, including that small amounts of radioactive substances are used. Some patients may be apprehensive about the amount of time required for the scan, and it is helpful to explain that the scanning device does not emit radiation but rather records radiation emanating from the injected radioisotope. Pregnant healthcare providers should not be assigned to the patient for at least 24 hours after the radionuclide injection [26; 27; 28].

Dye Clearance Studies

For dye clearance studies, the patient fasts for 12 hours prior to the test. Dye is injected intravenously (about 5 mg/kg of body weight). Blood is drawn 45 minutes after the injection and inspected for the presence of dye. Normally, less than 5% of the dye will be found in the serum; the presence of a greater proportion of the dye indicates liver cell damage, as the impaired

cells cannot absorb the dye from the blood. If hepatic damage is known to exist, lower dosages of dye are administered. The indocyanine green (ICG) clearance test is the most widely used quantitative liver function test [23; 28; 30].

Oral Cholecystography

An oral cholecystography, or gallbladder series, provides visualization of the gallbladder following oral ingestion of a radiopaque iodinated dye. In the first test of the series, gallstones (when present) may be visualized as dark shadows in a dye-filled gallbladder. Satisfactory visualization of the gallbladder can be obtained only if the gallbladder has concentrated the dye. Adequate concentrating depends on correct dosage of the dye, adequate absorption of the dye from the gastrointestinal tract (no nausea or vomiting), and absence of food in the digestive tract (NPO after midnight). If nonvisualization occurs, the test is repeated the next day with a doubled dosage of dye. Hepatocellular dysfunction, cystic duct obstruction, or inflammation of the biliary mucosa will prevent visualization. The patient's allergy history should be determined prior to testing [23; 28].

In the second phase of the series, the patient is given a fatty meal immediately following the first phase, and x-rays are taken to determine how well the gallbladder empties. The x-rays are repeated every 30 minutes until the dye is gone and the gallbladder can no longer be visualized. This may take one to five hours, but usually takes no more than three [23].

This is an older study that is rarely used today, as ultrasound or computed tomography (CT) are more accurate, faster techniques for identifying gallstones without exposure to iodine. Ultrasonography is typically the preferred modality, because it is less invasive, more accurate cholelithiasis, and can be safely used with most patients. In general, use of oral cholecystography is limited to cases in which gallstones are strongly suspected but ultrasonography does not show them. If it is indicated, oral cholecystography is contraindicated for pregnant women, patients too ill to swallow the tablets or to eat a meal, and persons allergic to iodine [23].

Patients undergoing oral cholecystography are required to swallow seven or eight tablets of absorbable iodine dye the evening prior to the test. After the tablets are swallowed, only water may be given until midnight; after midnight, patients are kept NPO. Nursing implications include [26; 27]:

- Verifying that no iodine allergy exists. The patient should be questioned about seafood allergies, as not all patients are aware that these foods contain iodine.
- Ascertaining that the patient is given a low-fat meal on the evening before the test.
- Verifying that serum bilirubin is less than 1.8 mg/dL (so visualization will be possible).
- Explaining the procedure to the patient.
- Administering the tablets at five-minute intervals.
- Observing for adverse effects of the dye (because anaphylactic reactions have occurred).
- Maintaining NPO status.

Oral and Intravenous Cholangiography

Oral and intravenous cholangiography allowed for visualization of the hepatic and common bile ducts in addition to the gallbladder and cystic duct. It was historically used for patients with acute inflammatory disorders, those with proven gallstones, and those who are NPO or unable to tolerate the orally ingested dye used in cholecystography [23; 26; 27; 28]. However, these studies have become obsolete, having been replaced by more advanced technologies, such as the endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTHC) and magnetic resonance cholangiopancreatography (MRCP) [31].

Intraoperative Cholangiography

Cholangiography may be performed during a surgical procedure to ascertain that all calculi have been removed from the common bile duct, reducing the probability of complications or follow-up surgery. Dye is injected to enhance visualization [23; 28].

T-Tube Cholangiography

A T-Tube cholangiography may be taken 7 to 10 days following a cholangiography. The T-tube is placed during surgery. Later, dye is injected via the T-tube so the common bile duct may be visualized and its patency ascertained [23; 28]. As with other older modalities, this technique has been largely superseded by MRCP and ERCP.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

As noted, ERCP, PTHC, and ultrasound have become the most valuable studies for assessment of the biliary tract [31]. ERCP studies allow visualization of the bile ducts as well as benign masses, cysts, and malignant neoplasms [23; 32; 33].

With ERCP, a type of fibrotic endoscope termed a duodenoscope is inserted into the duodenum via the esophagus. Intravenously administered secretin immobilizes the duodenum, facilitating visualization of the ampulla of Vater. Contrast material combined with a broad-spectrum antibiotic are administered through a small cannula inserted into the ampulla, and films are taken periodically for approximately an hour. The antibiotic is given to prevent gram-negative sepsis that may occur if bacteria are forced in the bloodstream by the pressure of the dye injections. Perforation of the esophagus, stomach, or duodenum is another possible complication of ERCP, so this technique is not used for combative patients [23; 32; 33].

A consent form is necessary for this procedure. On teaching the patient about the procedure, explain that an impulse to gag will be felt when the tube is passed. The patient is kept NPO after midnight. Meperidine and atropine are administered intramuscularly before the patient is taken to the radiology department. Emotional support should be given as needed.

After the procedure, the patient's pulse, temperature, and blood pressure are monitored for signs of shock that may arise from perforation or hemorrhage and for signs of sepsis. Pancreatitis may occur in response to the pressure exertion on the pancreatic duct during the procedure; therefore, a serum amylase test should be performed on the day following an ERCP [26; 27].

Percutaneous Transhepatic Cholangiography (PTHC)

Like ERCP, PTHC is used for icteric patients with serum bilirubin levels greater than 3.5 mg/dL. During this procedure, a combination of contrast medium and antibiotic is injected into the intrahepatic bile duct to visualize the biliary system. The area below the right costal margin is locally anesthetized, and a spinal needle is inserted directly into the liver, guided by fluoroscopy. When bile appears through the needle, it is withdrawn by syringe. Radiopaque dye is then injected directly into the biliary tree. Fluoroscopy is used to determine filling of the biliary tract [23; 28; 34].

The patient is intravenously sedated during the procedure, which takes about one hour. If obstruction is found, a catheter may be left in place for drainage of bile. A PTHC is contraindicated for patients who have prolonged clotting times or iodine allergy, for patients who have had recent gastrointestinal contrast studies or are unlikely to tolerate surgery, and for combative patients. Bile peritonitis, hemorrhage, and sepsis are possible complications [23].

A consent form is required for this procedure, and coagulation studies as well as information regarding possible iodine allergy must be verified. The patient is kept NPO after midnight. A laxative may be prescribed if gastrointestinal studies using barium have been recently administered. An intravenous infusion is started for venous access, and the patient is premedicated with meperidine and atropine before leaving the unit. After the procedure, the patient is kept NPO. Vital signs should be monitored as for any postsurgical patient. A sterile closed system should be maintained if a catheter has been left in place [26; 27].

Liver Biopsy

The purpose of a liver biopsy is to obtain a sample of tissue for histologic examination. Prior to the procedure, ultrasound may be done to determine the precise location of the liver. A coagulation profile should be obtained so the risk of hemorrhage can be calculated. The patient's blood is typed and crossmatched in case a transfusion is needed. Biopsy is contraindicated if the platelet count is below 100,000/mcL [23; 28; 35].

For percutaneous liver biopsy, the patient is assisted into a supine or left lateral position. The skin is aseptically cleansed and anesthetized, and a small incision is made to allow insertion of a specialized needle into the liver. In the case of transjugular biopsy, the right jugular vein is punctured under ultrasound guidance, and a guide wire is passed through, followed by placement of a 9-French sheath. The wire is then negotiated through the heart at to the right hepatic vein. Placement is verified with hepatic venogram with contrast. A stiffening cannula is placed, then the biopsy needle is introduced. With both techniques, a small core of hepatic tissue is then withdrawn and sent for microscopic evaluation. Following the procedure, the patient should assume the right lateral position to keep pressure on the liver to prevent hemorrhage [23; 28; 35].

These procedures require a consent form. The patient is kept NPO after midnight. Nursing responsibilities include:

- Checking coagulation studies and consent form.
- Maintaining NPO status.
- Recording preprocedure vital signs.
- Providing emotional support for the patient; this procedure can be frightening and uncomfortable.
- Explaining the procedure to the patient, emphasizing the importance of holding still.
- Immediately prior to needle insertion asking the patient to inhale deeply, exhale completely, and hold the breath at the end of expiration. This immobilizes the chest wall and keeps the diaphragm at its upper level during the procedure (which takes 5 to 10 seconds).
- Appling pressure to the biopsy site after needle removal.
- Turning patient onto right side with a pillow under the costal martin to maintain pressure to the site.
- Observing for bile-colored drainage on the patient's dressing. This could indicate that a biliary vessel has been penetrated.
- Monitoring post-procedure vital signs (every 15 minutes for an hour, then every 30 minutes for two hours, then every four hours), and administering comfort measures after the procedure.

The patient should remain immobile on the right side on bedrest for 24 hours and be closely observed for signs of hemorrhage, extravasation of fluid from the biopsy site, peritonitis, and pain. Pain in the right upper quadrant and right shoulder area is common. The patient should be reassured about this while being encouraged to report any change in pain level. Analgesics, if given, must be non-hepatotoxic and must not affect clotting [26; 27].

NURSING DIAGNOSES

Assessment of the patient with hepatic or biliary dysfunction, including evaluation of the patient's health history and results of laboratory tests and diagnostic studies, can lead to many possible nursing diagnoses.

ALTERATIONS IN COMFORT

Pain

Mild or moderate pain may occur in relation to hepatomegaly or splenomegaly associated with hepatitis, hepatic abscess, or infectious mononucleosis. Moderate pain may accompany late cirrhosis and chronic hepatitis. With cancer of the liver, whether the liver is a primary or a metastatic site, pain becomes severe and intractable. Severe, colicky pain in the right upper quadrant is common with cholelithiasis or cholecystitis [36; 37].

Pruritus

Regardless of whether icterus is prehepatic or hepatic, pruritus will be associated with the jaundice. The patient may scratch the skin until it bleeds. The condition may be intensified by damp clothing or bedding caused by perspiration or by poor ventilation [36; 37].

Potential for Impairment of Skin Integrity

If pruritus is severe and the patient scratches frequently, skin integrity may be broken. In cirrhosis and cancer of the liver, edema and negative nitrogen balance cause the skin to be susceptible to breakdown. If the patient does not frequently move, pressure injuries can form within 12 to 24 hours [36; 37].

Sexual Dysfunction and Disturbance in Self-Concept

Disturbance in self-concept may be related to body image alteration and role performance. Softening of the skin, loss of body hair, or gynecomastia may be related to impaired estrogen detoxification. In some, these feminizing changes disturb the patient's sense of masculinity. Ascites and icterus further affect self-image. Complications associated with severe disease such as cancer or cirrhosis (e.g., ascites, pleural effusion) may necessitate the patient changing occupation or retiring. Loss of occupational role can severely damage self-esteem.

Sexual dysfunction may also accompany impairment of estrogen detoxification. Loss of libido may occur in both sexes, and male patients may become impotent. The patient may be hesitant to discuss these matters with healthcare professionals [36; 37].

ALTERATION IN THOUGHT PROCESSES

Ammonia toxicity is related to the inability of the compromised hepatic cells to convert ammonia to urea for excretion in the urine. Ammonia interferes with brain metabolism, leading to alterations of mentation ranging from slight confusion to coma. Initially, patients may be somewhat confused or disoriented—unable, for example, to remember their names or where they are. Asterixis may also be apparent. Patients may then progress through lethargy to combativeness and abusiveness before collapsing into coma. Gastrointestinal hemorrhage further increases serum ammonia levels owing to bacterial action on blood in the gut. Wernicke-Korsakoff syndrome, characterized by confusion, disorientation, and amnesia with confabulation, may develop in patients with alcohol use disorder. The syndrome is related to thiamine deficiency [36; 37].

ALTERATION IN NUTRITION

What vitamin deficiencies are common in patients with hepatic dysfunction?

Hepatic dysfunction is associated with impaired metabolism of proteins, fats, carbohydrates, and vitamins. Weight loss, fatigue, negative nitrogen balance, vitamin B deficiency, and deficiencies of fat-soluble vitamins A, D, E, and K are common. The patient should be encouraged to consume a balanced diet high in carbohydrates, vitamins, and (unless ammonia toxicity is present) protein. Abdominal pressure from ascites may cause a constant feeling of fullness as well as flatulence and constipation. These conditions may also diminish appetite, further depleting nutritional status. Patients with cirrhosis experience muscle wasting and significant weight loss [36; 37].

In cholelithiasis or cholestasis, a low-fat, low-protein diet should be consumed because fat metabolism is reduced by disturbances in biliary function. Deficiency of vitamin K may also accompany these disorders [17; 21].

IMPAIRMENT OF GAS EXCHANGE

Several conditions related to hepatic and biliary disease impair exchange of oxygen and carbon dioxide. Retention of sodium and water is associated with plural effusion and ascites. Ascites exerts pressure on the diaphragm, interfering with inspiration. Inadequate oxygenation of body tissue related to erythrocytopenia also impairs gas exchange [36; 37].

ALTERATION IN FLUID VOLUME

Alterations in fluid volume may be either deficits or overloads. For example, when the compromised liver can no longer detoxify ADH and aldosterone, retention of sodium and water contributes to circulatory congestion and hypertension. Conversely, fluid volume deficit can be related to hemorrhage of esophageal varices (leading to shock) or to overuse of diuretics. If plasma colloidal osmotic pressure is reduced because of hypoalbuminemia, fluid extravasation into the interstitial space will cause edema despite intravascular dehydration. In this instance, diuretics alone will be ineffective in reducing edema and will, moreover, worsen dehydration [36; 37].

ALTERATION IN TISSUE PERFUSION

Increased cardiac output associated with hypertension is related to fluid volume alteration. Erythrocytopenia can lead to increased cardiac output as the heart attempts to compensate for tissue oxygen needs.

NURSE PLANNING AND IMPLEMENTATION

For the patient with hepatobiliary dysfunction, alterations in comfort are likely to be associated with pain or pruritus.

PAIN RELIEF

What is the first-line treatment for the management of biliary pain?

Mild-to-moderate pain associated with various disorders may be controlled with non-narcotic, non-aspirin analgesics. Patients with hepatic dysfunction are likely to have coagulation abnormalities related to poor absorption of vitamin K. As such, drugs causing hepatic damage should also be avoided; the drugs of choice are those excreted by the kidneys [26].

For pain associated with cholelithiasis, nonsteroidal anti-inflammatory drugs (NSAIDs) provide greater relief of biliary pain and are considered first-line management [38]. NSAIDs have been reported as superior to antispasmodics for pain control. For narcotic management, meperidine is usually the drug of choice; butorphanol or hydromorphone can also be utilized, especially if NSAIDs are contraindicated [39]. Morphine is rarely administered. Nitroglycerin or phenobarbital may promote comfort by relaxing smooth muscle. Nursing measures, such as giving a backrub, assisting the patient in changing position, providing distraction, and offering emotional support, may supplement analgesic medication [27].

PRURITUS RELIEF

Pruritus associated with icterus can be extremely upsetting to the patient. It is important to rule out any possibility that the condition is related to an allergy or irritation. Measures to alleviate itching include dry clothing and bedding, emollients, a well-balanced diet, and distraction. Alkaline soaps should be avoided, and baths should be taken only every two or three days, if possible. Whirlpool baths are preferred [27]. Biliary drainage can help to alleviate related pruritus. If indicated, the preferred pharmacotherapy is with ursodeoxycholic acid; cholestyramine, rifampicin, naltrexone, and sertraline are second-line options.

MAINTAINING AND IMPROVING SKIN INTEGRITY

Several nursing interventions are crucial to the maintenance of skin integrity. Relieving pruritus should be a high priority, and frequent turning and repositioning is necessary to relieve pressure of edematous areas and prevent formation of pressure injuries. A low-sodium diet, fluid restriction, and diuretic therapy may be prescribed to reduce diuresis and lessen peripheral and abdominal edema. It is important to remember that pressure injuries can form in as little as 12 to 24 hours if turning and repositioning are not done conscientiously every 1 or 2 hours [26; 27].

Preventing infection presents a challenge, because the patient's reticuloendothelial system is severely compromised. Careful handwashing is essential. Sterile technique should be maintained during dressing changes for surgical wounds and at catheter sites. Nutritional measures may be used to promote healing and improvement of skin integrity [26].

MAINTAINING AND IMPROVING THOUGHT PROCESSES

Evaluating the patient's mental status, promoting safety, and monitoring for ammonia toxicity are nursing responsibilities. Mentation may be monitored by assessing the patient's orientation to person, place, and time. One convenient technique for detecting changes in ammonia toxicity levels is having the patient write his or her name daily and compare the signatures. Severity of asterixis may be evaluated by pumping up a blood pressure cuff on the patients arm; the more rapidly the hand clenches and unclenches, the higher the serum level of ammonia. The patient's breath should be assessed for fetor hepatics, which is similar to the odor of acetone or old wine [26; 27].

Nurses should also be alert to the possibility that a hepatotoxic drug or dosage has been inadvertently prescribed. Detoxification capacity declines in older individuals, even under normal conditions; this impairment will be worsened in the presence of hepatic disease [40; 41].

Safety measures (e.g., padded side rails) may be necessary to protect patients who are confused or combative as a result of hepatic encephalopathy. The patient should be reminded not to get out of bed unassisted. Activities of daily living should be supervised [27].

REDUCING AMMONIA LEVELS

Various therapeutic measures may be prescribed to decrease serum ammonia levels. Intravenous administration of glucose may provide protein-conserving carbohydrates. Rest can decrease release of ammonia associated with muscle contraction [27].

Pharmacologic measures may also be employed. Potassium may be given to improve cerebral metabolism of ammonia. Hypokalemia has been identified as being a contributing factor for the increased risk of hepatic encephalopathy. Studies have shown that supplementing and correcting hypokalemia in patients with cirrhosis can decrease ammonia levels [42; 43]. Antibiotics such as neomycin may be administered orally or by enema to reduce the number of ammonia-synthesizing bacteria in the gut. Because neomycin is poorly absorbed from the intestine, its bactericidal action in the intestine is prolonged; however, this antibiotic may cause ototoxicity of nephrotoxicity if administered for more than six days [41; 44]. Metronidazole and rifampin are alternative choices.

Lactulose may be given orally or by nasogastric tube. This acts by acidifying the colon, so ammonia couples with hydrogen ions and is excreted in the feces. Improvement may be seen within 24 hours, with serum ammonia levels being reduced

by 25% to 50% in most patients. Diarrhea is common with lactulose therapy, so electrolyte levels should be monitored. In some cases, hemodialysis may be necessary to reduce serum ammonia levels [41; 44].

Nurses should routinely check stools for occult blood and monitor vital signs for changes that might indicate gastrointestinal hemorrhage. If esophageal varices are bleeding, treatments include beta blockers and medical procedures to stop bleeding [27].

IMPROVING NUTRITIONAL INTAKE

Unless ammonia toxicity is present, the patient with hepatic dysfunction should receive a diet high in protein to promote hepatic healing and prevent loss of muscle mass. The diet should be low in salt and high in vitamins, carbohydrates, and calories. If ammonia toxicity is present, potassium-rich foods should be provided. Although limiting protein can help address hyperammonemia, patients with hepatic dysfunction are often malnourished, and limiting protein intake is not generally recommended. Plant protein or milk-based protein can be used in patients with elevated ammonia levels [45]. The patient with biliary dysfunction should reduce the quantity of fats consumed [17].

Promoting a well-balanced diet with a patient who often has no appetite is a challenge. Appetite may be improved by providing oral hygiene and fresh air, minimizing movement, and administering prescribed antiemetics. Consultation with a dietitian is recommended to identify the best approach to feeding, perhaps in small, frequent feedings supplemented by nourishing snacks. As stated, plant protein supplements may be used if not contraindicated. It is helpful if the mealtime environment is pleasant and free of unpleasant odors. Food preferences elicited in the patient history should be considered. Explaining the rationale for the diet may encourage the patient to eat more. If the patient is unable to eat enough to meet caloric needs, feeding via nasogastric tube or total parenteral nutrition may be prescribed [17].

IMPROVING GAS EXCHANGE

Several measures may be prescribed to improve oxygenation. If dyspnea occurs at rest or upon exertion, oxygen therapy may be initiated. Oral iron supplements or a transfusion of packaged red cells may be given to improve hemoglobin and hematocrit levels. Intramuscular injections of vitamin K1 improve clotting. Diuretic therapy or administration of albumin may be prescribed to reduce pleural effusion, which hinders gas exchange, or to decrease ascites, which exerts pressure on the diaphragm [27].

Nurses may be called upon to assist with paracentesis to remove ascitic fluid from the abdomen. The patient is assisted to a sitting position. The abdomen is cleansed with an antiseptic solution and draped. Local anesthesia is administered, and a trocar is inserted and tubing attached. Fluid drains via gravity into a sterile container. Up to 2 L of fluid may be removed; removal of a larger quantity may lead to shock. The amount and color of ascitic fluid removed should be documented before sending a sample for laboratory evaluation. Paracentesis may be repeated periodically as fluid accumulates [27]. Ascites may also be controlled by a LeVeen or Denver shunt procedure, which will be discussed later in this course.

RESTORING NORMAL FLUID VOLUME

Edema related to hepatic dysfunction can be misleading, because vascular dehydration frequently accompanies it and diuretic therapy alone can worsen dehydration. Diuretics should not be overused and should be given in conjunction with albumin. Aldosterone antagonists are the diuretics of choice, as edema is related to inadequate detoxification of aldosterone. Intake-output records should be maintained and electrolyte values and skin turgor assessed. The patient should be weighed and girth measured daily to assess fluid volume status; weight loss should not exceed one-half pound (0.23 kg) per day. Greater losses may result in a shift of fluids into the abdominal cavity, promote electrolyte imbalance, and precipitate hepatic encephalopathy [27].

In the patient with ascites, accumulated fluid may stretch the skin so tightly that it tears. Patients should be urged to avoid restrictive clothing, take good care of the skin, and change positions frequently. A pillow may be placed under the costal margin for support if the patient is lying on his or her side. Compression stockings may be worn and the limbs elevated frequently to minimize peripheral edema. When seated, patients should be warned to support their legs, not to cross them or let them dangle. A fluid deficit may occur during episodes of variceal hemorrhage. Lost blood should be replaced, and vital signs closely monitored. Fluid restrictions of 1,000 mL in 24 hours may be required when peripheral edema and ascites are present [27].

IMPROVING TISSUE PERFUSION

Tissue perfusion may be improved by correcting anemia; iron supplements, vitamins B12 and K, and blood transfusions may be administered. When hemoglobin and hematocrit values are restored to normal levels, the heart pumps blood throughout the body more efficiently. Ecchymosis and gingival hemorrhage may indicate vitamin K deficiency. If the patient has coagulation disorders, intramuscular injections should be avoided whenever possible and pressure should be applied after any injection is given. Decreasing fluid overload, if present, will improve cardiac output [27].

NURSING EVALUATION

COMFORT

Nursing interventions related to alleviation of pain are considered successful when the patient is resting comfortably without severe pain and can perform activities of daily living

(ADLs) without undue discomfort. Observations verifying these outcomes would include sleeping soundly for at least four hours at a time, absence of facial grimaces, and absence of listlessness [36].

Nursing interventions related to pruritus are successful if the patient has relief from itching, rests comfortably without scratching, performs ADLs without scratching, and does not interrupt skin integrity by scratching [36].

SKIN INTEGRITY

Absence of pressure injuries or erythema at surgical and intravenous sites, normal temperature, and evidence that the patient is eating the prescribed diet support an outcome of maintaining or improving skin integrity [37].

THOUGHT PROCESSES

Orientation to person, place, and time, absence of asterixis, and the ability to write one's name the same way on sequential days are evidence that a patient's thought processes are intact. If asterixis develops or changes in handwriting are noted, the nurse may need to modify plans and interventions [37].

NUTRITION

Expected outcomes for improving nutritional status and knowledge of nutrition include the ability to list foods high in protein and potassium and low in salt and fats, evidence of increasing intake of well-balanced foods, and signs that nutritional deficiencies are being corrected. This can be a slow process. Consulting with the patient to make a list of favorite foods and seeing that those foods are served may improve consumption. Cultural and ethnic preferences should be considered in planning the diet [37].

GAS EXCHANGE

One expected outcome might be the patient's ability to ambulate without oxygen supplementation. Another is return of the hemoglobin level to normal. There might be an absence of dyspnea on exertion; an absence of cyanosis; or increased energy (e.g., ability to engage in usual activities). If these data can be observed, the nursing plan may be considered successful [37].

FLUID VOLUME

Expected outcomes related to fluid volume include good skin turgor, decreased circumference of edematous extremities or abdominal girth, and intake and output measurements are indications of correction of a fluid alteration. Correcting fluid volume alterations may take a long time, and several plans and revisions may be required [37].

TISSUE PERFUSION

A blood pressure no greater than 140/80 mm Hg and normal hemoglobin and prothrombin time are indications of adequate tissue perfusion. However, it is important to remember that hemoglobin and hematocrit values and blood pressure readings may be deceiving if vascular dehydration is present [37].

CONGENITAL DISORDERS

Congenital disorders of the hepatic and biliary system are present from birth, although they may not be visibly apparent or symptomatic until adulthood. These patients may seek medical care when symptoms of their disorder first appear or when exacerbations occur [46].

GILBERT SYNDROME

Gilbert syndrome is a familial disorder characterized by a deficiency of glucuronide transferase, an enzyme necessary for conjugation of bilirubin. Due to the enzyme insufficiency, serum levels of unconjugated bilirubin rise, with consequent hyperbilirubinemia and icterus. No pathologic changes occur in the liver with this disorder, so liver function studies will yield normal results except for the elevated bilirubin levels. There is no hemolysis or obstruction [46; 47]. Differential diagnosis includes non-alcoholic fatty liver disease, autoimmune hepatitis, drug-induced hepatitis, and primary biliary or sclerosing cholangitis.

In general, there is no required treatment for Gilbert syndrome aside from symptom management. Steps should be taken to avoid potential triggers in order to minimize fluctuations in unconjugated bilirubin. If there is evidence of hepatic decompensation, the patient should be referred to a specialist for further evaluation.

ALAGILLE SYNDROME

What are the main clinical manifestations of Alagille syndrome?

Alagille syndrome is a genetic disorder with manifestations in multiple systems throughout the body. Variability in presentation is seen even among individuals from the same family [48]. The major clinical manifestations of this disorder are bile duct paucity on liver biopsy, cholestasis, congenital cardiac defects (primarily involving the pulmonary arteries), butterfly vertebrae, ophthalmologic abnormalities, and characteristic facial features. The diagnosis is made through positive genetic testing and/or clinical diagnostic criteria.

Clinical management of Alagille syndrome is primarily supportive. For some patients, targeted therapy with ileal bile acid transporter inhibitors (e.g., maralixabat and odevixibat) may be indicated to increase the excretion of bile acids. In severe cases, liver transplantation may be indicated. Measures to address pruritus, xanthomas, and pain are recommended. Considering the multisystem manifestations of this syndrome, these patients benefit from care delivered by an interprofessional team, including physicians, nurses, dieticians, genetic counselors, and specialists.

Patients with Alagille syndrome should be monitored to allow for early identification of progression and potentially harmful complications. Liver function should be regularly assessed, and serum alpha-fetoprotein and liver ultrasound may be measured every six months [48].

DISORDERS OF MULTIFACTORIAL ORIGIN

Disorders of multifactorial origin are those for which no single, specific etiologic agent has been identified. For the hepatobiliary system, cirrhosis is the major disease process of multifactorial origin [49].

CIRRHOSIS

What are the two clinical categories of cirrhosis?

Cirrhosis is a chronic process in which the normal configuration of liver lobules is disrupted. Cell death occurs, and regeneration is associated with scarring. Nodular cells formed during regeneration distort the morphology of the liver and obstruct hepatic flow of blood and lymph. Eventually, cirrhosis leads to hepatic failure and portal hypertension [50].

Cirrhosis is the end stage of any chronic liver disease. In developed countries, the most common causes include nonalcoholic fatty liver disease, hepatitis infection, and excessive alcohol intake; in developing counties, hepatitis A and B infections are the most likely causes. There are two clinical categories of cirrhosis: compensated and decompensated. Patients who have compensated cirrhosis can be further categorized as:

- Stage 1: No varices, no ascites
- Stage 2: Varices, no ascites

Likewise, patients with decompensated cirrhosis may be staged as:

- Stage 3: Ascites with or without varices
- Stage 4: Bleeding with or without ascites

The diagnosis of cirrhosis can be made by clinical, laboratory, imaging, or liver stiffness findings. For patients with compensated cirrhosis, noninvasive parameters all may be normal and liver biopsy would be required for diagnosis. Decompensated cirrhosis is more easily diagnosed by laboratory analysis.

These patients are asymptomatic and overall have median survival times of more than 12 years. Presence of varices is the key prognostic factor for compensated patients and indicates higher likelihood of decompensation. The Child-Turcotte-Pugh (CTP) score is used as a prognostic scoring system in cirrhosis based on two clinical and three laboratory parameters:

- Ascites:
  - None: 1 point
  - Diuretic-sensitive or mild/moderate: 2 points
  - Diuretic-refractory or tense: 3 points
- Encephalopathy:
  - None: 1 point
  - Episodic or overt grade 2: 2 points
  - Recurrent/chronic or grade 3–4: 3 points
- Albumin:
  - >3.5 g/dL: 1 point
  - 3.4–2.8 g/dL: 2 points
  - <2.8 g/dL: 3 points
- Bilirubin:
  - <2 mg/dL: 1 point
  - 2–3 mg/dL: 2 points
  - >3 mg/dL: 3 points
- International normalized ratio (INR):
  - <1.7: 1 point
  - 1.7–2.3: 2 points
  - >2.3: 3 points

In the original scoring system, nutritional status (normal, moderately altered, malnourished) was used instead of INR, which reflects the importance of sarcopenia in cirrhosis. Patients who score 5–6 points are mostly those with compensated cirrhosis. A score of 7–9 points indicates decompensated cirrhosis, but decompensation is "early." Those who score 10–15 points have later or "further" decompensated cirrhosis. One-year mortality ranges from 1% for mildest disease to 57% for patients with severe disease.

Clinical Manifestations

Cirrhosis is often (but not invariably) part of a progressive disease that begins with fatty infiltration of the liver (steatosis) that progresses to fibrosis of the liver due to inflammation. If not adequately treated, cirrhosis can progress to hepatic failure. Cirrhosis may be related to nutritional disorders, biliary obstruction, hepatotoxicity, iron storage disorders, and alcohol ingestion. Histologic examination of the liver reveals fatty infiltration, cellular necrosis, and disruption of the lobes. Gross inspection reveals a "hobnail" appearance; the hepatic surface is often stippled and nodular [51].

Portal hypertension results in compensatory development of collateral blood vessels in the esophagus. These vessels, called esophageal varices, dilate as portal hypertension increases. Because such vessels are inadequate to accommodate the increased blood flow, hemorrhage may occur [51].

Patients with cirrhosis often have a characteristic appearance. Anorexia develops early in the course of the disease, resulting in significant weight loss. The skin is typically orange-yellow, the eyes are sunken, and the facial bones are prominent. The limbs are emaciated, but the abdomen is enlarged due to peripheral edema or ascites. Other symptoms include spider angiomas, palmar erythema, and changes in mental status [51].

Therapeutic Measures

Hemorrhage of esophageal varices may be controlled temporarily by administering infusions of vasopressin, somatostatin, octreotide, or terlipressin to promote diffuse arterial vasoconstriction and to lower portal pressure by constricting the

splanchnic arterial bed. The infusion may be given systemically or via the superior mesenteric artery and administered for five days, according to current guidelines [52]. This provides only temporary control and is associated with complications, including systemic arterial hypertension and coronary vasoconstriction, possibly leading to myocardial infarction. Whole blood should be available for immediate infusion [52; 53; 54]. If medication administration is unsuccessful, gastric lavage with ice-cold saline, use of the Minnesota tube or Sengstaken-Blakemore tube, or portal-systemic shunting may be implemented to control bleeding temporarily.

As noted, hepatic encephalopathy is a complication of advanced cirrhosis [52; 54; 55]. Lactulose and antibiotics may be used to manage these patients.

Injection sclerotherapy, an alternative long-term control measure, may be performed as a bedside procedure. The patient can be sedated using diazepam (Valium), meperidine hydrochloride (Demerol), propofol, fentanyl (Sublimaze), midazolam (Versed), or ketamine (Ketalar). The medications used are at the discretion of the anesthesia provider and surgeon based on the patient's medical history. It is important to be familiar with each, along with their respective reversal agents [57; 58]. Sclerosing solutions are then injected directly into the bleeding varices by means of fiberoptics endoscopy. Potential complications include chest pain, transient fever, ulceration of the injection sites, and formation of strictures. Most are self-resolving; strictures may be treated by dilatation. Perforation, a major complication, is rare. If perforation does occur, it is treated by keeping the patient NPO, suctioning gastric contents, and administering antibiotic therapy; surgery is seldom required [52; 55; 56].

Prophylactic antibiotics are also administered to lower rates of infection, death, and early rebleeding. IV ceftriaxone has demonstrated the most positive results in randomized controlled trials [52].

Specific Nursing Measures

It is important to emphasize that patients with cirrhosis must abstain from alcohol. Because cirrhosis is a chronic condition, most nursing interventions will be related to the patient's comfort. Teaching patients and the public about the effects of alcohol may have preventive benefits [59; 60; 61; 62].

Nursing measures for patients with esophageal hemorrhage include explaining treatments to the patient and assessing frequently to determine whether hemorrhage has ceased. As with any hemorrhage, the nurse is responsible for monitoring blood replacement therapy and administering vitamin K, as ordered. Bleeding esophageal varices create a crisis for patient and family. Timely explanations of ongoing interventions and anticipated results will help the patient cope with panic and fear of death. Providing nursing care in a decisive, supportive manner helps the patient regain control and to participate in the therapy. To provide optimum crisis care, the nurse should assess the family support structure and provide information and support to significant others as well as the patient. Fluid restrictions are generally maintained at 1,000 mL per 24-hour period [59; 60; 61].

ALCOHOL-INDUCED LIVER DISEASE

The spectrum of alcoholic liver disease incudes fatty liver disease, alcoholic hepatitis, and cirrhosis. Most deaths from alcoholic cirrhosis are attributable to liver failure, bleeding esophageal varices, or kidney failure. It has been estimated that there are 14 million persons in the United States with alcohol use disorder, and approximately 10% of those with alcohol use disorder develop cirrhosis with continued heavy drinking [64; 65; 68].

Portal Cirrhosis

What are the characteristic signs/symptoms of portal cirrhosis?

The metabolism of alcohol leads to chemical attack on certain membranes of the liver. But whether the damage is caused by acetaldehyde or other metabolites is unknown. Acetaldehyde is known to impede the mitochondrial electron transport system, which is responsible for oxidative metabolism and generation of ATP; as a result, the hydrogen ions that are generated in the mitochondria are shunted into lipid synthesis and cytogenesis. Abnormal accumulations of these substances are found in hepatocytes (fatty liver) and blood. Binding of acetaldehyde to other molecules impairs the detoxification of free radicals and synthesis of proteins. Acetaldehyde also promotes collagen synthesis and fibrogenesis. The lesions of hepatocellular injury tend to be most prevalent in the centrilobular area that surrounds the central vein, where the pathways for alcohol metabolism are concentrated. This is the part of the lobule that has the lowest oxygen tension; it is thought that the low oxygen concentration in this area of the liver may contribute to the damage [64; 65].

The amount of alcohol required to produce chronic liver disease varies widely, depending on body size, age, sex, and ethnicity, but the high end of the range is about 80 g/day for 10 to 12 years. This amount of alcohol can be in the form of 8 ounces of 86 proof (41% alcohol) whiskey, two bottles of wine, or six 12-ounce bottles of beer. Even after alcohol intake has stopped and all alcohol has been metabolized, the processes that damage liver cells may continue for many weeks and months. Clinical and chemical effects often become worse before the disease resolves. The accumulation of fat usually disappears within a few weeks, and cholestasis and inflammation also subside with time. However, fibrosis and scarring remain. The liver lobules become distorted as new liver cells regenerate and form nodules [64; 65].

Although the mechanism by which alcohol exerts its toxic effects on liver structure is somewhat uncertain, the changes that develop can be divided into three states: fatty changes, alcoholic hepatitis, and cirrhosis [65].

Fatty liver is characterized by the accumulation of fat in hepatocytes, a condition called steatosis. The liver becomes yellow and enlarges as a result of excessive fat accumulation. The pathogenesis of fatty liver is not completely understood and can depend on the amount of alcohol consumed, dietary fat content, body stores of fat, hormonal status, and other factors. There is evidence that ingestion of large amounts of alcohol can cause fatty liver changes even with an adequate diet. The fatty changes that occur with the ingestion of alcohol usually do not produce symptoms and are reversible after the alcohol intake has been discontinued [65; 68].

Alcoholic hepatitis is the intermediate state between fatty changes and cirrhosis. It often is seen after an abrupt increase in alcohol intake and is common in binge drinkers. Alcoholic hepatitis is characterized by inflammation and necrosis of liver cells. This stage usually is characterized by hepatic tenderness, pain, anorexia, nausea, fever, jaundice, ascites, and liver failure, but some people may be asymptomatic. The condition is always serious and sometimes fatal, with an associated mortality rate of 34%. The immediate prognosis correlates with severity of liver cell injury. In those who continue to drink, the acute phase often is followed by persistent alcoholic hepatitis with progression to cirrhosis in a matter of one to two years [65; 68].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Association for the Study of Liver Diseases, because abstinence is the single most important factor in improving survival from alcohol-associated liver disease, multidisciplinary management with addiction specialists and referral to treatment for alcohol use disorder, particularly in patients with moderate to severe alcohol use disorder or clinically evident liver disease, is mandatory.

(https://journals.lww.com/hep/fulltext/2020/01000/diagnosis_and_treatment_of_alcohol_associated.25.aspx. Last accessed August 12, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

Alcoholic Cirrhosis

Alcoholic cirrhosis and malnutrition is the end result of repeated bouts of drinking-related liver injury and designates the onset of end-stage alcoholic liver disease. The gross appearance of the early cirrhotic liver is one of fine, uniform nodules on its surface. The condition has traditionally been called monocular or Laënnec cirrhosis. With more advanced cirrhosis, regenerative processes cause the nodules to become larger and more irregular in size and shape. As this occurs, the nodules cause the liver to become relobulized through the formation of new portal tracts and venous outflow channels. The nodules may compress the hepatic veins, curtailing blood flow out of the liver and producing portal hypertension, extrahepatic portosystemic shunts, and cholestasis [64; 65; 69].

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

What is the cause of MASLD?

Metabolic dysfunction-associated steatotic liver disease (MASLD) was previously referred to as nonalcoholic fatty liver disease (NAFLD) but was renamed in 2023 to better reflect the underlying pathophysiology and embrace affirmative, nonstigmatizing terminology [70]. It is caused by metabolic dysfunction that affects the liver. As noted, in the United States, it is the most frequently occurring form of chronic liver disease. The condition can range from simple steatosis (fatty infiltration of the liver) to nonalcoholic steatohepatitis (steatosis with inflammation and hepatocyte necrosis). Although steatosis alone does not appear to be progressive, approximately 10% to 15% of people with nonalcoholic steatohepatitis progress to cirrhosis. Obesity, type 2 diabetes, metabolic syndrome, and hyperlipidemia are coexisting conditions frequently associated with fatty liver disease. The condition is also associated with other nutritional abnormalities, surgical conditions, drugs, and occupational exposure to toxins. Both rapid weight loss and parenteral nutrition may lead to MASLD. Jejunoileal bypass, a surgical procedure historically used for weight loss, has largely been abandoned for this reason [65; 71].

Pathogenesis

The pathogenesis of MASLD is thought to involve both lipid accumulations with hepatocytes and formation of free radicals, in a manner similar to that which occurs with alcohol metabolism. The primary metabolic abnormalities leading to lipid accumulation are poorly understood but are thought to include alteration in pathways for uptake, synthesis, degradation, or secretion of hepatic lipids and resulting from insulin resistance. Obesity increases the synthesis and reduces the oxidation of free fatty acids. Type 2 diabetes or insulin resistance also increases adipose tissue lipolysis and the subsequent production of free fatty acids. When the capacity of the liver to export triglyceride is exceeded, excess fatty acids contribute to the formation of fatty liver. Abnormal lipid peroxidation ensues, followed by direct hepatocyte injury, release of toxic byproducts, inflammation, and fibrosis [65; 71].

Clinical Manifestations

MASLD is usually asymptomatic, although fatigue and discomfort in the right upper quadrant of the abdomen may be present. Mildly to moderately elevated serum levels of AST, ALT, or both are the most common and often the only abnormal laboratory findings. Other abnormalities, including hypoalbuminemia, a prolonged prothrombin time, and hyperbilirubinemia, may be present in persons with cirrhotic-stage liver disease. The diagnosis of MASLD requires the presence of >5% macrovesicular steatosis, inflammation, and liver cell ballooning, typically with a predominantly centrilobular distribution; this is usually demonstrated by imaging. Exclusion of alcohol as a cause of the disorder is also required [65; 72].

Treatment

The aim of treatment is to slow progression of MASLD and to prevent liver-related illness. Weight loss and exercise improve insulin resistance and are recommended in conjunction with treatment of associated metabolic disturbances. Alcohol use should be avoided. Disease progression is slow and the magnitude of disease-related morbidity and mortality is uncertain. One study has shown the use of statins and antioxidants such as vitamins A and E have been effective in reducing the odds of hepatic steatosis in patients with MASLD. Liver transplantation is an alternative for some with end-stage liver disease, but MASLD may reoccur in up to 39% of people post-liver transplantation [65; 72; 73; 74].

In adults with MASLD, the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) recommend dietary and behavioral therapy-induced weight loss to improve liver injury, as assessed histologically or noninvasively.

(https://www.journal-of-hepatology.eu/article/S0168-8278(24)00329-5/fulltext. Last accessed August 12, 2024.)

Level of Evidence/Strength of Recommendation: 1, Strong Recommendation, Strong Consensus

INTRAHEPATIC BILIARY DISORDERS

Intrahepatic biliary diseases disrupt the flow of bile through the liver, causing cholestasis and biliary cirrhosis. Among the causes of intrahepatic biliary diseases are primary and secondary biliary cholangitis [55].

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), formerly primary biliary cirrhosis, is a chronic disease of the liver characterized by the autoimmune destruction of intrapolar bile ducts causing cholestasis. The disease is seen most commonly in women 40 to 60 years of age. Familial occurrences of the disease are found between parents and children and among siblings. With the possible exception of a reportedly higher risk of a polymorphism of the gene for the vitamin D receptor, there are no clear genetic influences for the disorder. As with other autoimmune disorders, possible environmental triggers include infections and chemical agents [63].

Clinical Manifestations

Primary biliary cholangitis is characterized by an insidious onset and progressive scarring and destruction of liver tissue. The liver becomes enlarged and takes on a green hue because of the accumulated bile. The earliest symptoms are unexplained pruritus, weight loss, and fatigue, followed by dark urine and pale stools. Osteoporosis occurs in 51% of women with the disorder. Jaundice is a late manifestation of the disorder, as are other signs of liver failure. Serum alkaline phosphatase levels are typically elevated [63].

Diagnosis and Treatment

What is the usual treatment of primary biliary cholangitis?

Diagnosis of primary biliary cholangitis is made when two of the following signs and symptoms are present [63]:

- Destruction of bile ducts and presence of nonsuppurative cholangitis on liver biopsy
- Cholestasis with alkaline phosphatase elevation for at least six months
- Presence of serum antimitochondral antibodies

Treatment is largely symptomatic. Ursodeoxycholic acid (ursodiol), the only drug approved for treating primary biliary cholangitis, increases bile flow, decreases the toxicity of bile contents, and has been shown to decrease the rate of clinical deterioration. Cholestyramine, a bile acid-binding drug, may prove beneficial for treatment of pruritus. Colchicine, which acts to prevent leukocyte migration and phagocytosis, and methotrexate, a drug with immunosuppressive properties, have also resulted in reported benefits in terms of symptom relief. Corticosteroids have been shown to improve liver histology and serum liver function tests, but are associated with serious long-term side effects. Liver transplantation remains the only effective treatment for advanced disease. Primary biliary cirrhosis does not recur after liver transplantation if appropriate immunosuppression is used [63].

Secondary Biliary Cholangitis

Secondary biliary cholangitis results from prolonged obstruction of the extrabiliary tree. The most common cause is cholelithiasis. Other causes of secondary biliary cirrhosis are malignant neoplasms of the biliary tree or head of the pancreas and strictures of the common duct caused by previous surgical procedures. Extrahepatic biliary cholangitis may benefit from surgical procedures designed to relieve the obstruction. The presence of dark urine is a sign that indicates emergent medical attention is necessary [64; 66; 67].

INFECTIOUS AND INFLAMMATORY DISORDERS

Infectious and inflammatory disorders of the hepatobiliary system can involve the liver or the gallbladder. Hepatic infections may be associated with inflammation of hepatic cells, hyperplasia of Kupffer cells, bile stasis, or tissue necrosis. Biliary inventions may be associated with dilation of the gallbladder, which will be filled with bile, pus, and blood. Although the signs and symptoms of different types of hepatitis are much the same, the major symptom present for all is anorexia [75; 76; 77].

TOXIC AND DRUG-INDUCED HEPATITIS

Certain agents, including carbon tetrachloride, yellow phosphorus, and acetaminophen (in large doses), are hepatotoxins. When ingested or inhaled, they cause necrosis of hepatic cells. Hepatitis related to these substances is called toxic hepatitis [76; 78].

Varying patterns of hepatic dysfunction are seen in response to use of other drugs and anesthetic agents. For example, halothane, methyldopa, and isoniazid can produce hepatitis. Chlorpromazine, erythromycin estolate, and methimazole can cause intrahepatic cholestasis with jaundice. Phenylbutazone and the sulfonamides can produce granulomas within the liver [76; 78].

Clinical Manifestations

Both drug-induced and toxic hepatitis are manifested by inflammation of hepatic cells, hyperplasia of Kupffer cells, and bile stasis; however, toxic hepatitis is also associated with acute cellular necrosis. The onset of both forms is similar to that of viral hepatitis from which they must be quickly distinguished if detoxification is to be initiated. Anorexia, jaundice, and hepatomegaly are common. In toxic hepatitis, the illness may progress rapidly, with rising fever, subdermal hemorrhage, and severe vomiting. Delirium, coma, and convulsions develop, and the patient dies within a few days. If the toxin is promptly identified and exposure is discontinued, however, the patient may recover quite rapidly. Cirrhosis sometimes develops after recovery [76; 78].

Drug-induced hepatitis may develop after repeated exposures have sensitized the patient to a drug. For this reason, any medication that causes pruritus or other symptoms of sensitivity should be immediately withdrawn and the sensitivity noted on the patient's record. Chills, fever, rash, pruritus, arthralgia, and nausea are early signs of drug-induced hepatitis. Icterus, hepatomegaly, and hepatic tenderness follow. The urine is dark. Symptoms may subside once the drug is withdrawn, but drug-induced hepatitis may be fatal, and postnecrotic cirrhosis also may develop [78; 79; 80; 81]. The anesthetic agent halothane has been linked to episodes of drug-induced hepatitis; therefore, anesthetics should be rotated for patients undergoing repeated surgical procedures [81].

Therapeutic and Specific Nursing Measures

Treatment is directed at the removal of the toxin or sensitizing agent, if known. Early diagnosis is important. The history can yield useful findings regarding exposure to toxins or medications. Attention should focus on occupational history, possible exposure to hepatotoxins during hobby activities (e.g., furniture finishing), and medication history, including over-the-counter medications and self-prescribed vitamin therapy. Once the disease has been diagnosed, nursing care focuses on comfort measures and the replacement of blood, fluids, and electrolytes [75; 78].

HEPATIC ABSCESS

Hepatic abscess is an invasion of the liver by micro-organisms producing a localized collection of pus in a cavity formed by destruction of tissue. Hepatic abscess may be caused by fungal, bacterial, or even protozoan infection. An infection anywhere in the body can lead to formation of an hepatic abscess, but gastrointestinal infections are especially likely to do so [75; 76; 82; 83].

Usually, micro-organisms that invade the liver are destroyed by the phagocytic Kupffer cells, but occasionally a few survive. The lobular structure of the liver tends to keep the infection small and circumscribed, but several lobules may be affected. As the micro-organisms multiply, the toxins they produce destroy hepatic cells. Concurrently, the body's defense system acts to destroy the invading organisms, and the cavity becomes filled with a mixture of leukocytes, micro-organisms, and dead and necrotic hepatic cells [75; 76].

Clinical Manifestations

Patients with hepatic abscess will have a high fever and a painfully enlarged liver, anemia, elevated WBC levels, and icterus. As the temperature rises, the patient has alternating episodes of chills and diaphoresis; toxic shock can occur within hours. If identified soon enough, the infective agent can be controlled with antimicrobial therapy. Sometimes, septicemia cannot be reversed, and the patient dies [76].

Therapeutic Measures

Non-aspirin analgesics, intravenous fluid therapy, and parenteral antimicrobial agents may be prescribed. Occasionally, surgical intervention may be indicated to drain large abscessed areas or to resect an abscessed portion of the liver. This is done rarely, however, because coagulation abnormalities associated with liver dysfunction increase the risk of severe hemorrhage. The most common surgical intervention is percutaneous drainage. This may be done intermittently, or continuous catheter drainage may be employed [76].

Specific Nursing Measures

Continual assessment is a crucial part of nursing care. A patient history should include inquiry regarding recent (within past six months) infection and presence of diabetes or insulin resistance [20].

Hourly monitoring of temperature and vital signs may be required to estimate whether the patient is becoming septic or whether antimicrobial therapy is taking effect. Hepatic abscess is accompanied by pain and fever, so supportive care with comfort measures is necessary. If surgical intervention is indicated or drainage initiated, the nurse will teach the patient about the procedure, provide reassurance, and assess for hemorrhage [20].

VIRAL HEPATITIS

Hepatitis is an inflammatory state of the liver and may be caused by exposure to toxic chemicals, autoimmune disease, fatty liver disease, or infection. Many common viral infections in humans are associated with mild, usually transient, secondary inflammation of the liver. The term "viral hepatitis" is applied to infection caused by a set of viruses unique in their primary trophism for the liver and their propensity to cause serious, often prolonged "primary" hepatitis. For clinical purposes, the viruses causing primary hepatitis are grouped and classified alphabetically in accordance with when each was identified: hepatitis A, B, C, D, and E. In 1994, hepatitis F was identified as a cause of fulminant liver failure [84]. This was later found to be a variant subspecies of another virus. Therefore, "F" is now omitted in the hepatitis alphabet. A virus similar in structure to hepatitis C was initially designated hepatitis G; however, this virus has been reclassified as a Pegivirus GB virus-C (GBV-C) [85]. This virus can cause subclinical infection in humans but is not linked to active disease.

Hepatitis A

How is hepatitis A virus transmitted?

The World Health Organization (WHO) estimates the annual worldwide incidence of hepatitis A to be 1.5 million per year [86]. Within the United States, diagnosed cases of hepatitis A virus must be reported to the local health authorities, who in turn report the incidence to the Centers for Disease Control and Prevention (CDC). Many persons who contract hepatitis A virus, however, do not have clinical symptoms. Therefore, the CDC must estimate the actual incidence of hepatitis A virus infection based upon CDC reports and projections. For the 10-year period 1999 to 2009, the CDC estimates that 749,000 cases occurred within the United States [87].

Since the introduction of hepatitis A vaccine in 1995, the incidence of hepatitis A in the United States has declined by 95% [87]. However, after falling to a low of 1,239 cases reported in 2014, a series of outbreaks from 2013 to 2023 resulted in a dramatic increase in cases, reaching 12,474 reported cases in 2018 and 18,846 in 2019 [88]. According to the CDC, the increase in incidence was primarily the result of contaminated organic fruit, including strawberries, pomegranate seeds, blackberries, and a mixed antioxidant blend [88].

Hepatitis A is transmitted via the fecal-oral route, most commonly from contaminated water or food. After the virus is ingested, it is transported from the intestines to the liver, where it invades the hepatocytes. The virus uses the hepatocytes for viral replication and is then released into the bloodstream and excreted in the stool. HAV that is acquired percutaneously travels directly from the bloodstream to the liver to invade the hepatocytes; viral replication and excretion follow the same pattern as in fecal-oral transmission.

Clinical Manifestations

Signs and symptoms of hepatitis A infection can vary from subclinical disease to fulminant (sudden and intense) illness. In symptomatic patients, the incubation period (i.e., time from exposure to onset of illness) is in the range of 15 to 50 days (average: 28 days). Clinical symptoms and signs include nausea, vomiting, headache, fever, chills, abdominal discomfort, hepatomegaly, and right upper quadrant tenderness. For most patients, symptoms are mild and subside in three to seven days. Others will have more significant disease and will progress to an icteric phase (jaundice). For these patients, recovery typically occurs after about three weeks.

Fulminant infection occurs in less than 1% of the cases. Some of these patients may have such severe damage that they require a liver transplant. Fatalities from hepatitis A are extremely rare. There is no known chronic carrier state.

Laboratory studies reflect leukopenia, atypical lymphocytes, and elevated ALT and AST levels. As discussed, anti-HAV IgM can be detected early in the disease, usually appearing in detectable levels 2 to 3 weeks after exposure, then declining to undetectable levels in 12 to 24 weeks. IgG levels begin to rise three to four weeks after exposure and remain elevated throughout life.

Therapeutic Measures and Prevention

Treatment of HAV is supportive and directed at maintaining adequate nutrition and controlling symptoms. Ingestion of alcohol and/or hepatotoxic medications is avoided. For patients with fulminant hepatic failure resulting from HAV, corticosteroids may be used. However, clinical research has not demonstrated improved outcomes in patients receiving corticosteroids when compared with those who did not receive steroid treatment [89].

As with any other disease, prevention is the most effective strategy. Hepatitis A vaccine is licensed in the United States for use in individuals 1 year of age and older. Immunoglobulin (Ig) can provide short-term protection, both pre- and post-exposure (administered within two weeks after exposure for maximum protection).

The U.S. Food and Drug Administration (FDA) has approved two single-antigen HAV vaccines and one combination vaccine for use in the United States, all of which are inactivated vaccines. The single-antigen vaccines are Havrix and VAQTA. Both are administered to adults in a dose of 1 mL intramuscularly. The dose for children is 0.5 mL [90]. Single-antigen vaccines are considered interchangeable. A second dose of either vaccine can be administered, regardless of which vaccine was administered as the first dose.

An alternative to single-antigen HAV vaccines is Twinrix, which contains inactivated HAV and HBV recombinant vaccines. It is immunogenic against HAV and HBV but requires three injections of 1 mL intramuscularly. The suggested schedule is an initial injection followed by boosters at one and six months.

This vaccine is not approved for use in children. Immunity is expected to persist for at least 20 years (and possibly longer) in those who receive all three doses [90; 91].

Passive immunization with human Ig, preferably administered within two weeks of known or anticipated exposure, provides short-term protection against HAV infection for persons who have not been vaccinated. The single human Ig product licensed for hepatitis A prophylaxis in the United States is GamaSTAN S/D.

Sanitation strategies are also important in controlling HAV. If in water, the virus is inactivated by boiling the water for five minutes. Hand hygiene using alcohol-based hand sanitizers containing 60% to 95% ethanol are ineffective against HAV, even when in contact with the virus for a full two minutes [92; 93]. Therefore, handwashing with soap and water for at least 20 seconds is recommended rather than hygiene using hand sanitizers. If handwashing with soap and water is not an option, cleansing the hands with povidone-iodine for at least 30 seconds may be considered.

Specific Nursing Measures

Persons with hepatitis A may often be cared for at home. Hospitalized patients will require enteric isolation and interventions for alternation in comfort (pruritus and pain), nutritional intake, and fluid volume; impairment of skin integrity and O_2/CO_2 exchange; and disturbances in self-concept. Persons giving care in the home should wear gloves if contact with feces is possible. Gowns should be worn in any situation in which gross soiling occurs. Careful attention to handwashing is essential for patients and for those giving care [95].

Discharge planning for hospitalized patients includes encouraging the patient to get ample rest, ingest a well-balanced diet, and avoid alcohol and over-the-counter medications for at least six months. There is no chronic carrier state with hepatitis A. The patient will not progress to chronic hepatitis or cirrhosis [95].

Hepatitis B

The hepatitis B virus is one of the smallest viruses known to cause disease in animals. Ten HBV genotypes, labeled A through J, and 30 subtypes have been identified [96]. The genotype of the virus influences the likelihood of developing cirrhosis and the response of the virus to therapy with interferon.

HBV consists of a core and an envelope. The envelope contains HBsAg proteins, glycoprotein, and lipids. The core of HBV includes viral DNA, enzymes necessary for replication, and antigenic protein particles distinctly different from those found in the envelope. The viral DNA is circular and predominantly double stranded, but with a single-stranded arc. The core antigen is termed HBcAg.

HBV is a bloodborne pathogen that is typically acquired parenterally, perinatally, or through sexual interaction. As with HIV infection, sexual contact and use of contaminated needles for drug injection are the primary risk factors for HBV [97]. However, HBV is considered 50 to 100 times more infectious than HIV, requiring a much smaller inoculum for transmission. Thus, a needlestick injury from a source patient who is coinfected with both HBV and HIV is more likely to transmit HBV, even when the needle is solid (e.g., a suture needle) and even when blood is not visible. Because HBV does not transfer across the placenta, perinatal transmission occurs when an infant is exposed to the blood of an infected mother at the time of delivery. Parenteral exposures include occupational exposure of healthcare workers (1%), use of injected drugs (15%), tattoos, ear and body piercing, acupuncture, and blood transfusions received prior to 1980. Rare cases of transfusion-associated HBV continue to occur, indicating that the virus was present in the blood but with antigen levels below the level of laboratory detection [98].

The U.S. Preventive Services Task Force recommends screening for hepatitis B virus infection in adolescents and adults at increased risk for infection.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening. Last accessed August 12, 2024.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Clinical Manifestations

The incubation period for HBV can be as little as 45 days or as long as 180 days, but most commonly is 60 to 90 days. The severity of primary HBV infection varies from subclinical to fulminant illness. The age of the patient, the integrity of the immune system, and the infecting dose of the virus influence the severity of acute disease. Persons younger than 5 years of age exhibit mild symptoms or no symptoms, while 70% of infected adults exhibit significant clinical symptoms [99].

Signs and symptoms associated with acute HBV infection are similar to those of other acute viral hepatitis syndromes and include malaise, nausea, abdominal discomfort, icterus, and dark urine. Physical examination of the patient typically reveals an enlarged, tender liver and a yellowish hue to the skin. The spleen is palpable in some patients. In patients with fulminant hepatitis, progressive signs of hepatic encephalopathy (e.g., somnolence, confusion, stupor, coma) are common.

Therapeutic Measures

There is no specific treatment for acute HBV infection; management is primarily supportive. Control of nausea and vomiting, maintenance of fluid and electrolyte balance, avoidance of potentially hepatotoxic drugs and alcohol, and extended periods of rest are the typical therapies.

In less than 1% of cases, fulminant acute liver failure develops. Treatment for fulminant hepatic failure includes compensating for coagulation defects, correcting acid-base as well as fluid and electrolyte disturbances, prevention of hypoglycemia, administering prophylactic antibiotics, and therapies to reduce ammonia levels and combat cerebral edema. With aggressive therapy, improved intensive care and the use of orthotopic liver transplantation, the mortality rate for fulminant acute hepatic failure has gone down to 40% [100].

The American Association for the Study of Liver Diseases (AASLD) recommends antiviral therapy for adults with immune-active chronic hepatitis B infection (hepatitis Be antigen negative or positive) to decrease the risk of liver-related complications.

(https://journals.lww.com/hep/pages/articleviewer.aspx?year=2018&issue=04000&article=00034&type=Fulltext. Last accessed August 12, 2024.)

Level of Evidence/Strength of Recommendation: Moderate/Strong

Preventive Measures

As with hepatitis A, prevention is the best method for dealing with hepatitis B. Hepatitis B vaccine has been available since the 1980s and has been recommended as a routine childhood immunization since the early 1990s. Hepatits B vaccine is available in the United States in seven different formulations. Of those seven formulations, only Engerix-B and Recombivax-HB are approved for neonates and in pregnancy. Other HBV vaccines include Heplisav-B and PreHevbrio. Combination vaccines that include HBV vaccine in the formulation include Twinrix (providing immunization against HAV and HBV), Pediarix (containing diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, recombinant HBsAg, and inactivated poliovirus) and Vaxelis (containing diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, inactivated poliovirus, recombinant HBsAg, and *Haemophilus influenzae* type b) [99].

Hepatitis B vaccine is typically administered as a series of three intramuscular injections, the second and third doses given at one month and six months, respectively, after the first dose [99]. In 2017, a two-dose series hepatitis B vaccine for unvaccinated or incompletely vaccinated individuals 18 years of age and older was approved by the FDA [101; 102]. In addition, evidence has indicated that two injections may be sufficient to achieve protection if administered in adolescence [99]. The ACIP recommends all adults 19 to 59 years of age and adults 60 years of age and older with risk factors for hepatitis B infection should receive hepatitis B vaccination [103]. Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) should be administered to infants weighing at least 2,000 grams born to persons with hepatitis B infection within 12 hours of birth, followed by completion of the vaccine series and postvaccination serologic testing. These neonates should receive hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series. If the HBsAg-exposed neonate weighs less than 2,000 grams, the first dose of vaccine should not be counted as part of the three-dose series. Instead, the series is administered when the infant attains a weight of 2,000 grams or 1 month of age, whichever comes first, and at 2 and 7 months of age. All unvaccinated children and adolescents younger than 19 years of age also should receive the vaccine [94].

Persons who have not been immunized (or did not respond to the vaccine) and are exposed to hepatitis B virus may achieve passive protection from infection by receiving HBIG within seven days of exposure. The usual dose of HBIG is 0.06 mL/kg. For persons who have not been immunized, an accelerated schedule of immunizations is recommended following the dose of HBIG. For documented nonresponders, a second dose of HBIG is appropriate.

Strict adherence to Standard Precautions is recommended in order to prevent exposure to hepatitis B virus or other bloodborne pathogens. Careful handling of needles is also imperative. Because of the hardiness of HBV even in adverse conditions, caution should be used when cleansing objects contaminated with blood or body secretions, regardless of whether or not the body fluids have dried.

Hepatitis B can be inactivated on surfaces with the use of 1:10 bleach solution or hospital-grade disinfectant. Unlike hepatitis A virus, alcohol-based hand sanitizers, used for 30 seconds, are effective against HBV [92].

Hepatitis C

HCV is a single-stranded RNA virus, with properties similar to those of the flaviviruses, a genus of the family of Flaviviridae that includes yellow fever and St. Louis encephalitis viruses. The genome contains a single open reading frame that encodes a polyprotein of about 3,000 amino acids. The transcript is cleaved into single proteins, including three structural proteins (one core and two envelope proteins) and four nonstructural proteins. The virus is genetically unstable, which leads to multiple genotypes and subtypes.

HCV is considered a bloodborne pathogen. The most common source of infection is percutaneous or parenteral exposure through transfusion, use of injectable drugs, and occupational injury of healthcare providers with a contaminated sharp object. The blood supply in the United States has been tested for hepatitis C since the early 1990s. Now that more advanced screening tests for HCV are used in blood banks, the risk is considered to be less than 1 chance per 2 million units transfused [104]. Therefore, the annual incidence rate of HCV transmission from transfusion therapy since 1994 is less than one case per 100,000 population. In 2016, the CDC issued a health advisory due to an increasing number of acute HCV infections among persons undergoing hemodialysis [105].

Hepatitis C virus is the leading cause of end-stage liver disease and the leading reason for liver transplantation in the United States [104; 106]. Chronic HCV infection has also been associated with membranoproliferative glomerulonephritis, cryoglobulinemia, and B-cell lymphoma [104]. Coinfection of HCV with HIV occurs in 50% to 90% of persons who acquired HIV through injection drug use [107].

HCV occurs throughout the world, with endemic rates varying widely. The WHO estimates that 10% of the population of the Middle East, Africa, and Eastern Europe are infected with HCV. In the United States, an estimated 1.8% of the population (approximately 4 million people) is infected with HCV, and only about half of those infected are aware that they are. Rates of HCV in the United States have increased dramatically since 2010. This has been primarily attributed to the nation's opioid crisis and increased infection among injecting drug users. In 2021, 5,023 new cases of acute HCV were reported, an increase of 492% since 2010 and 129% since 2014 [108]. After adjusting for under-ascertainment and under-reporting, an estimated 69,800 acute hepatitis C cases occurred in 2021 [108]. In addition, 107,540 cases of newly identified chronic hepatitis C were reported in 2021 [108].

The U.S. Preventive Services Task Force recommends screening for hepatitis C virus infection in adults 18 to 79 years of age. (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening. Last accessed August 12, 2024.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Clinical Manifestations

The incubation period for HCV varies widely, from a mean of 7 to 10 weeks and a range of 2 to 20 weeks. HCV antibody is detectable in 80% of cases 15 weeks after exposure and in 97% of cases by 6 months after exposure. People with recently acquired acute infection typically have detectable HCV RNA levels as early as one to two weeks after exposure to the virus [104]. During the acute phase of the infection, 60% to 70% of HCV positive persons will be asymptomatic; approximately 20% of patients will develop mild jaundice, and the remaining persons will have generalized nonspecific symptoms, such as anorexia, nausea, fatigue, malaise, and abdominal pain. During this phase, serum ALT and AST levels are elevated then return to normal range. Fulminant acute hepatitis associated with HCV is rare [100; 109].

After the acute infection, 15% to 25% of patients will demonstrate an absence of HCV RNA in the serum and normalization of liver enzymes, within six months indicating resolution of the infection and clearance of the virus from the body. The presence of detectable HCV RNA in persons who test positive for HCV antibody is 74% in the general population. However, the rate of progression to chronic infection is higher in some subpopulations. In particular, the progression rate is more than 90% in African American individuals and as high as 98% in African American men. In those persons in whom HCV RNA remains detectable, indicating continued presence of the virus, 30% to 40% will maintain normal ALT levels and will show no evidence of chronic liver disease. The remaining 60% to 70% of chronically infected patients will have fluctuating ALT levels indicative of chronic liver disease and risk of subsequent progression to cirrhosis. On rare occasions, a patient will demonstrate positive HCV RNA without the presence of HCV antibody. Therefore, in a patient who exhibits chronic hepatitis without apparent cause, assessment of HCV RNA may be indicated [104; 110].

Chronic hepatitis from HCV infection usually progresses slowly, with cirrhosis developing in 20% to 25% of patients over a period of 20 to 30 years. However, persons with HCV infection whose daily ethanol consumption exceeds 50 g (about 3.5 standard drinks) per day are twice as likely as nondrinkers to develop cirrhosis and progress to cirrhosis more quickly (in as little as 10 years) [111]. Of those with cirrhosis, 25% eventually develop hepatocellular carcinoma. Persons who ingest alcohol or who were older than 40 years of age at the onset of infection have a more rapid progression of cirrhosis. Men have a higher incidence of cirrhosis than women. Persons with MASLD and those receiving immunosuppressive therapy are also more likely to progress to cirrhosis [112].

Because acute HCV infection can be asymptomatic, the first indication of the presence of chronic HCV infection may be elevated liver enzymes on laboratory testing obtained in connection with another clinical condition or routine health examination. In evaluating the cause of liver enzyme elevation, a hepatitis panel is typically ordered. Testing for the presence of HCV RNA has become the accepted method of confirming current HCV infection (acute or chronic) [104]. Qualitative HCV RNA testing determines whether or not hepatitis C viral particles are present in the blood and can therefore differentiate between resolved and continued infection. Quantitative HCV RNA testing evaluates the amount of hepatitis C virus in the blood and can be used to guide therapy [104; 113]. In most commercial laboratories, a positive HCV antibody test triggers a reflex test for quantitative HCV RNA; qualitative HCV RNA is rarely performed.

Therapeutic Measures

Based upon genetic characteristics, eight genotypes and more than 90 different subtypes of HCV virus have been identified. Because the genotypes respond differently to therapy, genotypic testing should be performed for persons with chronic progressive HCV infection who are considering antiviral therapy [104]. In the United States, genotype 1 accounts for 60% to 75% of HCV infections and genotypes 2 and 3 account for about 25% [114].

The treatment of HCV infection has advanced rapidly following the introduction of anti-HCV protease inhibitors in 2011. These newer, direct-acting antiviral drug combinations are highly effective and relatively free of side effects; thus, therapy is now considered for virtually all patients diagnosed with HCV infection [115]. In order to provide healthcare professionals with timely guidance, the IDSA and the AASLD have developed evidence-based recommendations for the diagnosis and management of hepatitis C infection, last updated in 2023. However, due to the rapidly evolving nature of new therapies and other developments, the IDSA and the AASLD recommend reviewing current recommendations online, available at https://www.hcvguidelines.org [115].

The IDSA/AASLD 2023 guidelines emphasize that treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy [115]. Prior to treatment, patients should be educated regarding proper administration of medications, adherence, and prevention of reinfection. Pretreatment assessment to facilitate decision making regarding the treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (e.g., hepatocellular carcinoma screening) is recommended in all patients.

During treatment, routine laboratory monitoring of hepatic function or inflammation is not indicated in persons without advanced liver disease. Because of drug-drug interactions between warfarin and direct-acting antiviral therapy, periodic INR should be assessed for patients on warfarin in order to evaluate for subtherapeutic anticoagulation. Drug-drug interactions of direct-acting antiviral therapy and medications used to treat type 2 diabetes can lead to hypoglycemia. Thus, persons on oral diabetes medications should be counseled about the potential for this interaction. No other laboratory studies are required for monitoring.

HCV quantitative RNA should be assessed 12 to 24 weeks after the conclusion of the recommended course of therapy. Persons with sustained virological response at 12 weeks or greater have less than 1% chance of re-emergence of the original infection. They can, however, become re-infected if high-risk practices are continued or re-initiated.

Achieving and maintaining SVR has positive effects on both hepatic and extrahepatic manifestations of HCV infection. These improvements include fibrosis regression, reduction in portal hypertension, reduction in the incidence of hepatocellular carcinoma, reduced incidence of myocardial infarction, reduced incidence of stroke, lower rate of insulin resistance and type 2 diabetes, improved quality of life, and lower all-cause mortality rate [116].

Even in compliant patients, treatment failures can occur. Factors that correlate with treatment failure include degree of fibrosis; the presence of advanced fibrosis in genotype 3 is particularly prone to treatment failure. Other factors that can affect treatment success include age older than 55 years, male sex, and Hispanic or Black ethnicity/race. Fortunately, prior treatment with interferon-based regimens does not usually prevent achieving SVR with direct-acting antiviral therapy. However, prior incomplete or inconsistent treatment with direct-acting antiviral therapy can lead to medication-resistant infection and treatment failure [117]. Patients who experience treatment failure should be referred to a specialist for retreatment. Monitoring of liver function should be continued by the specialist or primary care provider at least every six months until retreatment is initiated [115].

As noted, infants who are noted perinatally exposed to HCV should have HCV RNA testing at 2 to 6 months of age. Repeat HCV RNA testing, with genotype determination, should be performed when the child is 3 years of age. If viremia remains and genotype 1, 4, 5, or 6 is identified, a weight-based course of ledipasvir-sofosbuvir can be initiated, with an expected SVR in 98% of children. For children with genotype 1-6 and no evidence of fibrosis level 3 or 4, treatment with a weight-based dose of either sofosbuvir-velpatasvir or glecaprevir-pibrentasvir can be accomplished. After successful treatment with any of these three regimens, liver damage caused by HCV usually resolves and these children show no evidence or residual effects [115; 118].

For patients with cirrhosis secondary to chronic HCV or HBV infection that has gone untreated or failed therapy, liver transplantation may be indicated. Replacing the liver, however, does not cure the infection. The transplanted liver will also become infected, and immunosuppressive agents facilitate the progression of this infection. At present, chronic viral hepatitis is the most common diagnosis of persons receiving liver transplants in the United States [104].

Preventive Measures

There is no vaccine to prevent hepatitis C. The best way to prevent hepatitis C is by avoiding behaviors that can spread the disease, especially injecting drugs with non-sterile injection equipment. Hepatitis C can spread when a person comes into contact with blood from an infected person. Injecting drugs is the most common way HCV is transmitted in the United States. For people who inject drugs, community-based prevention programs, such as medication-assisted treatment and syringe services programs, can reduce the transmission of HCV.

Although the risk of sexual transmission of HCV is considered to be low, avoiding unprotected sexual exposure by using condoms has been shown to reduce the chance of sexually transmitted infections.

Hepatitis D

HDV is an RNA virus, the core of which is distinctively different from other viruses. However, due to a defect in replication, HDV is unable to synthesize a viral coat. It must borrow a coat from HBV in order to complete the replication process.

Therefore, HDV cannot cause infection independently but instead must exist as a coinfection (acquired at the same time as HBV) or a superinfection (HDV acquired in a patient who is chronically infected with HBV). In the United States, the infection primarily occurs as a coinfection among intravenous drug users. In some areas of the world in which chronic HBV infection is endemic (including the Amazon Basin of South America, China, and Southeast Asia), HDV is more commonly a superinfection [119; 120].

Patients coinfected with HBV and HDV tend to have a more severe case of acute hepatitis. The mortality rate in coinfection has been reported to be as high as 20%. Superinfection with HDV results in rapid progression of cirrhosis, with 70% to 80% of coinfected individuals showing signs of liver failure, compared to 15% to 30% of patients with chronic HBV and no cirrhosis [121]. Prevention of HDV is accomplished through the same means as prevention of hepatitis B. A 12-month course of peginterferon alfa-2a is the recommended treatment for patients with elevated HDV-RNA levels and ALT elevation [96]. Nearly 25% of patients involved in an efficacy study of peginterferon alfa-2a treatment showed sustained clearance of HDV RNA over 48 weeks [122]. Given the limited efficacy of current therapies, it is reasonable to refer patients to specialized centers that offer access to experimental therapies for HDV [96]. Immunization against hepatitis B is effective prevention of HDV also because if the individual is immune to HBV, he/she cannot become infected with HDV. Avoidance of bloodborne pathogen exposure through observance of Standard Precautions is a primary mechanism of prevention for persons already chronically infected with HBV.

Hepatitis E

Like hepatitis A, hepatitis E virus is spread through the fecal-oral route, and like HAV, HEV was also first identified via electron microscope examination of stools of infected patients. HEV has been associated with outbreaks in India, Burma, Pakistan, Russia, China, northern and central Africa, Peru, and Mexico. Outbreaks are usually associated with a contaminated water supply. No outbreaks have occurred in the United States or Western Europe, though individual cases have been identified in persons who have recently traveled to areas in which the virus is endemic [119; 123].

HEV most often affects young adults. The incubation period is two to nine weeks, with an average of six weeks. Signs and symptoms are similar to HAV, but with a higher incidence of jaundice, which can be prolonged. The disease is self-limited in the majority of patients. The fatality rate in acute HEV is between 1% and 2%, except in pregnant women. In pregnant women with HEV infection, mortality can reach as high as 30% [123]. No cases of chronic liver disease associated with HEV have been reported.

The treatment of HEV is nonspecific and is directed toward supportive care. Because the incidence of HEV is low and most cases resolve without negative sequelae, the development of a vaccine against HEV has not been a priority for pharmaceutical companies or national and international health agencies. Primary preventive strategies, therefore, concentrate on improved sanitation [123; 124].

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a severe type of chronic hepatitis that is associated with interface hepatitis, circulating autoantibodies, and hypergammaglobulinaemia. Although the disorder is usually seen in young women, it can occur in either sex at any age.

Clinical and laboratory observations have led to the hypothesis that autoimmune hepatitis is a multifactorial disorder, with genetic and environmental factors playing important roles. Most knowledge of the genetics of the disease comes from the human leukocyte antigen (HLA), located on the short arm of chromosome 6. The environmental agents assumed to induce autoimmune hepatitis have not been delineated but include viruses and chemical agents [126; 127].

Two distinct types of autoimmune hepatitis have been identified. Type 1 autoimmune hepatitis, the most common form of the disease, is characterized by increased levels of anti-smooth muscle and antinuciler autoantibodies. Approximately 78% of cases occur in women, and 38% of patients with autoimmune hepatitis also have other autoimmune diseases. Susceptibility to type 1 autoimmune hepatitis resides mainly with the *HLA-DRBI* gene.

Type 2 autoimmune hepatitis occurs mainly in children 2 to 14 years of age and is characterized by the presence of antibody to liver and kidney microsomes and liver cytosol. The disorder is often accompanied by other autoimmune disorders, especially type 1 diabetes, vitiligo, and thyroiditis. The genetic component for this type of autoimmune hepatitis is less well defined [126; 127].

Clinical Manifestations

Clinical manifestations of the disorder covers a spectrum that extends from no apparent symptoms to signs of inflammatory liver disease or cirrhosis. Physical examination may reveal no abnormalities but may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease. In asymptomatic cases, the disorder may be discovered when abdominal serum enzyme levels are identified during performance of routine screening tests [126; 127].

Diagnosis and Treatment

The differential diagnosis of autoimmune hepatitis includes measures to exclude other causes of liver disease, including hepatitis B and C. A characteristic laboratory finding is that of a marked elevation in serum gamma globulins [126; 127].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Association for the Study of Liver Diseases recommends that all patients with autoimmune hepatitis should be screened for celiac and thyroid diseases at diagnosis. Further, these patients should be assessed for rheumatoid arthritis, inflammatory bowel disease, autoimmune hemolytic anemia, diabetes, and other extrahepatic autoimmune diseases based on symptomatology and medical provider concern.

(https://journals.lww.com/hep/fulltext/2020/08000/diagnosis_and_management_of_autoimmune_hepatitis.24.aspx. Last accessed August 12, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

Corticosteroid and immunosuppressant drugs are the treatments of choice for this type of hepatitis. Although some people remain in remission after drug treatment is withdrawn, most require long-term maintenance therapy. Liver transplantation may be required for those who are refractory to or intolerant of immunosuppressive therapy and in whom end-stage liver disease develops. All hepatotoxic medications should be avoided, even analgesics such as acetaminophen [125; 126; 127].

CHOLECYSTITIS

Cholecystitis is an inflammation of the gallbladder, and it may be either acute or chronic. An acute inflammation may begin in the mucosal layer as a primary infection. More often, it is superimposed on a chronic infection initially related to cholelithiasis (also known as gallstones). The gallbladder becomes dilated and filled with bile, pus, and blood. Common infective organisms include staphylococci, streptococci, and enteric organisms [128; 129].

Clinical Manifestations

Major symptoms of cholecystitis are intense pain, tenderness, and rigidity in the right upper quadrant of the abdomen associated with nausea, vomiting, and the usual signs of inflammation. Jaundice and icteric color of the sclera may be present if there is an obstruction. If the gallbladder is filled with frankly purulent matter, the condition is called empyema of the gallbladder. Although chronic cholecystitis may be related to an acute attack, it is almost always associated with cholestasis. Stools may be clay colored due to a stone obstructing flow of bile [128; 129].

Therapeutic Measures

Laparoscopic cholecystectomy may be indicated after acute inflammation has been relieved by medical intervention. The condition typically resolves following treatment of cholelithiasis [128; 129].

NEOPLASTIC AND OBSTRUCTIVE DISORDERS

CANCER OF THE LIVER

There are two major types of primary liver cancers: hepatocellular carcinoma, which arises from the liver cells, and cholangiocarcinoma, which is a primary cancer of bile duct cells [125].

Hepatocellular Carcinoma

Hepatocellular cancer (HCC) accounted for 41,210 new cases of liver cancer in the United States in 2023, making it the most common form of liver cancer. Globally, HCC was identified as the cause for nearly 906,000 new liver cancer cases and 830,000 deaths in 2020 [130]. In recent decades, there has been increased incidence in developed countries as a consequence of chronic HCV infection, and the incidence in the United States has more than tripled since 1980. Although primary tumors of the liver are relatively rare in developed countries of the world, the liver shares with the lung the distinction of being the most common site of metastatic tumor [125].

Among the factors identified as etiologic agents in liver cancer are chronic viral hepatitis (HBV, HCV, HDV), cirrhosis, smoking, heavy alcohol consumption, obesity, and long-term exposure to environmental agents (e.g., aflatoxin). The exact pathogenesis is unclear. With HBV and HCV, both of which become integrated into the host DNA, repeated cycles of cell death and regeneration afford the potential for development of cancer-producing mutations. Aflatoxin, produced by food spoilage molds (e.g., *Aspergillus flavus* and *Aspergillus parasiticus*), is a known human carcinogen and is endemic in certain areas. A particularly susceptible site for aflatoxin mutation is the *TP53* tumor suppressor gene [125].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Association for the Study of Liver Diseases recommends that patients at high risk of developing hepatocellular carcinoma be entered into surveillance programs, provided they would be candidates for hepatocellular carcinoma treatment.

(https://journals.lww.com/hep/fulltext/2023/12000/aasld_practice_guidance_on_prevention,_diagnosis,.27.aspx. Last accessed August 12, 2024.)

Level of Evidence/Strength of Recommendation: Level 2/Strong

Clinical Manifestations and Diagnosis

What are the usual initial signs and symptoms of hepatocellular cancer?

The manifestations of HCC often are insidious in onset and masked by those related to cirrhosis or chronic hepatitis. The initial signs and symptoms include weakness, anorexia, weight

loss, fatigue abdominal swelling, a sensation of abdominal fullness, and a dull, aching abdominal pain. Ascites, which can obscure weight loss, is common. Jaundice, if present, usually is mild. There may be a rapid increase in liver size and worsening of ascites in people with pre-existing cirrhosis. Usually, the liver is enlarged when these symptoms appear. Various paraneoplastic syndromes (disturbances due to ectopic hormone or growth factor productions by the tumor) have been associated with hepatocellular cancer, including erythrocytosis, hypoglycemia, and hypercalcemia. Serum α-fetoprotein is present during fetal life but barely detectable in the serum after 2 years of age. When high levels of α-fetoprotein are found in adults, it is usually indicative of hepatocellular carcinoma, although not all primary liver cancers produce α-fetoprotein.

Additional imaging, such as ultrasonography, computed tomography (CT) scan, and magnetic resonance imaging (MRI), are recommended for diagnosis. Liver biopsy may be used to confirm the diagnosis [131; 132; 133; 134]. Genetic testing can reveal susceptibility.

Treatment

There is no agreement on a single treatment strategy for patients with HCC. Selection of treatment is complex due to several factors, including [135]:

- Underlying liver function
- Extent and location of the tumor
- General condition of the patient

Several treatments for HCC are associated with long-term survival, including surgical resection, liver transplant, and ablation. There are no large, robust, randomized studies that compare treatments considered effective for early-stage disease, nor are there studies comparing these treatments with best supportive care. Often, patients with HCC are evaluated by a multidisciplinary team that includes hepatologists, radiologists, interventional radiologists, radiation oncologists, transplant surgeons, surgical oncologists, pathologists, and medical oncologists.

Best survival rates are achieved when the HCC can be removed either by surgical resection or liver transplant. Surgical resection is usually performed in patients with localized HCC and enough functional hepatic reserve. For patients with decompensated cirrhosis and a solitary lesion (<5 cm) or early multifocal disease (up to three lesions, ≤3 cm in diameter), the best option is liver transplant, but the limited availability of liver donors restricts the use of this approach.

Transarterial chemoembolization, multikinase inhibitors, and immunotherapy are noncurative treatments for HCC that improve survival. For patients with recurrent disease with metasteses and/or vascular involvement, palliative therapy is the most appropriate approach [135].

Cholangiocarcinoma

Cholangiocarcinoma, with an incidence of 1.6 per 100,000 in North America, occurs much less frequently than hepatocellular carcinoma [136]. The etiology, clinical features, and prognosis vary considerably with the part of the biliary tree that is the site of origin. Distal and perihilar bile duct cancers frequently cause biliary tract obstruction, leading to the following symptoms [137]:

- Jaundice
- Weight loss
- Abdominal pain
- Fever
- Pruritus

Intrahepatic bile duct cancer may be relatively indolent and difficult to differentiate clinically from metastatic adenocarcinoma deposits in the liver.

Cholangiocarcinoma is not associated with the same risk factors as hepatocellular carcinoma. Instead, most of the risk factors revolve around long-standing inflammation and injury of the bile duct epithelium. Bile duct cancer may occur more frequently in patients with a history of primary sclerosing cholangitis, chronic ulcerative colitis, choledochal cysts, or infections with the liver fluke *Clonorchis sinensis* [137].

Treatment

The treatment of bile duct cancer depends primarily on whether the cancer can be completely removed by surgery. Localized intrahepatic and extrahepatic bile duct cancer may be completely resected. However, these tumors represent a very small number of cases that are usually in the distal common bile duct. Among patients treated with surgical resection, long-term prognosis varies depending on primary tumor extent, margin status, lymph node involvement, and additional pathological features [137].

Extended resections of hepatic duct bifurcation tumors (also known as Klatskin or hilar tumors) to include adjacent liver, either by lobectomy or removal of portions of segments 4 and 5 of the liver, may be performed. If major hepatic resection is necessary to achieve a complete resection, postoperative hepatic reserve should be evaluated [137].

Unfortunately, most cases of intrahepatic, distal, and perihilar bile duct cancer are unresectable and cannot be completely removed. Often, the cancer invades directly into the portal vein, the adjacent liver, along the common bile duct, and to adjacent lymph nodes. Portal hypertension may result from invasion of the portal vein. Spread to distant parts of the body is uncommon, but intra-abdominal metastases, particularly peritoneal metastases, do occur. Transperitoneal and hematogenous hepatic metastases also occur with bile duct cancer of all sites. Moreover, most patients who undergo resection will develop recurrent disease within the hepatobiliary system or, less frequently, at distant sites.

In locally advanced disease, trials have evaluated chemoradiotherapy with the goal of improved local control and potential downstaging for surgical resection [137]. These approaches have not been compared with standard therapy, and the curative potential is unknown. For patients with unresectable bile duct cancer, management is directed at palliation.

Metastatic Tumors

Metastatic tumors of the liver are much more common than primary tumors. Common sources include colorectal cancer and those spread from breast, colon, lung, or urogenital cancer. In addition, tumors of neuroendocrine origin can spread to the liver. It often is difficult to distinguish primary from metastatic tumors with the use of CT scans, MRI, or ultrasonography. The diagnosis may be confirmed by biopsy [132; 133].

CANCER OF THE GALLBLADDER

Cancer of the gallbladder is rare. In 2024, there will be an estimated 12,350 new cases diagnosed and 4,530 deaths [138]. Malignant tumors are usually columnar cell carcinomas that cause symptoms of inflammation and obstruction. In part because of its rarity, biliary carcinoma may be overlooked or confused with cholelithiasis [139; 140]. The most common symptoms caused by gallbladder cancer are jaundice, pain, and fever.

Treatment

Patients with stage I disease have cancer confined to the gallbladder wall that can be completely resected. Patients with stage I tumors that are discovered incidentally and resected during routine cholecystectomy have five-year survival rates of nearly 100% [138]. Previously unsuspected gallbladder cancer that is incidentally discovered in the mucosa of the gallbladder during pathological examination is curable in more than 80% of patients. However, symptomatic gallbladder cancer that is suspected prior to surgery often penetrates the muscularis and serosa. This type of gallbladder cancer is curable in less than 5% of patients [138].

Treatment options for localized and locally advanced gallbladder cancer include [138]:

- Surgery
- External-beam radiation therapy (EBRT)
- Clinical trials exploring the use of radiation therapy and radiosensitizer drugs to improve local control

During laparoscopic removal of an unsuspected cancer, implantation of carcinoma at all port sites (including the camera site) is possible. All port sites are typically excised completely, even for stage I cancers.

Patients with T2 (tumor invades the perimuscular connective tissue on the peritoneal or hepatic side) or T3 (tumor perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure) disease have higher rates of unsuspected invasive disease at the time of diagnosis [138]. Eligible patients may undergo re-exploration to resect liver tissue near the gallbladder bed, portal lymph nodes, and lymphatic tissue in the hepatoduodenal ligament. Retrospective analyses suggest that extended re-resection can delay recurrences and potentially improve survival [138].

For patients with locoregional lymph node involvement (at the cystic duct, common bile duct, hepatic artery, and portal vein), long-term disease-free survival can occasionally be achieved with radical resection. In patients with jaundice, preoperative percutaneous transhepatic biliary drainage for relief of biliary obstruction should be considered [138].

Surgery with curative intent is not considered possible in patients with metastatic spread beyond the locoregional lymph nodes or to distant organs [138].

The use of EBRT with or without chemotherapy as a primary treatment has been reported to produce short-term disease control in small groups of patients. Similar benefits have been reported for radiation therapy, with or without chemotherapy, administered after resection [138]. However, there is limited evidence supporting the use of adjuvant radiation therapy, even for patients with high-risk localized disease [138].

CHOLEOLITHIASIS

Cholelithiasis, the formation of gallstones, can lead to obstruction of the bile ducts associated with obstructive icterus and severe, colicky pain. An estimated 20 million Americans have cholelithiasis, and almost 1 million new cases are diagnosed each year [129; 139; 140; 141].

Several predisposing factors are related to development of cholelithiasis [129; 139; 140; 141]. Women are affected four times as frequently as men, and taking oral contraceptives are twice as like likely as other women to develop gallstones. Further, multigravidas women are more likely to develop the condition than those who have not been pregnant. Persons older than 40 years of age are affected more often than younger persons. High fat intake and cholesterol saturation of bile are considered predisposing factors, and obesity and diabetes are associated with increased risk of gallstone formation. Persons who have had extensive bowel resections (as for Crohn disease) have a threefold to fivefold higher incidence of cholelithiasis, possibly because recirculation of bile salts is interrupted.

Cholesterol saturating of bile appears to be a major factor in development of gallstones. The underlying cause may be dysfunction of the hepatic cells where bile is synthesized. Bile salts precipitate from supersaturated bile, forming nuclei for accretion of layers of cholesterol, calcium, and bilirubin to form calculi within the gallbladder.

Gallstones are classified as either cholesterol or pigment stones. Cholesterol stones are usually of mixed composition and contain more than 70% cholesterol plus calcium salts, bile pigments, fatty acids, and proteins. There is a high incidence of cholesterol stones in North America. Pigment stones are

primarily calcium and bilirubin and contain less than 10% cholesterol. Pigment stones are less common in North America but have a high prevalence in Japan [139; 140; 141; 142].

Clinical Manifestations

Calculi formed in the gallbladder may move into the cystic duct, the common bile duct, or even into the liver via the hepatic ducts. Calculus obstruction of the pancreatic duct may cause pancreatitis [141; 143].

The most common symptom of cholelithiasis is colicky pain believed to be related to spasms of the sphincter of Oddi. Pain may also be related to obstruction and distention of a bile duct. Usually, the pain is felt in the epigastrium or the right upper quadrants of the abdomen, but it may radiate up the back between the scapulae to the right shoulder or around the abdomen to the back, making it difficult for the patient to assume a comfortable position. Some patients will report laying in the supine position often worsens the discomfort. Biliary colic may occur at varying intervals following meals or may wake the patient from sleep. Usually, symptoms occur at progressively shorter intervals after ingestion of almost any food. Occasionally, however, a single pain episode will never be repeated [129; 139; 140; 141].

In addition to the characteristic pain, nausea and vomiting are common, as is elevated temperature. Distention of the bile ducts stimulates the vomiting center. If the common bile duct is obstructed by a calculus, greenish-yellow jaundice develops. Pruritus often develops before the jaundice is visible in the sclera. Icterus is accompanied by pale stools and dark, frothy urine. Ecchymoses may be evident [139; 140; 141].

Laboratory and diagnostic studies assist in confirming the diagnosis. White blood cell levels, direct bilirubin levels, prothrombin time, alkaline phosphatase, and serum lipid levels will be elevated. Urine urobilinogen levels will decrease, but bilirubin will be found in the urine. Abdominal ultrasound and increased alkaline phosphatase (ALP) levels can help establish a diagnosis of cholelithiasis. Cholecystography, cholangiography, or endoscopic retrograde cholangiopancreatography (ERCP) may be required [139; 140; 141].

Therapeutic Measures

If symptoms are mild, a low-fat diet may be sufficient to control them. The diet would be high in proteins and carbohydrates [144]. Depending on the patient's nutritional status, intravenous glucose and protein supplementation may be indicated. A nutritious diet promotes healing and helps prevent hepatic damage. Vitamin K may be required if coagulation abnormalities are demonstrated [145].

For acute attacks, treatment often includes medications such as butylscopolamine, flopropione, and nonsteroidal anti-inflammatory drugs (NSAIDs). For patients at risk for the development or exacerbation of cholelithiasis, oral ursodeoxycholic acid (UDCA) is recommended for prophylaxis [146].

There are a variety of options for minimally invasive management. Extracorporeal shock wave lithotripsy (ESWL) and oral chemical dissolution therapy were previously used, but both have largely been replaced in recent years. . Both techniques are rarely used in clinical practice in recent years.

Today, many patients with recurrent and/or severe disease undergo ERCP with or without stent placement. If surgical Management is indicated, the preferred approach is laparoscopic cholecystectomy [146].

Specific Nursing Measures

In addition to comfort measures and administering analgesics and other prescribed medications, nurses can consult with the dietitian and the patient to work out a palatable low-fat diet. The patient may find a list of preferred, appropriate foods useful [59].

LIVER TRANSPLANTATION

What is the usual duration of liver transplantation surgery?

Liver transplantation, one of the most common types of solid organ transplant, is the replacement of the diseased liver by an allograft from a brain-dead donor or a partial replacement of the liver by a living related donor. Dr. T.E. Starzl and associates at the University of Colorado pioneered this treatment modality in the early 1960s. By the end of the decade, surgeons in Pennsylvania and England were performing the procedure. By the beginning of the 21st century, liver transplantation had been performed at dozens of medical centers in the United States, Canada, and Western Europe. Although survival rates in the early programs were only 30%, improvements in technique and timing of the transplant have now brought the one-year survival rate to approximately 90% and the five-year survival rate to approximately 75% [147].

Children and adults who have irreversible liver disease or defects that cannot be overcome or managed by medical options are candidates for liver transplants. In children, the most common reasons for liver transplantation include biliary atresia, neonatal hepatitis, congenital hepatic fibrosis, alpha 1-antitrypsin deficiency, and disorders of metabolism that result in inappropriate storage within the liver or significant liver damage from the buildup of metabolites. The most common diseases necessitating liver transplantation in adults are chronic viral hepatitis (HCV in the United States, HBV in Europe), biliary cirrhosis, alcoholic cirrhosis, sclerosing cholangitis, cryptogenic cirrhosis, Caroli disease, primary hepatocellular malignancies, hepatic adenomas, and hepatic vein thrombosis [148; 149]. Biliary atresia remains a common indication for liver transplantation in pediatric patients [150].

The Model for End-Stage Liver Disease (MELD) is a prognostic system that is now widely accepted as a tool for predicting survival of patients with cirrhosis. MELD, in conjunction

with international normalized ratio, serum creatinine, serum bilirubin, and sodium, has been evaluated as a prognostic indicator for cirrhosis regardless of cause. Transplant centers utilize the MELD score in prioritizing clients for transplant [147; 151]. The Pediatric End-Stage Liver Disease (PELD) is used for children younger than 12 years of age [147].

Though patients may have a disease process that is an indication for liver transplant, the presence of compounding factors may provide a contraindication for the therapy. At one time, HIV disease was considered a contraindication for liver transplant. While patients with advanced HIV disease are not transplant candidates, HIV disease that is in an early stage or is controlled by antiretroviral therapy is no longer a contraindication for transplantation therapy. Similarly, persons older than 60 years of age were at one time excluded from this therapy, but persons older than 60 years of age who are healthy other than their liver disease can now be considered for candidacy. Active drug or alcohol use, metastatic cancer, uncontrolled bacterial or fungal infections, advanced cardiac or lung disease, and uncorrectable life-threatening congenital anomalies remain contraindications for liver transplantation.

Relative contraindications for liver transplantation are those factors that in isolation would not preclude a patient from receiving a transplant but in combination might decrease the probability that the patient would be approved. Examples of relative contraindications include chronic HBV with rapidly replicating virus, significant psychiatric disorder that may interfere with the patient's ability to follow the post-transplant regimen, significant renal disease not associated with the hepatic disease, and previous hepatic or biliary surgery [149].

Historically, donor organs have been obtained from cadavers. In 1998, the use of living related donors became an option in certain cases [152; 153]. Partial liver transplantation from living related donors results in a 20% morbidity rate for the donor. Therefore, cadaveric transplant remains the procedure of choice. The following discussion addresses only cadaveric transplants.

In 2020, the Organ Procurement and Transplantation Network implemented a new liver distribution system called the acuity circle policy, which emphasizes the medical urgency of liver transplant candidates and the distance between the donor and transplant hospitals. The new system replaces the use of decades-old geographic boundaries of 58 donation service areas and 11 transplant regions [154]. Under the new policy, livers from all deceased donors will first be offered to the most urgent liver transplant candidates listed at transplant hospitals within a radius of 500 nautical miles of the donor hospital. Following offers to the most urgent candidates, livers from adult donors will be offered to candidates at hospitals within distances of 150, 250, and 500 nautical miles of the donor hospital. These offers are grouped by medical urgency [147].

Donor livers are usually obtained from brain-dead persons younger than 60 years of age who are free from bloodborne pathogen infections (HCV, HBV, HIV), are not septic, have no existing liver disease, and have not recently experienced abdominal trauma. Some centers consider the use of livers from HBV- or HCV-infected donors for recipients infected with the same strain or subspecies of virus [155]. When donor livers are infected but not yet showing signs of cirrhosis, preliminary results indicate that recipient outcomes are not significantly different from those receiving uninfected livers.

Donor and recipient should have compatible body size and A, B, O blood groups. Unlike kidney transplants, however, donor and recipient do not have to have matching tissue types. The liver is viable for up to 20 hours after removal from the donor, but most centers prefer for the transplant surgery to be completed within 12 hours after organ harvest.

Liver transplantation surgery typically requires a procedure of 6 to 12 hours in duration; in more complex circumstances, the surgery has lasted up to 18 hours. During the procedure, the patient is at risk for coagulopathies, electrolyte disturbances, hypoglycemia, and a large volume of blood loss.

Various combinations of immunosuppressive drugs (monoclonal and polyclonal antibodies) have been used to reduce the probability of post-transplant rejection. It is desirable to try to prevent or minimize the adverse effects of these drugs, including infections, malignancy, and general drug toxicity. In the immediate post-transplant period, a common drug regimen includes a combination of a monoclonal antibody, mycophenolate mofetil, corticosteroids, and a calcineurin inhibitor such as cyclosporine or tacrolimus [148]. According to Hanto, the addition of an anti-IL-2 receptor monoclonal antibody (basiliximab or daclizumab) can result in a decrease in rejection rate from 43.5% to 35.1% [156]. Sirolimus is a newer drug that appears to be useful, especially in patients with renal insufficiency.

Chronic suppressive therapy is usually accomplished with tacrolimus and mycophenolate mofetil. Steroids are weaned within a few weeks of transplantation, except in the presence of autoimmune hepatitis. Liver transplant recipients require lower doses of immunosuppressive therapy than patients receiving other solid organ transplants. Nevertheless, providers should be attentive to drug-drug interactions and therapeutic monitoring of these medications [157].

The process of rejection is insidious in the majority of liver transplantation cases; hyperacute rejection rarely occurs. Most episodes of acute rejection occur within the first six months after the transplant (usually between three and six months) but can be reversed with steroids. In approximately 10% to 20% of patients, steroid resistance occurs, requiring treatment with a monoclonal antibody, such as muromonab-CD3, or a polyclonal antibody, such as thymoglobulin [156]. Acute rejection episodes seldom threaten graft survival. Patient survival rates are 84% with living-donor grafts and 83% with deceased-donor grafts at one year and 34% with living-donor grafts and 46% with deceased-donor grafts at five years [157].

CONCLUSION

With knowledge of hepatic and biliary structure and function and the dynamic pathology that intrudes and impedes normal function, nurses are better able to provide quality and often life-saving actions. An awareness of why symptoms appear leads to quicker reporting of changes in the patient's condition. Nurses should also be prepared to perform immediate interventions based on standing orders and the recognition of what needs to be done in order to provide safe, quality care. This knowledge changes what could be only technical care to professional care through use of decision making skills built upon the knowledge of pathophysiology.

CASE STUDIES

CASE ONE: ESOPHAGEAL VARICES

Present Illness

Patient A is a man, 60 years of age, who is admitted to the hospital for treatment of acute gastrointestinal bleeding. The patient had a similar episode five weeks ago. An upper endoscopic exam at that time revealed a bleeding esophageal varix for which he received band ligation therapy. He is well-known to the medical community for chronic alcohol use. He has lost several jobs for drinking in the workplace or showing up for work drunk. He has lost his driver's license for drunk driving, and his drinking has placed a significant strain on his marriage. He and his wife are currently separated. He has tried several self-help programs to stop drinking as well as Alcoholics Anonymous, all with little success.

Medical History

Patient A has been hospitalized five times during the previous 30 months. Most recently, he was discharged five weeks ago following treatment for bleeding esophageal varices. He has a 44-year history of cigarette smoking (one pack per day), was diagnosed five years ago with alcoholic cirrhosis, and currently drinks an unknown amount of liquor daily. He previously reported drinking 6 to 12 beers per day for many years.

On previous admissions, Patient A has been treated for acute pancreatitis twice, alcohol withdrawal seizures, delirium tremens, ascites, coagulopathy, esophageal varices, peptic ulcer disease, anemia, and gastritis, all of which were determined to be related to his alcohol use. Medications at last discharge included:

- Lactulose (30 mL four times per day)
- Spironolactone (100 mg per day)
- Furosemide (80 mg per day)
- Propranolol (30 mg per day)
- Famotidine (40 mg twice per day)

Assessment and Diagnosis

Patient A was found unconscious and face down in a pool of bright red, bloody vomitus by his neighbor. He is resuscitated and taken to the hospital by ambulance and is admitted to the intensive care unit (ICU). Upon admittance to the ICU, a full physical exam is conducted (***Table 1***) and laboratory blood testing is ordered (***Table 2***). Intravenous infusion with a solution of D5W and colloid is started through a central line. Oxygen is started at 3 L/min. Octreotide is administered to help stop the bleeding. An echocardiogram is conducted.

Based on the results of the assessment, Patient A is diagnosed with acute alcohol-related pancreatitis.

Study Questions

1. *Explain the pathophysiology of each of the following clinical manifestations in this patient.*
   a. *Spider angiomas*
   b. *Splenomegaly*
   c. *Edema*
   d. *Jaundice and icteric sclera*
2. *Why has the primary care provider noted the absence of asterixis?*
3. *What is the significance of the renal test results?*
4. *What is the significance of the liver enzyme test results?*
5. *What are the pathophysiology and significance of the total and indirect bilirubin test results?*
6. *Is blood clotting a concern at this time in this patient?*
7. *Why might hemoglobin concentration and hematocrit be abnormal?*
8. *Does this patient have an arterial blood gas problem?*
9. *Give a reasonable explanation for the pathophysiology of the patient's blood glucose concentration.*
10. *What evidence is provided that this episode is not associated with another attack of alcohol-induced acute pancreatitis?*
11. *What is the purpose of prescribing lactulose for patients with chronic liver disease?*
12. *Why are diuretics appropriate for patients with chronic hepatic disease?*

CASE STUDY TWO: CIRRHOSIS

Present Illness

Patient B is a woman, 48 years of age, who presents to the emergency department complaining of a four-week history of progressive abdominal swelling and discomfort. She has no other gastrointestinal symptoms and has a normal appetite and normal bowel habits. Her past medical history is significant only for three pregnancies, one of which was complicated by hemorrhage, requiring a blood transfusion. She has been married for 20 years, exercises, does not smoke, and drinks only occasionally. On pointed questioning, she admits that she was

PATIENT A'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Thin, unkempt White man Height: 5 feet 10 inches (177.8 cm) Weight: 151 pounds (68.5 kg)
Skin	Markedly jaundiced Spider angiomas evident on arms Normal turgor No palmar erythema
Head and eyes	Icteric sclera Pupils are equal, round, and reactive to light and accommodation Extra-ocular motion intact Oropharynx dry, with no erythema or lesions present
Ears	Tympanic membranes intact
Neck	Supple with no nodules Negative for jugular vein distention, thyromegaly, and lymphadenopathy
Chest	Good air exchange bilaterally
Abdomen	Soft, with mild distension and hyperactive bowel sounds Splenomegaly Negative for guarding or rebound tenderness
Extremities	Warm with mild (1+) edema Pulses symmetric at 2+ Muscle tone normal Full range of motion throughout
Genitourinary system	Normal male Stool positive for heme
Neurologic status	Alert and oriented Slow to answer questions Cranial nerves II–XII intact Deep tendon reflexes brisk and equal bilaterally
Cardiovascular system	Tachycardia with normal rhythm Normal S1 and S2 with no additional heart sounds No murmurs or rubs heard Normal sinus rhythm
Vital Signs	
Blood pressure	90/60 mm Hg
Temperature	98.0° F
Heart rate	112 bpm with regular irregular rhythm
Respiratory rate	14 breaths per minute
Source: Author	*Table 1*

"wild' in her youth and did use cocaine once or twice at parties many years ago. She does not currently use illicit drugs. She tested HIV-negative at the time of the birth of her last child.

On examination, her temperature is 100.3 degrees F, her heart rate is 88 bpm, and her blood pressure is 94/60 mm Hg. She is thin, her complexion is sallow, her sclerae are icteric, her chest is clear, and her heart is regular with no murmur. Her abdomen is distended and with mild diffuse tenderness, hypoactive bowel sounds, shifting dullness to percussion, and a fluid wave. She has no peripheral edema. Laboratory studies are normal except for the following:

- Sodium: 120 mEq/L
- Albumin: 2.8 mg/dL
- Total bilirubin: 4 mg/dL
- Prothrombin time: 15 seconds

PATIENT A LABORATORY BLOOD TEST RESULTS	
Test	**Result**
Blood type	B+
Sodium	135 meq/L
Potassium	4.6 meq/L
Chloride	103 meq/L
Bicarbonate	22 meq/L
Blood urea nitrogen (BUN)	10 mg/dL
Creatinine	1.1 mg/dL
Fasting blood glucose	140 mg/dL
Hemoglobin	9.4 g/dL
International normalized ratio (INR)	2.3
Hematocrit	28%
White blood cell count	10,000/mm^3
Platelets	160,000/mm^3
Total bilirubin	10.4 mg/dL
Indirect bilirubin	9.9 mg/dL
Amylase	43 IU/L
PaO_2	85 mm Hg
$PaCO_2$	245 mm Hg
pH	7.38
NH_3	59 mcg/dL
Prothrombin time (PT)	23 seconds
Partial thromboplastin time (PTT)	54 seconds
Aspartate transaminase (AST)	119 IU/L
Alanine transaminase (ALT)	94 IU/L
Total protein	4.9 g/dL
Albumin	2.9 g/dL
Calcium	8.9 mg/dL
Phosphorus	2.8 mg/dL
HIV RNA	Negative
Source: Author	*Table 2*

- Hemoglobin: 12 g/dL, with a mean cell volume (MCV) of 102 fL
- Platelet count: 78,000/mm^3

Patient B is diagnosed with ascites caused by portal hypertension as a complication of hepatic cirrhosis. Paracentesis is performed to evaluate the ascitic fluid to try to determine its likely etiology, as well as evaluate for the complication of spontaneous bacterial peritonitis.

CASE STUDY THREE: JAUNDICE

Present Illness

Patient C is a Black man, 33 years of age, who presents to the office for an acute visit with nausea and diarrhea that he has had for the past week. Along with these symptoms, he has had a low-grade fever, some right upper quadrant abdominal pain, and has noticed that his eyes seem yellow.

Medical History

Patient C has no significant medical history and takes no medications regularly. He denies alcohol, tobacco, or IV drug use. He works as a pastor in a local church that went on a mission to build a medical clinic in a rural area of Central America about five weeks ago. While there, he had a mild case of diarrhea, but otherwise has felt well.

Assessment and Diagnosis

On examination, Patient C is a well-developed man who appears to be moderately ill. His temperature is 99.8°F, his blood pressure is 110/80 mm Hg, his pulse is 90 beats/minute, and his respiratory rate is 14 breaths/minute. He has a prominent yellow color to his eyes and under his tongue. His mucous membranes are moist. Lung and cardiac examinations are normal. His abdomen has normal bowel sounds and tenderness in the right upper quadrant. His liver edge is palpable just below the costal margin. There are no other masses felt, no rebound, and no guarding. On rectal examination, he has clay-colored soft stool that is hemoccult negative.

Based on the examination and history, Patient C is diagnosed with jaundice, likely related to acute hepatitis A infection. Anti-hepatitis A IgM testing confirms infection. The most probable source of infection is ingestion of contaminated food or water while on his mission.

For this patient, treatment focuses on supportive care and palliation of symptoms. The infection is also reported to the local health department. Close household or sexual contacts are provided with hepatitis A prophylaxis.

CASE STUDY FOUR: CHRONIC HEPATITIS C

Patient D is a paramedic, 48 years of age. Laboratory work obtained during his annual physical examination reveals hyperlipidemia; complete blood count, glucose, blood urea nitrogen (BUN), and electrolytes are within normal range. With the exception of his weight (15 pounds heavier than indicated for his height), his exam identifies no abnormalities.

After two months of a diet and exercise program, his cholesterol level is 256. Therefore, his physician elects to begin a lipid-lowering agent. A baseline liver profile is drawn prior to initiation of the medication. Because the patient is in a profession that is high-risk for bloodborne pathogen exposure, an HCV antibody test with reflex to qualitative HCV RNA is ordered. The liver profile reveals an AST of 226 Units/L and an ALT of 282 Units/L. HCV antibody and reflex quantitative HCV RNA are both positive.

The physician reviews Patient D's history and medications. He has been a paramedic for 25 years. He was immunized against HBV in 1999. During his career, he has experienced several exposures to blood (usually blood splashes, but also two needlesticks from IV needles). His most recent exposure was two years ago. An HIV test six months post-exposure was negative. He does not recall hepatitis testing being performed at that time.

Patient D's surgical history includes a hernia repair in childhood and removal of skin lesions three times in the past eight years. He has had no transfusions. He is the widowed father of two teenage children. His wife died six years ago from ovarian cancer.

The patient has never smoked. He drinks about six beers per week and rarely drinks hard liquor. He denies any history of illicit drug use. Although the patient has no current prescription medications, he uses several herbal preparations including garlic, ginkgo, and an antioxidant preparation. The patient takes ibuprofen for pain, consuming 6 to 10 tablets (200 mg each) per month.

Although alcohol consumption and herbal antioxidants can both cause liver inflammation, the degree of his liver inflammation is much higher than would be expected from limited use of these two factors. The patient is diagnosed with chronic HCV infection.

In order to evaluate the extent of liver damage and determine an appropriate treatment plan, the physician orders an HCV RNA quantitative PCR and genotype as well as a repeat hepatic panel, platelet count, and PT. Shear wave elastography is also ordered. The laboratory results are:

- Platelets: 237 × 10^9/L
- ALT: 253 Units/L
- AST: 214 Units/L
- PT INR: 1.0
- HCV RNA: 350,000 IU/L
- HCV genotype: 3

Based upon these laboratory results, the calculated Fib-4 score is 2.72. The elastography reflects a fibrosis score of F1. No masses are identified on ultrasound. Because the genotype of the virus is 3, resistance testing is ordered. Substitution mutation *Y93H* is not present.

Treatment options appropriate for HCV genotype 3, and the timing of therapy in relation to his degree of fibrosis and anticipated progression of disease are discussed with Patient D. He is advised to eat a nutritious, balanced diet and abstain completely from alcohol. Although he is not currently sexually active, the patient is educated about the low but present risk of sexual transmission of HCV and how to minimize the risk of transmission. A test for HAV antibody is found to be negative. Immunization against HAV is also recommended, as acquiring an acute case of HAV in a patient with pre-existing chronic hepatitis can be much more serious that either condition alone. He is also provided pneumococcal immunization, as persons with chronic liver disease are at increased risk of pneumococcal infection and complications. Because of uncertainty as to how recently he acquired the infection, the decision is made to defer treatment for three to four months while monitoring the course of the infection.

Four months after the initial diagnosis, there has been no improvement in Patient D's liver function tests: the ALT is 318 Units/L and AST is 287 Units/L. The HCV RNA remains detectable in the blood, and the viral load has increased to 450,000 phages/cc. He is advised to begin antiviral treatment; therapeutic options are discussed in relation to efficacy, potential drug interactions, and cost reimbursement priorities, bearing in mind that he is a treatment-naïve patient with no evidence of cirrhosis. The recommended course of therapy is the 12-week, two-drug oral regimen of sofosbuvir (400 mg) and velpatasvir (100 mg) for a duration of 12 weeks (reported SVR rate: 95% in clinical trials for genotype 3).

On treatment, the patient experiences transient nausea and persistent mild fatigue, but is compliant with the recommended duration of therapy. At 12 weeks, the ALT and AST are both within normal range and HCV RNA is undetectable. Patient D is asked to return in three months to continue his hyperlipidemia treatment follow-up.

CASE STUDY FIVE: PANCREATITIS-GALLSTONE-INDUCED

Present Illness

Patient E is a Hispanic woman, 42 years of age, who presents to the emergency department complaining of 24 hours of severe, steady epigastric abdominal pain, radiating to her back, with several episodes of nausea and vomiting;. She has had similar painful episodes in the past, usually in the evening following heavy meals, but they always resolved spontaneously within an hour or two. This time, the pain has not improved, so she is seeking medical attention.

Medical History

Patient E has no prior medical history and takes no medications. She is married, has three children, and does not drink alcohol or smoke cigarettes.

Assessment and Diagnosis

On examination, Patient E is afebrile. She is experiencing tachycardia, with a heart rate of 104 beats per minute. Her blood pressure is 115/17 mm Hg, and she has shallow respirations of 22 breaths per minute. She is moving uncomfortably on the stretcher, her skin is warm and diaphoretic, and she has scleral icterus. Her abdomen is soft and mildly distended, with marked right upper quadrant and epigastric tenderness to palpation, hypoactive bowel sounds, and no masses or organomegaly appreciated. Her stool is negative for occult blood. Laboratory studies are significant for:

- Total bilirubin: 9.2 g/dL, with a direct fraction of 4.8 g/dL
- Alkaline phosphatase: 285 IU/L
- Aspartate aminotransferase (AST): 78 IU/L
- Alanine aminotransferase (ALT): 92 IU/L
- Amylase: 1,249 IU/L (elevated)
- Leukocyte count: 16,500/mm^3, with 82% polymorphnuclear cells and 16% lymphocytes

Right upper quadrant abdominal ultrasonography shows a distended gallbladder, with several stones.

Based on the assessment, Patient E is diagnosed with acute pancreatitis resulting from choledocolithiasis. The patient is started on systemic antibiotics and prepared for removal of the stones.

CASE STUDY SIX: HIV AND CHRONIC HBV COINFECTION

Patient C is a man, 32 years of age, with a history of injection drug use, who participated in a free HIV testing day. His screening test was found to be positive. A confirmatory test conducted at the health department was also positive. He has therefore been referred to the Infectious Disease Clinic of a large university medical center for follow up.

During his first visit, the patient indicates that he injected drugs off and on beginning at 19 years of age. His first two experiences with rehabilitation failed, but he has been "clean" for two years, since his best friend died of an overdose. He reports that he also snorted cocaine occasionally during the years he used injected drugs.

The patient's medical history includes a hospitalization for a motorcycle accident at age 24, with surgery on his right leg both on that admission and again about a year later. He received 2 units of blood during the first admission. The patient denies a history of heart disease, neurologic disorders, or endocrine disorders. He has had pneumonia both in adolescence and again last year.

The patient's parents are living and in good health. Grandparents all have hypertension, and maternal grandmother has type 2 diabetes. The patient smokes 1/2 to 1 pack of cigarettes per day and consumes two or three drinks per day. The patient's current medications include acetaminophen or ibuprofen as needed for leg pain and paroxetine for anxiety and depression.

Physical examination reveals no acute distress. Vital signs are within normal limits, and sclerae are non-icteric. Oral cavity is free from thrush and leukoplakia. Cervical lymph nodes are palpable but moveable and nontender. Heart sounds are normal; lungs are clear. Abdomen is soft; both liver and spleen are palpable. Neurologic exam is normal. The patient has full function in upper extremities and left leg; right leg has a slight decrease in strength and a moderate decrease in range of motion.

Initial laboratory tests ordered by the nurse practitioner (NP) include an HIV PCR viral load, a CD4 count, a CBC, a chemistry panel, and a liver profile. Because of the high incidence of HCV and/or HBV coinfection in persons whose HIV was acquired percutaneously, the NP also orders a hepatitis profile. Baseline tuberculosis testing is also recommended for persons with HIV who are entering care. Therefore, a T-SPOT interferon gamma release assay is also ordered. The patient is instructed to return in 72 hours to review lab results and formulate a treatment plan.

Upon his return, all results except the HIV PCR are available. His CD4 count is 246. Hematocrit is 44%, hemoglobin 15 gm/dL, and WBC is 3,800. The liver profile reveals an alkaline phosphatase of 143 Units/mL, AST 358 Units/L, ALT 383 Units/L, total bilirubin 1.2 mg/dL, and albumin 2.8 gm/dL. The remainder of the chemistry panel is unremarkable. Hepatitis profile is positive for HBsAg, HBeAg, and total anti-HBc. The anti-HAV, anti-HCV and anti-HBc IgM are negative. The T-SPOT TB test is negative.

The NP informs Patient C that he is coinfected with HIV and HBV and instructs him about the problems associated with HIV/HBV coinfection. He is given HAV and pneumococcal immunizations and options for antiretroviral therapy are discussed. Because of its effectiveness against both HIV and HBV, a medication regimen including tenofovir with lamivudine or tenofovir with emtricitabine should be utilized. A third medication for HIV viral suppression should be added, with consideration of the hepatotoxicity profile of the medication. After discussing available options with limited hepatotoxicity, an integrase inhibitor is selected as the third active agent in the combination. A single tablet medication containing bictegravir, emtricitabine, and tenofovir alafenamide in a once daily formulation was therefore selected to treat both HIV and HBV.

Information is provided to Patient C regarding safe sex practices. He is also instructed to abstain from alcohol and to use ibuprofen (or no more than 2 g acetaminophen in 24 hours) for pain control. The NP also orders a PT to be drawn; in addition, the patient is referred to hepatology for a liver biopsy to be performed in order to evaluate the progression of the liver disease. The patient is scheduled for a follow-up visit in four weeks, with a repeat HIV PCR performed at that time. In the interim, his baseline HIV PCR is found to be 123,000.

Upon his return to the office, Patient C is advised that the liver biopsy revealed periportal inflammation with focal necrosis and bridging fibrosis. PT is 15.6 seconds (control: 12 seconds). These findings indicate severe, advanced liver disease and the guarded prognosis. Because of the severity of his liver disease, he is not a good candidate for PegIFN therapy. The patient's current HIV status precludes his being a transplant candidate at the time. The recommended treatment plan for Patient C is to maximize his HIV suppression while minimizing his continued liver damage. If he is compliant with his therapy, he should be able to maintain a fairly good quality of life and postpone liver failure for three years or more. Prolonging the time until liver failure also provides the opportunity to improve immunocompetency. Some liver transplant centers now accept HIV-positive patients, provided that HIV viral loads are undetectable and CD4 counts are sufficiently high (usually >500). Patient C's future, therefore, depends upon his tolerance of the regimen, his compliance with the treatment plan, and his body's response to therapy.

The patient will initially be followed on a monthly basis. The viral load will be checked one month after the initiation of therapy, then every three months thereafter. Liver profile, CBC, and amylase will be assessed after one month, then bimonthly. After three months, HIV and HBV quantitative PCRs will be measured. If both are well suppressed, follow-up will be extended to every two to three months. If the patient's liver function significantly deteriorates, supportive therapy for end-stage liver disease will be instituted.

Customer Information and Evaluation are located on pages 87–88.

Course Availability List

These courses may be ordered by mail on the Customer Information form located on page 87.
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MODERATE SEDATION/ANALGESIA
#30464 • 15 ANCC / 15 Pharm Hours
Book By Mail – $98 • ONLINE – $90
Purpose: The purpose of this course is to provide nurses with the knowledge required for safe drug delivery based on standardized operational guidelines. Preprocedural, intraprocedural, and postprocedural patient care are presented, as well as a thorough review of the drugs used, their advantages and disadvantages, and the safe administration of these agents.
Audience: This course is designed for all nurses, especially those in procedural and diagnostic areas, such as radiology, endoscopy, cardiac cath, outpatient surgery, intensive care, and emergency departments.
Additional Approvals: AACN Synergy CERP Category A, CCMC

TREATMENT OF HEART FAILURE: AN UPDATE
UPDATE
#30934 • 10 ANCC / 3 Pharm Hours
Book By Mail – $68 • ONLINE – $60
Purpose: The purpose of this course is to provide nurses and ancillary nursing personnel with current information about the scientific advances in the treatment of acute heart failure.
Audience: This course is designed for nurses and ancillary nurse personnel involved in the treatment and continued assessment of patients with heart failure.
Additional Approvals: AACN Synergy CERP Category A, CCMC

COMMUNICATION AND SOFT SKILLS IN NURSING PRACTICE
NEW!
#31350 • 3 ANCC Hours
Book By Mail – $26 • ONLINE – $18
Purpose: The purpose of this course is to provide nurses with strategies to support the soft skills needed to provide optimal patient care and enhance professionalism in health care.
Audience: This course is designed for nurses in all practice settings.
Additional Approvals: AACN Synergy CERP Category C

BURNOUT: IMPACT ON NURSING AND QUALITY OF CARE
#31434 • 5 ANCC Hours
Book By Mail – $38 • ONLINE – $30
Purpose: Given the integral relationship between work-related stress, job dissatisfaction, burnout, and patient care, properly addressing nursing burnout is essential. The purpose of this course is to provide nurses with information to identify burnout and with effective strategies to manage work-related stress and prevent burnout.
Audience: This course is designed for nurses and nurse practitioners at all levels and in all settings, especially oncology, palliative care, mental health, and critical care.
Additional Approvals: AACN Synergy CERP Category C, CCMC

WOMEN AND CORONARY HEART DISEASE
UPDATE
#33224 • 15 ANCC / 5 Pharm Hours
Book By Mail – $98 • ONLINE – $90
Purpose: The purpose of this course is to identify the unique challenges that face women with heart disease, including prevention, diagnosis, and treatment.
Audience: This course is designed for all nurses in family practice or medical/surgical areas, especially critical care or cardiac units.
Additional Approvals: AACN Synergy CERP Category A, CCMC

DIABETIC HYPOGLYCEMIA
#34654 • 5 ANCC / 5 Pharm Hours
Book By Mail – $38 • ONLINE – $30
Purpose: The purpose of this course is to provide nurses and healthcare professionals with a foundation of understanding hypoglycemia in order to assure the highest quality of care is provided to patients.
Audience: This course is designed for nurses in any healthcare venue and dietitians with a desire to better understand the causes, recognition, and treatment of hypoglycemia in a variety of settings.
Additional Approvals: AACN Synergy CERP Category A, CCMC

ETHICAL DECISION MAKING
UPDATE
#37074 • 15 ANCC Hours
Book By Mail – $98 • ONLINE – $90
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.
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approvals: AACN Synergy CERP Category B, CCMC

VENOUS DISEASE AND ULCERS
#38632 • 5 ANCC Hours
Book By Mail – $38 • ONLINE – $30
Purpose: The purpose of this course is to enable nurses to accurately assess and treat venous disease and venous ulcers and to provide patient and family education for preventive care and lifestyle changes.
Audience: This course is designed for nurses in all care settings who may care for patients with venous disease or ulcers.
Additional Approvals: 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)*

CARING FOR THE GERIATRIC PATIENT

#39102 • 3 ANCC Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide nurses with an overview of the physical and psychosocial considerations necessary when providing care to geriatric patients.

Audience: This course is designed for nurses in a variety of practice settings who work with older patients.

Additional Approvals: AACN Synergy CERP Category A, CCMC

PULMONARY EMBOLISM

#90120 • 2 ANCC / 1 Pharm Hour

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.

Audience: This course is designed for nurses, physicians, and PAs, involved in assessing, triaging, and managing patients with suspected pulmonary embolism.

Additional Approvals: AACN Synergy CERP Category A

AGITATION, SEDATION, AND DELIRIUM IN ADULT ICU PATIENTS

#90180 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.

Audience: This course is designed for nurses, physicians, and physician assistants, involved in the care of patients in intensive care units.

Additional Approvals: AACN Synergy CERP Category A

ISCHEMIC STROKE

#90284 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The early identification and management of the risk factors for ischemic stroke can lead to substantial health benefits and reductions in cost. However, research has documented gaps between healthcare professionals' knowledge and practice with respect to prevention, demonstrating that adherence to evidence-based or guideline-endorsed recommendations pertaining to all interventions for primary and secondary prevention are underutilized or ineffective. The purpose of this course is to provide needed information about the roles of diagnosis and screening, timely 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.

Audience: This course is designed for nurses, physicians, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.

Additional Approvals: AACN Synergy CERP Category A, CCMC

AUTISM SPECTRUM DISORDER

#92204 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ASD. Additionally, this course will provide the information necessary to screen children seen in primary care for ASD in order to appropriately refer patients and their families for more expansive assessment and treatment referral as rapidly as possible in order to avoid unnecessary morbidity and mortality.

Audience: This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.

Additional Approvals: AACN Synergy CERP Category A, CCMC

CONTRACEPTION

#93114 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: Newer contraceptive methods and new techniques for old methods (such as hysteroscopic sterilization) are attractive to patients, and their contraceptive provider (or referring provider) should have a grasp of the wide range of options. The purpose of this course is to provide healthcare professionals with the information necessary to advise patients and prescribe effective and appropriate contraceptives.

Audience: This course is designed for gynecologists, primary care physicians, nurse practitioners, and other primary care health providers, such as pharmacists, physician assistants, and nurses, who care for women of childbearing age.

Additional Approvals: AACN Synergy CERP Category A

PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES

#94194 • 15 ANCC / 7 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.

Audience: This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.

Additional Approvals: AACN Synergy CERP Category A

Prices are subject to change. Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

INFLUENZA: A COMPREHENSIVE REVIEW

#94424 • 10 ANCC / 5 Pharm Hours

Includes Bird Flu

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide healthcare professionals with an updated review of influenza, including clinical aspects, public health issues, and strategies for prevention. The goals are to minimize the burden of influenza on patients and communities, prevent complications and hospitalizations, and save healthcare dollars.

Audience: This course is designed to help healthcare professionals and allied personnel understand influenza and their role in its prevention.

Additional Approvals: AACN Synergy CERP Category A, CCMC

HUMAN TRAFFICKING AND EXPLOITATION

#96313 • Training Only

MI MANDATE

Book By Mail – $38 • ONLINE – $30

Purpose: As human trafficking becomes an increasingly more common problem in the United States, healthcare and mental health professionals will require knowledge of human trafficking patterns, the health and mental health needs of human trafficking victims, and successful interventions for victims. The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.

Audience: This course is designed for physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.

Additional Approvals: AACN Synergy CERP Category B, CCMC

Special Approval: This course meets the Michigan requirement for training in identifying victims of human trafficking.

IMPLICIT BIAS: THE MICHIGAN REQUIREMENT

#97440 • 2 ANCC Hours

MI MANDATE

ONLINE ONLY – $30

Purpose: The purpose of this course is to provide healthcare professionals with an overview of the impact of implicit biases on clinical interactions and decision making.

Audience: This course is designed for the interprofessional healthcare team and professions working in all practice settings in Michigan.

Additional Approvals: AACN Synergy CERP Category B

Special Approval: This course meets the Michigan requirement for 2 hours of implicit bias training.

DIETS AND DIETARY APPROACHES TO WEIGHT LOSS

#98120 • 4 ANCC Hours

NEW!

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to counsel patients regarding diets and dietary approaches to weight management.

Audience: This course is designed for all nurses, physicians, and allied professionals involved in the care of patients who are interested in exploring dietary options to weight control.

Additional Approvals: AACN Synergy CERP Category A

SUPPLEMENTS FOR AGING

#98190 • 5 ANCC / 5 Pharm Hours

NEW!

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the supplements that may be used by their older adult patients.

Audience: This course is designed for healthcare professionals whose older patients are taking or are interested in supplements.

Additional Approvals: AACN Synergy CERP Category A

MEDICINAL MUSHROOM SUPPLEMENTS

#98210 • 3 ANCC / 1 Pharm Hour

NEW!

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to help healthcare professionals in all practice settings increase their knowledge base on medicinal mushrooms.

Audience: This course is designed for healthcare professionals in any practice setting whose patients may be taking mushrooms for potentially medicinal uses.

Additional Approvals: AACN Synergy CERP Category A

ALZHEIMER DISEASE AND DEMENTIAS: EARLY DETECTION AND CARE PLANNING

#99090 • 3 ANCC Hours

NEW!

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals with a clear understanding of Alzheimer disease and other dementias, including early signs, stages, and progression, in order to support effective early diagnosis, care planning, and management that improves patients' quality of life.

Audience: This course is designed for nursing professionals, physicians, and PAs who are involved in the care of patients who have or may develop dementia.

Additional Approvals: AACN Synergy CERP Category A

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	90073	Migraine: Diagnosis and Therapeutic Advances / 5 Contact Hours	$30
	95173	Medical Marijuana and Other Cannabinoids / 5 Contact Hours	$30
	38910	Pathophysiology: The Hepatobiliary System / 15 Contact Hours	$90

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☐	31350	Communication & Soft Skills in Nursing Practice / 3	$26
☐	31434	Burnout: Impact on Nursing and Quality of Care / 5	$38
☐	33224	Women and Coronary Heart Disease / 15	$98
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☐	37074	Ethical Decision Making / 15	$98
☐	38632	Venous Disease and Ulcers / 5	$38
☐	39102	Caring for the Geriatric Patient / 3	$26
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☐	97440	Implicit Bias: The Michigan Requirement / 2 ONLINE ONLY	$30
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3. Would you recommend this course to your peers?
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?

#90073
Migraine: Diagnosis and Therapeutic Advances
5 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#95173
Medical Marijuana and Other Cannabinoids
5 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#38910
Pathophysiology: The Hepatobiliary System
15 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#90073 Migraine: Diagnosis 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?_____
_____
_____

#95173 Medical Marijuana and Other Cannabinoids — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team?_____
_____
_____

#38910 Pathophysiology: The Hepatobiliary System — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team?_____
_____
_____

May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

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