NetCE
Continuing Education

2019
CONTINUING EDUCATION FOR ADVANCED PRACTICE NURSES

30 Hours
20 Pharmacology Hours
$39

INSIDE THIS EDITION:

Medical Marijuana

Dizziness and Vertigo

Palliative Care and Pain Management at the End of Life

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

NetCE.com/GIA19

NetCE
Continuing Education

SPECIAL OFFER $39

30 Hours
(20 Pharmacology Hours)
Regular Price $120

Medical Marijuana and Other Cannabinoids (5 contact hours) 1
Dizziness and Vertigo (10 contact hours) 26
Palliative Care and Pain Management at the End of Life (15 contact hours) 60

Special Offer price of $39 valid through January 31, 2020
After January 31, 2020, price increases to $49

LEARN.

Read the enclosed course(s).

Study questions will appear throughout the courses to create a link between the learning objectives and the supporting text.

CLICK.

Go to **NetCE.com/GIA19**
Enter your Quick Code and Customer ID (found on the back of your booklet), or complete the enclosed forms located between pages 112–113.

DONE.

Receive certificates of completion:
FAST By Mail
FASTER Fax/Email
FASTEST Online
Print from your NetCE transcript.

Advanced Practice Nurses
Need more hours?

Get One Year of Unlimited Online CE for ONLY $69!
See details on inside back cover.

NetCE | P.O. Box 997571 | Sacramento, CA 95899 | 800-232-4238 | Fax: 916-783-6067

Copyright © 2019 NetCE, Sacramento, CA

CONTINUING EDUCATION FOR NURSES 2019

Published by NetCE,
a division of CE Resource, Inc.
P.O. Box 997571
Sacramento, CA 95899
Tel: 800-232-4238 (within the U.S.)
916-783-4238 (outside the U.S.)
Fax: 916-783-6067
Email: Info@NetCE.com
Website: www.NetCE.com

CE RESOURCE, INC.
Chief Executive Officer, Dennis Meinyer
Chief Information Officer, Kevin Bluck
Chief Operating Officer, Lisa Patterson
Director of Academic Affairs, Freda O'Brien

NETCE
Executive Director, Erin Meinyer
Director of NetCE, Julie Goodwin
Director of Public Relations, Roland Meinyer
Director of Development, Sarah Campbell
Director of Graphic Services, Kathryn Harris
Director of Operations, Alma Parra

Division Planners
Eli English, PT, DPT
Abimbola Farinde, PharmD, PhD
Alice Yick Flanagan, PhD, MSW
William E. Frey, DDS, MS, FICD
John V. Jurica, MD, MPH
John M. Leonard, MD
Jane C. Norman, RN, MSN, CNE, PhD
Ronald Runciman, MD
Shannon E. Smith, MHSC, CST, CSFA
James Trent, PhD

Featured Contributing Faculty
Lori L. Alexander, MTPW, ELS, MWC
Mark Rose, BS, MA

Copyright © 2019 NetCE

Medical Marijuana and Other Cannabinoids

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, physicians, physician assistants, 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, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders 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 various law firms on matters related to substance abuse, 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, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Accreditations & Approvals

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 11/21/2021); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2019); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

How to Receive Credit

- Read the following course.
- Complete the Evaluation.
- Return your Customer Information/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/GIA19**.
- A full Works Cited list is available online at www.NetCE.com.

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.

 Copyright © 2019 NetCE

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 2017, voters in an additional 28 states and the District of Columbia have followed suit. In addition, eight states, including California, 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 pulmonary harm, 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 [6; 7]. However, about 11% of recreational marijuana users report daily use, compared with one-third of medical marijuana users [198]. 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 nonmedical 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 2017) [11]. In fact, a congressional spending bill (as of 2017) prohibits the U.S. Drug Enforcement Administration 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 [199].

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 [13]. 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; 14].

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 [15].

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 [16].

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 [17]. Over time, cannabis spread to all regions with human habitation, reflecting the value placed on its medicinal, spiritual, and dietary utility [18].

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 [19; 20]. 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 [19; 21].

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 [19; 20]. 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

 Copyright © 2019 NetCE

onset of action (when given orally), variable potency, difficulty in standardized dosing, and individual differences in response. The importance of dose titration was stressed [19; 21]. 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 [19; 21]:

- 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" [18]. 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 [22; 23]. Prohibition of medical marijuana culminated with the 1970 Controlled Substance Act that categorized marijuana, along with heroin, as a Schedule I substance. Drugs with Schedule I listing are deemed highly addictive and devoid of medical value or safety. In tandem with the Controlled Substance Act, the "War on Drugs" was launched in 1968. Possession of a Schedule I substance potentially confers severe legal consequences, and possessing small amounts of cannabis has led to the lengthy incarceration of many. 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 [24]. 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 [23].

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 [23]. 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 2017, 29 states and the District of Columbia had followed suit [1]. (For information on laws pertaining to medical marijuana in your state, visit http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.) 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 [23].

Long-standing federal law enforcement obstruction of cannabis efficacy research led to the disproportionate study of harmful effects, perpetuating the 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 [25]. 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 [26; 27]. 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 [28].

THE ENDOGENOUS CANNABINOID SYSTEM

The endogenous cannabinoid system (ECS) is a signaling system that includes cannabinoid receptors, endogenous receptor ligands (termed endocannabinoids), and their synthesizing and degrading enzymes [29]. Core functions of the ECS have been described as "relax, eat, sleep, forget, and protect," shorthand for the diversity of processes involving the ECS [30]. 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 [31; 32].

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 [27; 33].

CANNABINOID RECEPTORS

CB1 Receptors

What are the most abundant G-protein-coupled receptors in the brain?

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 [29; 34].

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 [35]. The location and relative density of CB1 receptors in the brain and function mediated by CB1 activation are outlined in ***Table 1*** [36; 37; 38; 39].

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 migration and cytokine and chemokine release, and CB2 receptor expression on CNS microglia may explain cannabinoid efficacy in reducing cytokine-mediated neuroinflammation [29; 40; 41; 42].

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) [29].

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" [36]. 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 [35]. Anandamide is hydrolysed by the enzyme fatty-acid amide hydrolase (FAAH) as the primary metabolic pathway [43].

 Copyright © 2019 NetCE

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: [36; 37; 38; 39]	*Table 1*

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 [35]. 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) [35; 43].

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 (DEA). 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" [44; 45; 46]. PEA has become a research focus, with a growing number of clinical trials evaluating its pain-reducing efficacy in diverse chronic pain conditions [202].

MECHANISMS OF ECS ACTION

Cannabinoid binding and activation of CB1/CB2 receptors produce many pharmacologic effects resulting from ECS modulation of other neurotransmitter systems [47].

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 [48].

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 [48; 49; 50].

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" [35; 51; 52].

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 [35; 51; 52].

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; 14]. 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 [36].

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 [36; 53].

Serious gastrointestinal and cardiovascular adverse effects are associated with all nonsteroidal anti-inflammatory drugs (NSAIDS), and their use is now recommended at the lowest effective dose over the shortest duration possible [203; 204; 205]. 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 [53]. 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 [54]. Also, tolerance is a main unwanted development with all analgesic drugs, including cannabinoids, and COX-2 inhibition may prolong cannabinoid analgesia [55].

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; 56].

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 [13; 57; 58]. Phytocannabinoids are discussed in detail later in this course.

 Copyright © 2019 NetCE

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 [59; 60]. Analgesic and anti-inflammatory activity have been found in several cannabis terpenoids [61]. Myrcene is an analgesic that inhibits inflammation via PGE2 activity. Naloxone blocks this activity, suggesting an opioid-mediated mechanism [62]. 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 [63]. Other possibly therapeutic terpenoids include the PGE1 inhibitor α-pinene and the local anesthetic linalool [60; 64].

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 [65]. This flavonoid is unique to cannabis and has not been subsequently investigated [66].

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 [67]. Cannabis root contains significant amounts of β-sitosterol and other sterols that can be extracted by various methods [201]. 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 [68]. 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 [36]. 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 [192].

Nabilone

Nabilone (Cesamet) is a Schedule II THC analog that is chemically similar but not identical to THC [36]. 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) [69]. 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 [192].

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 [70; 192].

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 [69].

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 [71]:

- 22%, 14%, or 13.5% THC with <1% CBD
- 6.3% THC/8% CBD
- <1% THC/9% CBD

In Canada, cannabis is available in potencies of [72]:

- 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 [25]. In contrast, legal medicinal cannabis purchased from dispensaries in the United States lacks government-controlled standardization of cultivation, potency, and purity [73]. 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 [206].

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 [57; 58]. 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 [74].

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 [30; 75].

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 [76]. Cannabinoids inhibit pre-synaptic glutamate release, and THC reduces NMDA response by 30% to 40%. THC is also neuroprotective through antioxidant activity [77]. THC inhibits calcitonin gene-related peptide to reduce hyperalgesia, and preclinical studies show that THC blocks capsaicin-induced hyperalgesia at sub-psychoactive doses [66; 78].

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 [79; 80].

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 [30; 81].

 Copyright © 2019 NetCE

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 [57; 58].

Δ8-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 [82; 83]. Δ8-THC is psychoactive, but the effect is very weak and substantially overshadowed by THC due to its low concentration [8].

Cannabidiol

What are the pharmacologic actions of CBD?

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 [84]. 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 [84; 85; 86]. 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 [36].

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) [77]. 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 [87]. 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 [30; 88]. Many effects of CBD follow a bell-shaped dose-response curve, suggesting that dose is a key factor in CBD pharmacology [85].

Outside of 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 seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older [208].

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 [61; 85; 89].

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 [85; 89]. Cannabigerol possesses anti-inflammatory and analgesic properties and also demonstrates anti-proliferative and antibacterial activity [85].

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 [90; 91]. 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 [85].

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 [85].

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 [51]. 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 [92]. 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 [57; 93].

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 [57].

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 two to 3 hours [51]. 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 [73]. The THC dose absorbed systemically is 25% to 27% of the total available THC content in a marijuana cigarette ("joint") [57; 94].

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 [95]. 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 [96; 97].

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 [98].

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 [57]. 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 [13].

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 [51; 57]. 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 [99].

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 [100]. The 11-hydroxy THC plasma level parallels observable drug action [57]. Relative to inhalation, first-pass hepatic metabolism with oral ingestion yields a greater proportion of 11-hydroxy THC [51].

 Copyright © 2019 NetCE

Elimination

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 [51; 101].

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 [13].

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 [51].

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 [102]. 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 [103].

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 [104; 105; 207]. 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 [106; 107]. 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 [73]. For example, in standard therapies for chronic pain or spasticity, opioids often produce sedation, nausea, constipation, physiologic dependence, and a substantially 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 [73].

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 [14].

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: [110; 111]	*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 [104]. 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 [104].

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 [13].

A dose-effect relationship was found, with higher rates of sedation, ataxia, and loss of balance following higher dose levels [108; 109]. Tolerance to cardiovascular, autonomic, and other subjective and cognitive side effects developed rapidly over the initial 2 to 12 days of therapy [73]. 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 [13]. 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 [52]. Successful resolution or management of cannabis side effects has been described with several agents (***Table 2***) [110].

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 [112]. 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 preemptively irradiate all cannabis products before distribution to medical or research users [26; 71]. This is not currently done to most cannabis available in the United States.

 Copyright © 2019 NetCE

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 [113]. This has contributed to reluctance over medical smoked cannabis use, but more recent scientific data challenge these assumptions.

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 [114; 115; 116].

These factors appear in the results of a 20-year longitudinal study of pulmonary health in 5,115 participants who smoked cannabis [117]. 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 [117]. 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 [118].

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 [95; 96].

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 [119]. 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 [120]. 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 [121]. An exception comes from preclinical trial results suggesting that increased CB2 activity may impose risks in immunocompromised patients with specific infection, such as *Legionella* [51].

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 [122]. 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 [122; 123].

Results from the 2012 Dunedin study provide the most definitive data on neurocognitive effects from cannabis use [124]. 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 [124].

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 [122].

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; 207].

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 [125; 207]. Furthermore, cannabis use in the general population soared between 1949 and 1995, while the population rates of schizophrenia remained stable [126].

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 [51; 127].

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 [36].

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 [103; 128]. 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 [71; 129].

The greatest risk for toxicity and potential overdose is among children who may consume cannabis edibles, beverages, or candies inadvertently [130; 131]. In adults, most toxic reactions are mild, but in children, overdose can result in significant respiratory depression [131]. 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 [18; 200]. Alcohol and nicotine use are more significant primers for hard drug use in many individuals [200]. Further research is necessary to clarify these points.

 Copyright © 2019 NetCE

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 [132]. 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 [133]. 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 [27; 207].

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 [27].

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 [18; 134]. This compares with lifetime prevalence rates of 32% for nicotine, 23% for heroin, 17% for cocaine, and 15% for alcohol [18; 135; 136].

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 [137].

EVIDENCE-BASED PRACTICE RECOMMENDATION

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://www.guideline.gov/summaries/summary/43939. Last accessed November 20, 2017.)

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 [135]. 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 [135].

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 [138].

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) is characterized by severe cyclic nausea and vomiting in chronic (usually heavy) cannabis users [195]. It is a relatively rare adverse effect, but increasing case reports have been noted with the liberalization of cannabis in several states [196]. 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) [197]. 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 [197]. Symptoms resolve with cessation of cannabis use; relapse to use often results in a recurrence of the syndrome.

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 [128]. 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 [134]. 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 [139; 140].

Chronic pain is a highly prevalent, heterogeneous group of disorders that in many patients is refractory or only partially responsive to treatment [139]. 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 [25]. 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 [73].

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 [141; 193]. 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 [142; 143]. In one study, use of nabiximols was found to be the most effective cannabinoid for multiple sclerosis-associated central pain [193]. Unless otherwise noted, the RCT methods in the following sections were double-blinded and placebo-controlled with inert, non-active cannabis and/or pills.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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.guideline.gov/summaries/summary/47701. Last accessed November 20, 2017.)

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 [144].

 Copyright © 2019 NetCE

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 developing early in the only cannabis-naïve subject, all side effects were "mild" and no safety concerns emerged [145].

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 [52].

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 [146]. 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 [146].

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 [109]. 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 [109].

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 [147]. 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 [147].

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 [148]. 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 [148]. This biphasic dose-response effect of cannabinoids in acute neuropathic pain is consistent with the previous body of research [52].

Nociceptive Pain

Cannabis has not been found effective in acute nociceptive pain and has shown a biphasic dose-response effect with acute neuropathic pain [52]. However, chronic pain results from the development of abnormal sensory processing and other alterations in peripheral and CNS pain pathways [149]. 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 [53].

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 [150]. 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 [52].

Reducing Opioid Requirements

How does addition of a cannabinoid modify opioid therapy for chronic non-malignant pain?

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 [151; 152]. 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 [52; 153]. 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 [154]. 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) [97]. 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 [155].

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 [141].

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 [156]. 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 [157]. Several clinical trials of cannabis in multiple sclerosis have been performed, and these studies have demonstrated cannabis efficacy in reducing spasticity and pain [158; 159]. 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 [160; 161; 162]. A 2004 study also found that cannabis helped alleviate bladder dysfunction, a problematic multiple sclerosis symptom [163]. 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 [159]. 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 [159]. 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 [164].

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.guideline.gov/summaries/summary/47909. Last accessed November 20, 2017.)

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

 Copyright © 2019 NetCE

Post-Traumatic Stress Disorder

Numerous case reports describe substantial reduction in PTSD symptoms with cannabis use [165]. 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 [166]. More robust research supporting this use is lacking.

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. Long-term safety and tolerability data are not yet available [167].

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 [168]. 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 [168].

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 [169]. 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 [170].

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 [86; 171]. 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 [86].

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 [86]. 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 [83]. 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 [86; 172].

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. 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 [173]. 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 [174].

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 [175].

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 [176].

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 [177]. 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 [177].

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 [52]. 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 [36]. Research in chronic pain patients has consistently shown beneficial cannabinoid effects on sleep quality [52].

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 [73]. 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 [178]. 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 [179].

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 [180]. 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 [181].

 Copyright © 2019 NetCE

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 [182]. 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 [5; 182]. 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 [5]. 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 [14]. 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 [183].

These patients differed from those in a 2005 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%) [184]. 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%) [185]. 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 [185].

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 [186]. 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 [31].

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 [187]. 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 [73].

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 [188; 189; 190]:

- 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. For the treatment of refractory pain, the recommended daily dose of inhaled or ingested cannabis is 2.5 g for refractory pain and not more than 5 g for other indications (e.g., nausea and vomiting, anorexia); larger doses are divided to two or three doses per day [190]. 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 [26; 191].

The recommended initial dose of dronabinol is 2.5 mg at bedtime [190]. 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 [192].

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 [71]. 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 [71]. Patients orally ingesting cannabis or cannabinoids should be advised of the slow onset and the need to ingest small amounts spaced several hours apart [13].

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 in 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 [13; 71; 189]. There are several other contraindications to the use of medical marijuana, including [13; 189]:

- 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 [13; 189]:

- 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

 Copyright © 2019 NetCE

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 [103; 193; 194]. 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 [13].

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/Evaluation insert located between pages 96–97.

Dizziness and Vertigo

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses and physicians involved in the diagnosis, treatment, and care of patients with dizziness and/or vertigo.

Course Objective
The purpose of this course is to provide clinicians with the information necessary to appropriately diagnose and treat causes of dizziness and vertigo and improve patients' quality of life.

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

1. Identify models used to describe vertigo and dizziness.
2. Outline anatomy and physiology of structures involved in vestibular disorders.
3. List peripheral etiologies of vertigo.
4. Describe the clinical presentations of central etiologies of vertigo.
5. Discuss the causes and underlying pathophysiology of other dizziness/vertigo etiologies (e.g., trauma).
6. Devise a best practice, cost-effective diagnostic workup for patients presenting with dizziness and/or vertigo.
7. Apply diagnostic reasoning and appropriate clinical evaluation and management strategies to the differential diagnosis of dizziness and vertigo.
8. Compare and contrast pharmacotherapy agents that may be used to manage vertigo and dizziness.
9. Analyze the role of vestibular rehabilitation in the clinical management of dizziness/vertigo.
10. Describe other approaches to the management of specific dizziness etiologies.
11. Outline preventive approaches and safety considerations for patients with dizziness/vertigo.

Faculty
Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders 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 various law firms on matters related to substance abuse, 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, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Designations of Credit
NetCE designates this continuing education activity for 10 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

A full Works Cited list is available online at www.NetCE.com. ***Mention of commercial products does not indicate endorsement.***

 Copyright © 2019 NetCE

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

AACN Synergy CERP Category A.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 11/21/2021); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2019); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

How to Receive Credit

- Read the following course.
- Complete the Evaluation.
- Return your Customer Information/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/GIA19**.
- A full Works Cited list is available online at www.NetCE.com.

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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

What are limitations in the Drachman-Hart dizziness and vertigo paradigm?

Advances in knowledge of pathophysiology and newer imaging techniques have led to a paradigm shift in the classification system and diagnostic algorithm for managing dizziness and vertigo. With this newly identified connectivity between vestibular, balance, and anxiety disorders comes an enhanced ability to identify the stroke mimics of benign dizziness or vertigo. These and other breakthroughs are transforming the clinical care of patients with dizziness and vertigo complaints, connecting clinical syndromes previously considered unrelated, and expanding the range of effective treatment options for patients.

The modern paradigm for the clinical management of dizziness and vertigo was introduced by Drachman and Hart in a seminal 1972 publication [1]. Based on patient response to the question "What do you mean by 'dizzy?'," dizziness was classified into one of four types that best reflected the subjective descriptions of the symptoms [2; 3]:

- Vertigo: Dizziness experienced as a definite sensation of movement or rotation in space
- Presyncope: A sensation of impending faint or loss of consciousness
- Disequilibrium: A sense of unsteadiness or loss of balance without head sensations
- Lightheadedness: Cannot be classed as vertigo, syncope, or disequilibrium

The Drachman-Hart model also suggested that vertigo had a vestibular cause, presyncope a cardiovascular cause, disequilibrium a neurologic cause, and nonspecific dizziness (lightheadedness) a psychiatric or metabolic cause [4]. In accordance with this framework, the character of symptoms reported by the patient determined the type (pathophysiology) of disorder and guided subsequent clinical evaluation, differential diagnosis, testing, and treatment [3].

By current standards, the Drachman-Hart model was based on weak evidence and developed in the absence of modern diagnostic imaging. In reality, patients often have difficulty describing their symptoms and may give conflicting accounts at different times. In one study, an estimated 62% of patients presenting to the emergency department (ED) with past-week dizziness selected more than one type of dizziness on a multiresponse questionnaire, and 52% chose a different type when retested six minutes later [5; 6]. As such, the character and quality of symptoms alone does not reliably predict the cause of dizziness or serve as a dependable guide to management.

Primary care providers see at least 50% of patients who seek medical attention for dizziness or vertigo. The differential diagnosis is large, and each common etiology accounts for 5% to 10% of cases [7]. The central task for providers is to distinguish benign from serious or life-threatening causes of dizziness and vertigo, such as posterior circulation stroke. Misdiagnoses are common and diagnostic testing can be costly, especially if too much reliance is placed on this outdated diagnostic paradigm [8].

These factors can make the medical care of patients with dizziness/vertigo seem daunting. However, a new diagnostic paradigm has replaced the standard symptom-based approach with an algorithm that streamlines the differential diagnosis, increases diagnostic accuracy for benign and dangerous causes alike, and reduces the use of expensive and unhelpful brain imaging [3; 9].

A "timing and triggers" approach to patient history guides the diagnostic workup. The onset (timing), precipitating factors/events (triggers), evolution, associated symptoms and signs, and the context of dizziness episodes can be used to classify cases as triggered or spontaneous forms of episodic, acute, or chronic vestibular syndromes. Placement within one of six vestibular syndromes informs the differential diagnosis, targeted physical exams, and testing. Targeted exams are a range of procedures that assess for peripheral or central causes of dizziness/vertigo without using less accurate, expensive brain imaging [8].

ANATOMY AND PHYSIOLOGY

What structures comprise the vestibular system?

The labyrinth in each inner ear houses the systems that serve the functions of hearing (auditory) and balance (vestibular). The auditory system involves the cochlea, which transmits sound signals to the brainstem via the cochlear branch of the 8th cranial nerve. The vestibular system is comprised of the vestibular end-organs in the labyrinth, the vestibular nuclei in the brainstem and cerebellum, and the vestibular branch of the 8th nerve, which relays labyrinthine input to the vestibular nuclei. The 8th cranial nerve is also called the vestibulo-cochlear nerve [10; 11; 12].

Within each labyrinth are five vestibular end-organs (three semicircular canals and two otolith organs) that help maintain spatial orientation, postural control, and egocentric perception. Changes in angular and linear head acceleration, movement, and orientation to gravity are detected and signaled via the 8th nerve to brainstem and cerebellar circuits, through thalamic and spinal vestibular projections, and finally to the cerebral cortex [13; 14; 15].

 Copyright © 2019 NetCE

This vestibular input, along with visual input from the eyes and proprioceptive input from peripheral sensory nerves (via the spinal cord), is relayed to the cerebral cortex, which integrates the sensory inputs and adjusts outgoing motor responses to maintain balance, posture, and gaze stabilization of retinal images (via the vestibulo-ocular reflex) [11; 14; 16].

Vertigo, dizziness, spatial disorientation, and disequilibrium can result from: asymmetrical vestibular inputs; vestibular hypofunction causing sensory mismatch in brain integration of sensory inputs; pathologies that affect any peripheral (e.g., inner ear, 8th cranial nerve) or central (e.g., vestibular nuclei and brainstem or cerebellar connections) vestibular system component; or a host of systemic, drug-effect, psychiatric, and physical trauma-related factors [14; 16; 17]. Around 80% of dizziness or vertigo cases are peripheral and 20% are central in origin [11; 18].

EPIDEMIOLOGY

Dizziness is a general, umbrella term that encompasses symptoms of impaired spatial perception. Vertigo is often consolidated into the umbrella term dizziness due to highly variable descriptions of the experience. Dizziness/vertigo is the second most common complaint in the ambulatory setting and constitutes 25% of neurology outpatient referrals, 13% of ED neurology consultations, and more than 3 million ED visits annually [9; 19]. The primary complaint of dizziness accounts for 5.6 million clinic visits annually in the United States. Vertigo is roughly two-thirds more common in women than men. Prevalence increases with age but varies depending on the etiology [20].

Benign paroxysmal positional vertigo (BPPV) is the most frequent vestibular disorder and the most common cause of peripheral vertigo, with a lifetime prevalence of 10% [21]. In the general population, the one-year prevalence rate is about 5% for vertigo, 1.6% for BPPV, and <1% for vestibular migraine [20]. An estimated 17% to 42% of vertigo cases are diagnosed as BPPV [22].

Peripheral causes of vertigo are usually, but not always, benign, while central vertigo often indicates a more serious pathology [18]. The negative impact of vertigo should not be underestimated; around 80% of patients report interruption in daily activities, including employment, from symptoms and the need for medical attention [20].

Dizziness, vertigo, and associated symptoms do not always fall easily into either a peripheral or central syndrome or disorder. Patients can have a dominant group of symptoms more closely tied to peripheral or central origin, while others will show a mix of both groups [23].

In the following discussion of pathophysiology, the diagnostic entities associated with dizziness or vertigo are mainly organized by peripheral or central origin and by shared etiologies or clinical features in a few instances. Throughout this course, "benign" is a pathologic and not a clinical descriptor; "benign" vestibular conditions can be intensely distressing for the patient.

PERIPHERAL CAUSES OF DIZZINESS AND VERTIGO

BENIGN PAROXYSMAL POSITIONAL VERTIGO

As indicated by the name, BPPV describes benign (not life-threatening or malignant) paroxysmal (comes in sudden, brief spells) positional (triggered by certain head positions or movements) vertigo [24]. It is characterized by rotational vertigo induced by head position changes, especially when extending or turning the neck, lying down, or rolling over in bed [21].

Epidemiology

As noted, BPPV is the most frequent vestibular disorder and the most common cause of peripheral vertigo, with a lifetime prevalence of 10% [21]. Women are more often affected than men, with a female-to-male ratio of 1.5–2.2 to 1 [22; 25; 26].

The most frequent age of onset is between the fifth and seventh decades of life. BPPV has an overall prevalence of 3.4% in persons older than 60 years of age and is present in 40% of geriatric patients seen for dizziness [27]. The incidence increases with age due to age-related degeneration of otolithic membrane [9]. The adverse impact on health and quality of life is more severe in older individuals, and BPPV is an important health concern in the elderly because it contributes to falls and associated morbidity and mortality [15; 22].

With a 27% to 50% rate of spontaneous resolution, BPPV can be self-limiting or may persist to become a chronic recurrent disorder [15; 22]. An estimated 85% of patients experience interrupted daily activities/lost days at work, 68% reduce their workload, 4% change their job, and 6% quit their job from the disruptive impact of BPPV [28].

The direct and indirect costs of BPPV are significant. Delayed diagnosis and treatment is frequent. It costs an average $2,000 to arrive at the correct diagnosis, and costs related to BPPV diagnosis alone approach $2 billion annually [22].

Only 10% to 20% of patients with BPPV seen by a physician receive recommended repositioning therapy. Before specialist referral, more than 65% of patients receive potentially unnecessary diagnostic testing or treatment, including magnetic resonance imaging (MRI) (70%), computed tomography (CT) (45%), electrocardiogram (41%), and medication therapy (53%). Delayed diagnosis and treatment of BPPV has cost and quality-of-life implications for patients and their caregivers [22; 28].

Across disciplines, the practice variations in BPPV management are considerable, and medication treatment of BPPV varies substantially among primary care providers and across specialties [22].

Pathophysiology

The vestibular system includes three semicircular canals (or simply "canals") and two otolith organs (the saccule and utricle). The canals (posterior, lateral, and anterior) are positioned at right angles to each other to detect angular accelerations of the head. The canals are organized as functional pairs (left and right ear) in the same spatial plane; any rotation in that plane excites one pair member and inhibits the other [29; 30]. The canals are filled with endolymph fluid and lined with sensitive hair cells to act like a gyroscope. Motion from head rotation induces endolymph movement in the canal oriented in the spatial plane, which stimulates hair cells, activates the ampulla (the motion sensor) and cupula, and sends sensory output to the brain via the vestibular nerve [15; 29].

The saccule and utricle contain sensory epithelium and function to detect linear or translational acceleration forces (e.g., gravity, accelerating or braking a car) [15]. Hair cells in the saccule and utricle are embedded in a matrix of calcium carbonate crystals (otoliths). Deflection of otoliths by gravity stimulates or inhibits neuronal output from the attached hair cells [11].

Otoliths that dislodge and migrate into a canal are called otoconia. Endolymph fluid is usually non-reactive to gravity, but otoconia moves with gravity, causing inappropriate endolymph motion and hair cell stimulation and false signaling of head motion to the brain [24].

The brain receives and integrates peripheral sensory inputs. A false vestibular input conflicts with inputs from ocular, proprioceptive, and the unaffected vestibular systems. This causes a sensory mismatch in the brain integration, perceived as a spinning sensation (vertigo) normally lasting less than 60 seconds after cessation of head movement and inappropriate endolymph motion [24; 31].

BPPV is subtyped by afflicted canal and mechanism. Posterior canal BPPV (85% to 95%) is the most common. Lateral canal BPPV (5% to 15%) is less common, likely because it self-resolves sooner. Anterior canal BPPV (<1%) is uncommon due to the orientation. Rare variants include multi-canal and bilateral multi-canal BPPV [15; 22].

Otoconia contact abnormally stimulates the cupula, triggering vertigo and nystagmus. BPPV is subtyped as [21; 32]:

- Canalolithiaisis: Head movements cause free-floating otoconia to stimulate the cupula
- Cupulolithiasis: Otoconia attach to the cupula, rendering it hypersensitive to linear acceleration and gravity

Canalolithiasis is much more common because the otoconia particulate mass required to exceed the symptomatic threshold is much lower than in cupulolithiasis (0.087 ug vs. 0.69 ug) [21; 33].

Recurrence and Cardiovascular Risk Factors

Cardiovascular comorbidities are significantly associated with, and potentially important risk factors for, recurrent BPPV. In a nationwide study of 2,682 patients with BPPV (mean age: 59.3 years; 61% female), the prevalence of high blood pressure (55.8%), hypercholesterolemia (38.6%), diabetes (17.7%), and family history of cardiovascular disease (49.4%) were significantly higher than the national averages. A high percentage of patients had hearing loss (42.9%), tinnitus (41.2%), or both (26.8%). The presence of hypertension, dyslipidemia, and pre-existing cardiovascular comorbidities were significantly related to recurrent BPPV episodes, and the presence of diabetes or thyroid/autoimmune disease was also relevant [34].

VIRAL OR BACTERIAL INFECTIOUS CAUSES

Vestibular Neuritis

Vestibular neuritis, the second most common cause of vertigo (after BPPV), is a viral or post-viral inflammatory disorder affecting the vestibular portion of the 8th cranial nerve. It most commonly affects persons 30 to 50 years of age, and men and women are equally affected. New cases are more common in the spring and early summer [10; 35]. Histopathologic nerve studies of these patients are consistent with a viral inflammatory etiology [15].

Vestibular neuritis is characterized by the sudden, acute onset of severe vertigo, nausea, vomiting, and gait instability without hearing loss, typically preceded by an upper respiratory tract infection [36]. The course and treatment of vestibular neuritis and viral labyrinthitis are similar; in both, the severity of acute vestibular symptoms can raise concerns of a central etiology, and the severity of vertigo, nausea, and vomiting reflects the severity of vestibular asymmetry [7; 15; 35].

 Copyright © 2019 NetCE

Viral Labyrinthitis

Labyrinthitis is an inflammatory disorder affecting both the vestibular and cochlear components of the 8th cranial nerve, caused by local or systemic viral or bacterial infection resulting in acute loss of vestibular and hearing function [10]. Viral labyrinthitis, the most common form of labyrinthitis, often results from varicella zoster, influenza, or herpes simplex-1 infection [36]. Sudden sensorineural hearing loss in the affected ear is due to pan-labyrinthine inflammation affecting the cochlea. The estimated prevalence of sudden sensorineural hearing loss is 1 case in 10,000 persons; up to 40% of these patients have prominent vertigo or disequilibrium symptoms, and up to 15% of patients presenting with positional vertigo have viral labyrinthitis [36].

The acute onset of sudden sensorineural hearing loss with severe vertigo, nausea, and vomiting can leave patients bedridden until the symptoms subside. Upper respiratory tract infection precedes the onset of vestibulo-cochlear symptoms in up to 50%. Vertigo usually resolves after several days to weeks, due to spontaneous partial recovery of vestibular function and central compensation of residual unilateral vestibular deficits. Unsteadiness and positional vertigo can persist for months, and return of hearing usually coincides with return of vestibular function [35; 36].

Herpes zoster oticus (Ramsay-Hunt syndrome) is labyrinthitis due to reactivation of a latent varicella zoster virus infection. Inflammation of the vestibulo-cochlear nerve causes vertigo and symptoms of deep, burning, auricular pain followed by eruption of a vesicular rash in the external auditory canal and concha. Symptoms usually improve after several weeks, but permanent hearing loss is common [15; 20].

Bacterial Labyrinthitis

What are the common symptoms of bacterial labyrinthitis?

Viral labyrinthitis should be differentiated from the more dangerous disorder of bacterial labyrinthitis, which occurs through direct bacterial invasion (suppurative labyrinthitis) or passage of bacterial toxins and other inflammatory mediators into the inner ear (serous labyrinthitis) [36; 37]. The bacteria that cause labyrinthitis are the same bacteria responsible for meningitis and otitis; potential bacterial causes include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus* species, *Staphylococcus* species, *Escherichia coli*, and *Mycobacterium tuberculosis* [36].

Profound hearing loss, severe vertigo, ataxia, and nausea and vomiting are common symptoms of bacterial labyrinthitis. Suppurative labyrinthitis almost always results in permanent, profound unilateral hearing loss (or bilateral loss with meningitis). Serous labyrinthitis results in unilateral, high-frequency hearing loss in the affected ear. Regardless of etiology, bacterial labyrinthitis accounts for 35% of all adult-onset cases of hearing loss [36].

MÉNIÈRE DISEASE

Ménière disease is a clinical syndrome of cochlear and vestibular symptoms with a prevalence of 34 to 190 per 100,000 population, an age of onset ranging from the third to seventh decades of life, and a slight female predominance. The odds of Ménière disease are greater among older subjects, persons of European descent, and severely obese persons. Common comorbid conditions in Ménière disease include arthritis, psoriasis, gastroesophageal reflux disease, irritable bowel syndrome, and migraine [15; 38].

The clinical features of Ménière disease are characterized by sudden, fluctuating, unilateral low- frequency sensorineural hearing loss with tinnitus and aural fullness and by spontaneous attacks of vertigo with nausea and vomiting, usually lasting hours [15]. Cochlear symptoms can occur between vertigo episodes. Vertigo is often more frequent in the first years of Ménière disease, but the clinical course is variable, with cochlear and vestibular symptoms taking years to develop in some patients. Bilateral sudden sensorineural hearing loss, migraine, BPPV, or systemic autoimmune disease develops in a subgroup of patients [38].

Ménière disease is idiopathic but is also associated with endolymphatic hydrops, a process whereby accumulation of excess pressure within the inner ear endolymphatic system causes fluctuating hearing loss, episodic vertigo, tinnitus, and aural fullness (i.e., pressure and uncomfortable fullness in the ears) [39]. An interaction of genetics and environmental factors is thought to determine the onset of Ménière disease. While associated with the accumulation of endolymph in the cochlear duct and vestibular organs, endolymphatic hydrops per se does not fully account for the frequency of vertigo attacks, progression of hearing loss, and other clinical features of Ménière disease [38].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Bárány Society recommends that familial Ménière disease should be considered if at least one other relative (first- or second-degree) fulfills all the criteria of definite or probable Ménière disease.

(http://www.jvr-web.org/images/55807-Lopez-Escamez.pdf. Last accessed September 18, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

BILATERAL VESTIBULOPATHY

Bilateral vestibulopathy (also called bilateral vestibular loss) has both central and peripheral processes. The cardinal symptoms of bilateral vestibulopathy reflect the pathophysiology, including motion-dependent postural vertigo with unsteady gait and stance that worsens in darkness and on uneven ground (vestibulo-spinal impairment), and oscillopsia with blurred vision when walking or moving the head (vestibulo-ocular reflex impairment). Patients with bilateral vestibulopathy are typically symptom-free when sitting or lying [40; 41].

The prevalence of bilateral vestibulopathy in the U.S. adult population is 28 per 100,000. The age distribution ranges from youth to old age, depending on etiology, and the mean age at diagnosis is 50 to 60 years. About 60% of patients develop bilateral vestibulopathy slowly and progressively; depending on etiology, 40% of patients have a clinical course marked by episodes of dizziness leading incrementally to bilateral loss of vestibular function [41; 42].

Bilateral vestibulopathy involves atrophy of the hippocampus, with associated impairments in spatial memory and navigation. It is the most frequent cause of motion-dependent postural vertigo in older patients. The three most frequently identified causes of bilateral vestibulopathy are ototoxic aminoglycosides, bilateral Ménière disease, and meningitis, but most cases are idiopathic [40; 41].

A connection between bilateral vestibulopathy and degenerative cerebellar diseases has been established. A syndrome comprised of bilateral vestibulopathy, sensory axonal polyneuropathy, cerebellar ataxia, and oculomotor disturbances accounts for around 30% of cases previously considered idiopathic [40; 43]. Bilateral vestibulopathy can be severely debilitating but is partially reversible with vestibular rehabilitation. It is important for clinicians not to overlook this condition when assessing patients with complaints of dizziness/vertigo [44].

VESTIBULAR PAROXYSMIA

Vestibular paroxysmia is characterized by recurrent spontaneous vertigo attacks that are brief (several seconds up to one minute), and frequent (up to 30 per day) [45]. In one study, vestibular paroxysmia accounted for 3.7% of 17,718 consecutive outpatients in a multidisciplinary vertigo and balance disorders center. Men are affected twice as often as women, and the bimodal age of onset peaks in early childhood and again between 40 and 70 years of age [46].

Vestibular paroxysmia symptoms are triggered by neurovascular compression involving the anterior inferior cerebellar artery and the 8th cranial nerve. More than 95% of cases show vessel-nerve contact at the exit point of the 8th nerve from the brainstem, but the finding is nonspecific because it may be seen in healthy, asymptomatic adults as well [47].

CENTRAL CAUSES OF DIZZINESS AND VERTIGO

The vestibular nuclei and its connections to cerebellar, brainstem, spinal cord, and higher cortical structures comprise the central vestibular system. Dizziness, vertigo, ataxia, or disequilibrium can result from pathologies involving central vestibular structures, the most common of which are migraine-related vestibulopathy, brainstem strokes, head trauma, multiple sclerosis, and cerebellar degeneration [48].

Vertigo, vestibular dysfunction, and anxiety disorders are now recognized as co-factors, and the inter-relationship is substantial. Dizziness and vertigo are associated with diverse systemic disorders, trauma, and toxic exposures. Etiologies in psychiatric and systemic disorders are complex and diffuse.

Central abnormalities cause about 20% of dizziness complaints, and patients may present with disequilibrium or ataxia rather than vertigo. Dizziness/vertigo may be the sole presenting symptom of an impending cerebrovascular event origination in the brainstem or cerebellum [7]. In these presentations, distinguishing benign from potentially or imminently dangerous cerebrovascular causes has been the focus of extensive research effort.

VESTIBULAR MIGRAINE

What is the most common cause of recurrent spontaneous vertigo attacks?

Vestibular migraine is the most common central cause of recurrent spontaneous attacks of vertigo. "Vestibular migraine" is the preferred name for this disorder, because patients may experience a range of vestibular symptoms not limited to vertigo (e.g., dizziness, nausea, vomiting) [19; 49].

Vestibular migraine accounts for 7% of patients seen in dizziness clinics and 9% of patients seen in headache clinics, but it remains underdiagnosed [49]. It is three times more common in women and occurs most often between 20 and 50 years of age. A family history of migraine is a risk factor, and vestibular migraine may involve a genetic susceptibility to enhanced excitability during sensory information processing, which induces interactions of vestibular and pain pathways [7; 49].

Pain and vestibular sensory inputs converge in brainstem structures that modulate pain sensitivity and anxiety responses to pain and vestibular signaling. Vestibular stimulation activates some higher cortical regions involved in pain perception. Vestibular and pain pathways also overlap at brainstem and thalamic levels. This may explain, in part, the frequent clinical overlap of migraine (including vestibular migraine), balance, and anxiety disorders [49; 50].

 Copyright © 2019 NetCE

Vestibular migraine is a clinical diagnosis in which central and peripheral mechanisms arise from genetic and environment interactions. Mechanistic interactions cause excessive sensitivity to pain perception (e.g., headache, allodynia), hearing (e.g., phonophobia), vestibular stimulation (e.g., vertigo, motion sickness, visual vertigo), vision (e.g., photophobia), and sense of smell (e.g., osmophobia) [49; 50; 51].

Vestibular migraine is diagnosed primarily by patient history and exclusion of alternative causes; neurologic exams performed between episodes generally show normal findings [49]. The migraine may occur with episodic vertigo, chronic motion sensitivity, or other vestibular symptoms. Vertigo and motion sickness, with or without headache, is the common presentation, and some patients report mild, transient auditory symptoms of tinnitus, muffled hearing, or ear pressure [15; 19].

CEREBROVASCULAR ETIOLOGIES

Patients with potentially serious or life-threatening stroke may present with vestibular symptoms without other focal neurologic signs. This acute presentation is linked to stroke involving one of several branches that supply the brainstem, cerebellum, or inner ear. Early differentiation is an area of intense research focus. Early recognition of isolated vertigo as a stroke sign allows specific intervention and secondary prevention. Misdiagnosis of stroke-related vertigo as a peripheral cause may result in significant morbidity or mortality, and overdiagnosis of stroke as peripheral vertigo leads to expensive and unnecessary workups, medication, and hospital admissions [52; 53].

Vertebrobasilar Artery Territory (Posterior Circulation) Infarcts or Strokes

Around 20% of all ischemic events occur in the vertebrobasilar artery territory, with dizziness/vertigo the sole presentation in up to 33% of patients. Inferior cerebellar and small brainstem infarctions are an increasingly recognized cause of isolated vertigo, and transient isolated vertigo is a common manifestation of vertebrobasilar artery ischemia. Vertebrobasilar artery transient ischemic attacks (TIAs) typically last eight minutes on average [52; 54]. Several syndromes are associated with TIAs, ischemia, or infarcts in vertebrobasilar artery territories (e.g., the brainstem, cerebellum) [48].

Numerous arteries extend from the posterior inferior cerebellar artery to supply the medial, lateral, and dorsal aspects of the medulla. Vertigo is more frequent in posterior inferior cerebellar artery strokes, and these are the most common cerebellar infarcts [55]. Dizziness/vertigo is one of the most common symptoms of cerebellar ischemic stroke. A large prospective study showed 11% of patients with cerebellar infarction had isolated vertigo, of whom 96% had an infarct in the medial branch of the posterior inferior cerebellar artery [56].

Medial Medullary Infarcts

Medial medullary infarctions usually cause a vertiginous labyrinthian syndrome that mimics peripheral vestibulopathy. Severe vertigo and nystagmus are prominent, and some patients describe feeling as if being pulled to the ipsilateral side by a magnet [53].

Lateral Medullary Infarcts

The vestibular nuclei are more vulnerable to ischemia than other structures in the posterior fossa, and ischemia of the lateral medulla (including the vestibular nuclei) may be a common mechanism of isolated vascular vertigo [52]. Wallenberg syndrome describes a lateral medullary infarction that presents with a range of focal neurologic signs.

Vestibulo-cerebellar symptoms/signs are almost always present, because lateral medullary infarcts involve the vestibular nuclei and their connections. The symptoms/signs include dizziness or disequilibrium; acute vertigo, nausea, or vomiting; ipsilateral facial pain, numbness, and ataxia (falling to the side of the infarct); and decreased contralateral pain and thermal sensitivity. The nystagmus has horizontal and rotational components [48; 53; 54].

Dorsal Medullary Infarcts

Less prevalent than medial or lateral medullary infarction, dorsal medullary infarcts typically cause dizziness/vertigo, imbalance, and ocular motor abnormalities. This is because the dorsal medulla also contains the vestibular nuclei and other structures that relay and process vestibular and ocular motor signals [57].

Anterior Inferior Cerebellar Artery Distribution

The anterior inferior cerebellar artery supplies the lateral pons and branches off to form the internal auditory artery, which irrigates the cochlea and vestibular labyrinth. The labyrinth is especially vulnerable to ischemia, because the internal auditory artery is an end-artery with minimal collaterals. Isolated acute audio-vestibular loss may herald an impending anterior inferior cerebellar artery territory infarction. Aortic arch occlusion causes loss of auditory and vestibular function [48; 52].

Pontine syndrome is a partial pontine ischemia produced by anterior inferior cerebellar artery occlusion, characterized by vertigo, tinnitus, and hearing loss [48; 54].

STRUCTURAL ABNORMALITIES AND LESIONS

Malformations or lesions that affect the vestibular system can cause dizziness or vertigo, as can any process that leads to acute vestibular asymmetry. The brain may adapt to this asymmetry over time to prevent or diminish vertigo, but imbalance may persist when vestibulo-cerebellar pathways are impacted. For example, sudden-onset vertigo is more likely with stroke, but less likely with a slow-growing acoustic neuroma (a vestibular tumor) because central adaptation to the asymmetry is gradual and imperceptible [15].

Superior Canal Dehiscence Syndrome

Superior canal dehiscence syndrome is caused by an abnormal opening (dehiscence) in the thin bony roof of the superior semicircular canal. This is thought to be related to congenital thinning of the temporal bone and occurs in 0.1% of the population. Development of the bony opening renders the membranous labyrinth unusually susceptible to changes in sound and pressure. In addition to dizziness and sensitivity to loud noises, patients with superior canal dehiscence syndrome experience autophony, whereby one's voice, breathing, or bodily sounds are excessively audible [58]. The dizziness/vertigo induced by sound and pressure stimuli can be associated with auditory symptoms of conductive or mixed hearing loss [59].

Chiari Malformation

A Chiari malformation is defined as descent of the cerebellar tonsils ≥5 mm past the foramen magnum [19]. This occurs when the lower part of the cerebellum does not fully migrate rostrally during fetal development. Compression of the cerebellum from this condition may lead to occipital headaches, vertigo, nystagmus, and ataxia in early childhood or later in life [15]. Patients also commonly describe occipital and neck pain provoked by physical activity or maneuvers that increase intracranial pressure [19].

Symptomatic Chiari malformations should be referred for neurosurgical evaluation and considered for posterior fossa decompression. Asymptomatic Chiari malformations can be discovered incidentally during MRI for dizziness from a different etiology. Asymptomatic patients should be spared the risks of surgery [19].

Acoustic Neuroma (Vestibular Schwannoma or Schwann Cell Tumors)

Acoustic neuromas are tumors of the vestibular portion of the 8th cranial nerve, diagnosed in roughly 3,000 cases annually. Acoustic neuromas can expand and compress surrounding structures along the brainstem, potentially leading to sensorineural hearing loss and vertiginous symptoms [20; 60].

DEMYELINATING AND NEURODEGENERATIVE DISORDERS

Multiple Sclerosis

Multiple sclerosis (MS), an idiopathic demyelinating disorder of the central nervous system (CNS), is considered an autoimmune disease most likely caused by an autoantigen to a myelin protein [48]. MS has an annual incidence of 10 to 80 cases per 100,000 individuals in the United States and affects twice as many women than men [60].

CNS demyelinization usually occurs in the white matter, where plaque formation disrupts signal conduction and leads to symptoms [48]. Demyelinating plaques that develop in central vestibular pathways may cause recurrent episodes of vestibular symptoms, especially during illness and with heat exposure (Uhthoff phenomenon). The plaques may be visible on MRI [19; 20].

Vertigo is the presenting symptom at onset in 5% of MS cases, and more than 50% of patients present with vertigo at some point in the disease course. MS can mimic an 8th cranial nerve lesion when plaque develops in the entry of the nerve root in the brainstem to produce vertigo and horizontal nystagmus [48].

MS may present with dizziness, vertigo, or imbalance, especially with brainstem or cerebellum lesions that affect the vestibular system; these lesions may also result in nystagmus, ataxia, slurred speech, and diplopia. Despite the increased risk of CNS vertigo in patients with MS, non-MS (peripheral and central) causes (e.g., BPPV, vestibular migraine) can co-occur [15].

Parkinson Disease and Parkinson-Plus Syndromes

Dizziness may be a manifestation of many neurodegenerative disorders. At presentation, patients with Parkinson disease may describe the shuffling or festinating gait as being "dizzy" or "off balance." Medications such as levodopa or dopamine agonists (e.g., pramipexole, ropinirole) may cause orthostatic hypotension, and hence presyncopal dizziness [19].

The Parkinson-plus syndromes (e.g., multiple system atrophy, dementia with Lewy bodies) often cause many symptoms that are construed as "dizziness." Multiple system atrophy causes dysautonomia (causing orthostatic presyncope or syncope), vertigo, nystagmus (causing oscillopsia), and/or cerebellar findings (leading to gait ataxia). Progressive supranuclear palsy often presents with falls and complaints of imbalance; loss of downgaze often causes imbalance when descending stairs [19].

 Copyright © 2019 NetCE

Cerebellar Vertigo Syndromes

Neurodegenerative and hereditary diseases of the cerebellum often lead to postural vertigo, gait disorders with ataxia, and cerebellar oculomotor disorders such as saccadic dysmetria, gaze saccades, gaze nystagmus, and downbeat nystagmus [61].

Episodic ataxia type 2 is a rare but important disorder to identify because the random attacks of vertigo, ataxic gait, and slurred speech lasting minutes to days often respond dramatically to acetazolamide. The onset of recurrent episodes may occur in childhood or early adulthood, but the condition is often undiagnosed into late adulthood. This disorder is due to a voltage-sensitive calcium channel mutation [15].

PERSISTENT POSTURAL PERCEPTUAL DIZZINESS

Persistent postural perceptual dizziness (PPPD) develops when a precipitating condition (typically an acute vestibular event, vestibular migraine, panic attacks, or anxiety with prominent dizziness) occurs in individuals with a maladaptive behavioral response to the acute symptoms [62]. In this way, PPPD is a new diagnostic entity that bridges previous knowledge gaps by connecting persistent non-vertiginous dizziness, perceptual hypersensitivity, and chronic anxiety [15; 62].

PPPD may be a highly prevalent cause of chronic non-vertiginous dizziness. The population and primary care prevalence is not yet known, but the female-to-male ratio is 5:1. PPPD symptoms are often worsened by sleep deprivation and stress but not by head motion to the degree seen with most vestibular disorders [15; 62].

The central etiology relates to behavioral factors, neurotransmitter function, and other probable CNS mechanisms [15]. Brain imaging of patients with PPPD shows reduced connectivity in multisensory vestibular processing and spatial cognition, with increased connectivity between visual and emotional processing. Dizziness burden, anxiety, and depression correlate with connectivity in clinically relevant brain regions [63]. PPPD may linger following minor head injury and become entwined with other symptoms of post-concussive syndrome [15].

MAL DE DÉBARQUEMENT SYNDROME

A transient experience of "sea legs" after returning to land from riding on a boat is not uncommon, but in mal de débarquement syndrome it persists for weeks, months, or years. Mal de débarquement syndrome is an uncommon vestibular disorder in which a sense of rocking first appears soon after disembarking and is most common in women. Travel by aircraft or automobile can also trigger the persistent unsteadiness. Symptoms typically abate during passive motion (e.g., a boat or car ride) but resume when motion ceases. The cause is unknown, but it may be a disorder of the vestibular velocity storage mechanism with a limited adaptive ability [15; 62].

SYSTEMIC ETIOLOGIES

Dizziness and vertigo are associated with systemic diseases or conditions as symptoms, comorbidities, risk factors, or shared pathophysiologic pathways. These most commonly involve hemodynamic (orthostatic hypotension), metabolic (diabetes), cigarette smoking, and cardiovascular origins.

ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is typically defined by a sustained decline in blood pressure of at least 20 mm Hg systolic or 10 mm Hg diastolic within three minutes of standing, with symptoms of lightheadedness or presyncope on arising. Vertigo is a common and under-appreciated symptom [8].

Orthostatic hypotension is common in older people and a frequent complication of (excessive) hypertensive medication. Such patients experience postural dizziness without documented syncope based on transient reductions in cerebral blood flow. Orthostatic hypotension may occur 5 to 30 minutes after remaining asymptomatic in the upright position, or when orthostatic vital signs have been normal. It may be missed as a cause of periodic syncope or presyncopal dizziness [15].

DIABETES

Vestibular dysfunction is a complication of type 2 diabetes, with reported rates 70% higher compared with age-matched controls. Both central and peripheral vestibular dysfunction are observed in type 1 and type 2 diabetes. Hypertension mediates 42% of the association between type 2 diabetes and BPPV, suggesting that hypertension provides the mediating pathway for diabetes' impact on the vestibular system [177].

CIGARETTE SMOKING

In one study, the association between peripheral vestibular disorders and smoking was examined in patients (mean age: 65.3 years) treated for hypertension, dyslipidemia, or diabetes in primary care and followed over one year for new peripheral vestibular disorder events [64]. Compared with never-smokers, the risk of new-onset peripheral vestibular disorder was 2.22 times greater for ever-smokers and 2.70 for all ever-smokers with ≥30 pack-years. Compared with male never-smokers, the risk of new onset peripheral vestibular disorder was 4.41 greater for male ever-smokers with ≥30 pack-years. There were too few female heavy smokers to compare against female never-smokers [64].

VESTIBULAR IMPAIRMENT, ANXIETY, AND PERCEPTION

Clinically relevant vestibular system interactions with traumatic stress, depressive disorders, and other psychiatric disorders have been described. However, vestibular-anxiety interactions are the most extensively studied and compelling and will be the focus of this section.

Anxiety disorders account for 8% to 10% of cases with vestibular symptoms as primary complaints [65]. In patients presenting with dizziness concerns, the rates of panic disorder are 5 to 15 times greater than the general population. Patients with panic disorder frequently experience significant dizziness and often demonstrate vestibular dysfunction [66].

The high co-occurrence of vertigo and anxiety has been described since antiquity [51]. By the late 1800s, dizziness and vertigo, anxiety, autonomic arousal, appraisal of spatial orientation, and threat assessment were appreciated as core contributors to agoraphobia; otologic disease was found to precipitate agoraphobia in patients with anxiety. As otology, neurology, and psychiatry matured into separate specialties in the early 20th century, agoraphobia became a psychiatric disorder and lost its spatial and motion context [62; 67].

While traditional medical teaching describes a narrow range of vestibular system functions (e.g., gaze stability, balance) and dysfunctions (e.g., dizziness, unsteadiness, vertigo), vestibular involvement in brain processes beyond balance, spatial orientation, and gait is established. The inter-relationship of anxiety and balance disorders is being rediscovered more than a century later [68; 69; 70].

Increasingly demonstrated is the extent of multi-directional connectivity and interaction between threat/anxiety, vestibular, visual, and somatosensory systems, and how this helps explain the shared pathophysiology, clinical features, and prevalent comorbidity [71]. As such, it is important to assess for, and treat when present, anxiety disorders, cognitive impairment, and perceptual disturbances in patients with dizziness/vertigo complaints [50; 68; 69]. The suggestion is made that dichotomous thinking (structural disease vs. "emotional issues") should be discarded in order to effectively assess vestibular, psychiatric, and perceptual dysfunction. Each of these domains should be addressed simultaneously for favorable treatment outcomes [72].

SHARED CLINICAL FEATURES

Patients with vestibular or balance disorders often have anxiety symptoms. Likewise, patients with anxiety disorders often show vestibulo-ocular and/or peripheral vestibular dysfunction [73]. Vestibular and balance abnormalities are especially common in panic disorder with agoraphobia [70].

Chronic anxiety and anxiety disorders may be causes or complications of vestibular symptoms or disorders. These psychiatric disorders affect 30% to 50% of patients who seek specialist care for vestibular symptoms, and they adversely affect the treatment outcomes of patients with vestibular disease, especially when unrecognized [62; 71]. Vestibular function is linked to emotional states through complex bidirectional interactions; vertigo worsens emotional symptoms, and emotional states can amplify perceptions of vertigo or disequilibrium [69].

ANXIETY, BALANCE, AND VESTIBULAR INTERACTIONS

Anxiety can impair ocular motor reflexes and gaze control, which may contribute to visual and visual-vestibular syndromes. Anxious states can amplify a normative gaze bias toward potentially threatening stimuli in the visual field, which, in patients with social anxiety disorder, may drive hypervigilance-avoidance gaze patterns. The impairing effect of anxiety on gaze control reduces gaze stability on visual targets, which may underlie dizziness and visual symptoms in PPPD [73; 74].

Exposure to heights reflexively increases body sway in normal subjects by reducing visual feedback to body sway (in the absence of motion). Body sway is more pronounced in subjects with height phobia, and anxiety-related gaze diversion may increase gait instability in patients with fear of falling [74; 75].

Space-motion discomfort describes symptoms of uneasiness over spatial orientation and hyperawareness of motion stimuli. In affected individuals, space-motion discomfort is triggered by movement in visually rich environments and exposure to moving or patterned objects while stationary. It is especially prevalent in patients with panic disorder and agoraphobia; persons with panic symptoms often become destabilized under conflicting sensory conditions. Visual vertigo and other situation-specific interactions between balance and anxiety may be part of a broader space-motion discomfort profile [62; 73; 76].

 Copyright © 2019 NetCE

DISRUPTED MULTISENSORY INTEGRATION

The vestibular system maintains equilibrium through vestibular spinal reflexes, stabilizes visualization through the vestibular-ocular reflex, and contributes to spatial orientation [77]. Accurate perception of gravity and maintenance of spatial orientation, balance, and gait rely on brain integration of visual, vestibular, proprioceptive, and somatosensory signals and cognitive processes [78].

The brain normally resolves mismatched sensory information by updating and realigning the internal spatial representation of the body with the surrounding space. Impairment of one sensory signal is compensated by reweighting of intact sensory inputs [62; 77]. Unsuccessful reweighting impairs multisensory integration, leading to incongruity between visual and vestibular information and visual-vestibular sensory mismatch. This can elicit an erroneous cortical representation of the body within the surrounding space, producing spatial disorientation, anxiety, dizziness, balance problems, and increased risk of falls [62; 77; 78; 79].

Visual Dependence

Visual dependence is an over-reliance on visual information to maintain spatial orientation, which compensates for vestibular dysfunction that impairs multisensory integration. Space-motion discomfort, a prominent feature resulting from the visual-vestibular conflict, may cause symptoms of imbalance, discomfort, anxiety, or phobic avoidance in situations where moving, complex, or conflicting visual environments trigger intense dizziness/vertigo symptoms [70; 79].

Depersonalization and Derealization

Depersonalization and derealization are perceptual abnormalities, described primarily from the psychiatric perspective for more than a century. Depersonalization (feeling detached, numb from one's emotions, experiences), derealization (objects, people, and surroundings experienced as unreal, distant, artificial, lifeless), and intact reality testing are symptoms of depersonalization/derealization disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [80; 81]. The DSM-5 also lists derealization and depersonalization as potential panic attack symptoms in the diagnostic criteria for panic disorder [81].

Trauma history and anxiety disorders are prevalent cofactors and antecedents of depersonalization/derealization. Phencyclidine or cannabis use can trigger acute symptoms [82]. Derealization symptoms are particularly distressing, if not profoundly intolerable; an anxious or panic response can amplify depersonalization/derealization symptoms, creating a vicious cycle [80].

Patients diagnosed with depersonalization/derealization disorder have high rates of past-year inpatient hospitalization (25.6%) and ongoing outpatient psychotherapy (40.4%). Depersonalization/derealization disorder has been described as highly chronic, severely underdiagnosed, and often refractory to pharmacotherapy and psychotherapy [83].

The psychiatric perspective is important, but inadequate by failing to consider recent evidence implicating vestibular dysfunction, impaired multisensory integration, and sensory mismatch in depersonalization/derealization [84; 85]. Vestibular inputs provide a frame of reference within which spatial information from other senses is interpreted. Depersonalization/derealization associated with vestibular dysfunction is a consequence of a sensory mismatch between disordered vestibular input and other sensory signals of orientation, creating a misleading frame of reference and impaired bodily representation in the cortex. This leads to a perception of disembodiment and other "unreal" perceptions [84; 85; 86].

Stimulation of semicircular canals or otoliths can provoke depersonalization/derealization symptoms in healthy volunteers without a history of depersonalization/derealization [86]. However, depersonalization/derealization symptoms in vestibular patients with anxiety are more frequent, more severe, and qualitatively distinct from symptoms in patients without anxiety. Anxiety is essential to the appearance and intensity of depersonalization/derealization symptoms in vestibular patients [87].

Out-of-Body Experiences

Out-of-body experiences are states in which the individual experiences the center of awareness as located outside his or her physical body, with the sensation of seeing the environment from this elevated vantage point. Persistent vestibular dysfunction disrupts the integration of visual, somatosensory, and vestibular signals. Perceptual incoherence, a byproduct of the resultant visual-vestibular mismatch, can produce an out-of-body experience, with anxiety a significant co-factor in out-of-body experience etiology. In non-dizzy persons, out-of-body experience is associated with depersonalization or derealization symptoms [88].

COGNITIVE FUNCTION

Vestibular input activates a broad neural network in the cortex for visuospatial processing and memory. Vestibular function is strongly linked to visuospatial ability—how the mind organizes and understands two- and three-dimensional space. Impaired vestibular input can fundamentally change one's mental representation of, and awareness of one's position in, three-dimensional space [69].

Vestibular dysfunction is also implicated in impaired attention, cognitive processing ability, memory, and executive function [69]. This is especially relevant in the elderly, for whom cognitive impairment from vestibular dysfunction is broader and more diffuse. It should be considered in any older patient with dizziness or vertigo [89].

POST-TRAUMA OR TOXIC EXPOSURE

POST-CONCUSSIVE AND CERVICOGENIC VERTIGO

Patients with post-concussive syndrome or cervicogenic dizziness following a whiplash can experience chronic dizziness with headache, insomnia, cognitive symptoms, or mood lability [62].

Post-Concussion Syndrome

In the United States, there are approximately 3.8 million sports-related concussions annually in adolescents and adults. Concussion, the mildest form of traumatic brain injury (TBI), is a transient functional disorder caused by direct trauma, rapid acceleration-deceleration of the head, or blast forces. Post-concussion syndrome persists beyond three months in up to 20% of affected individuals [90].

Headache and dizziness are common symptoms. Other symptoms include light and sound sensitivity, nausea, tinnitus, cognitive dysfunction (mental fog), problems with visual focus, sleep changes, depression, anxiety, and irritability. Dizziness may be due to the direct CNS effects of the trauma (e.g., axonal injury, other microstructural damage), vestibular migraine, or neuropsychiatric disorders (e.g., anxiety, depression, post-traumatic stress disorder). Post-concussion BPPV is not uncommon. A detailed history and examination are crucial when assessing dizziness in these patients, because treatment should address the underlying etiology [91; 92].

Mild TBI

Balance disorders, migraine, and anxiety are also components of mild TBI that appear following exposure to blunt-force or blast trauma, along with symptoms of headache, nausea, vomiting, dizziness/balance problems, fatigue, sleep disturbances, and difficulty with memory or concentration [90; 92]. Dizziness and headache are reported in more than 70% of cases presenting acutely or chronically post-exposure; vertigo emerges sub-acutely. Other significant sequelae are hearing loss, emergent and delayed post-traumatic balance disorders, and chronic migrainous disorders without radiologic evidence of damage, often accompanied by tinnitus and sensitivity to light or sound [50].

Patients with chronic (at least six months) post-traumatic head injury vestibular symptoms (e.g., imbalance, dizziness) show high rates of multiple peripheral and central vestibular disorders. Despite expert neuro-otologic management, 20% of patients have persistent vestibular symptoms at two years. Treatment-resistant vestibular symptoms in these patients may result from brain trauma-induced impairment of brain plasticity-mediated repair mechanisms [93].

Cervicogenic Vertigo

Cervicogenic dizziness is characterized by imbalance, unsteadiness, disorientation, neck pain, limited cervical range of motion, and headache. It is closely related to changes in cervical spine position or cervical joint movement. Common etiologies are post-whiplash injury and inflammatory, degenerative, or mechanical cervical spine dysfunction. The cause of imbalance, unsteadiness, and disorientation symptoms is suggested to involve pain, faulty cervical proprioceptive inputs, and disrupted signaling from upper cervical proprioceptor to vestibular nuclei [94].

Cervicogenic dizziness is diagnosed after mimics are ruled out, including central and peripheral vestibular disorders, vestibular migraine, labyrinthine concussion, cervical arterial dysfunction, and whiplash-associated disorder [94].

EXPOSURE TO TOXINS

Lead or mercury exposure can be ototoxic and may cause vertigo through temporary or permanent damage to the inner ear or auditory nerve [95].

ADVERSE DRUG EFFECTS

Dizziness or vertigo can occur as a direct side effect of medication that resolves after discontinuation without cochleovestibular damage, or it may develop (and persist) secondary to cochleo-vestibular damage (ototoxicity).

SIDE EFFECTS

The list of drugs that may cause vertigo or dizziness is extensive and diverse. Medications consistently associated with dizziness include the antihypertensive drugs amlodipine and hydrochlorothiazide; the antibiotics ciprofloxacin, amoxicillin, and clavulanic acid; pantoprazole (a proton pump inhibitor); aripiprazole (an atypical antipsychotic); and atazanavir (a protease inhibitor). Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline can induce vertigo or dizziness as side effects or with abrupt cessation; mirtazapine may cause dizziness side effects [95].

 Copyright © 2019 NetCE

Antiepileptic drugs in particular are linked to adverse effects on auditory or vestibular systems that may be reversible or irreversible. Even at therapeutic dose ranges, long-term treatment with oxcarbazepine, carbamazepine, lamotrigine, phenytoin, valproate, gabapentin, or vigabatrin may result in auditory, central, and/or peripheral vestibular dysfunction [96].

OTOTOXIC DRUGS

What are the most vestibulotoxic of all ototoxic medications?

Ototoxic drugs can damage cochleo-vestibular structures, which may result in hearing loss, tinnitus, dizziness, or disequilibrium [97]. Cochlear damage can present acutely as tinnitus. Early hearing loss, which patients may not recognize, manifests in the highest frequencies (>4,000 Hz). With progression, the lower frequencies are affected, and patients may become profoundly deaf if the drug is continued. Stopping the drug early, before extensive damage, may prevent further loss. Partial recovery of auditory thresholds is possible, but the loss is usually permanent [97; 98].

Vestibular toxicity typically includes imbalance and visual symptoms. As with bilateral vestibulopathy, imbalance is worse in the dark or situations in which footing is uncertain; oscillopsia occurs when the head is moving. Patients do not present with nystagmus or vertigo complaints, because vestibulotoxicity is bilateral [97].

Ototoxicity is linked to more than 100 drug classes. The best-known and most ototoxic are aminoglycosides, amiodarone, macrolides, vancomycin, loop diuretics, antineoplastic agents, salicylates, and antiseptics.

Aminoglycosides

Aminoglycosides are the most vestibulotoxic of all ototoxic drugs. The introduction of streptomycin in 1944 for treatment of tuberculosis brought ototoxicity to clinical attention, as a substantial number of treated patients developed irreversible cochleo-vestibular dysfunction [97; 98].

The aminoglycosides remain widely used and differ in cochleo-vestibular toxicity. Kanamycin, amikacin, neomycin, and dihydrostreptomycin are preferentially cochleotoxic. Gentamicin affects both cochlear and vestibular systems but is primarily vestibulotoxic, as are streptomycin, tobramycin, and netilmicin [97; 98].

The onset or progression of hearing loss can occur long after cessation of treatment, because aminoglycosides are cleared more slowly from inner ear fluids than from serum. Patients should be monitored for vestibulotoxic effects up to six months after discontinuation [97; 98].

Amiodarone

Amiodarone is a widely used antiarrhythmic drug. Reports of amiodarone-induced vertigo and gait instability followed its introduction in the 1980s, and the drug was first implicated in bilateral vestibulopathy causality in 2017. The prevalence of bilateral vestibulopathy is as high as 81 per 100,000. Most cases are idiopathic, and amiodarone may account for a substantial proportion of bilateral vestibulopathy with unexplained causation [99].

Macrolides

Erythromycin has been sporadically linked to reversible ototoxicity in patients with ototoxic risk factors. Azithromycin and clarithromycin have also been suggested as possibly ototoxic [97].

Vancomycin

Vancomycin is a glycopeptide antibiotic introduced in the 1950s and commonly used for efficacy in methicillin-resistant staphylococcal infections. Ototoxicity is reported in patients with other risk factors, but vancomycin monotherapy at therapeutic doses has not shown ototoxicity [97].

Loop Diuretics

Loop diuretics are used for treating congestive heart failure, renal failure, cirrhosis, and hypertension. The most effective and widely used (i.e., ethacrynic acid, furosemide, and bumetanide) can cause ototoxicity [97].

Antineoplastic Agents

Antineoplastic agents most associated with ototoxicity are the platinum-based compounds cisplatin and (to a lesser extent) carboplatin. Ototoxicity and nephrotoxicity are dose-proportional with both compounds [97].

Salicylates

Salicylate (aspirin) can produce tinnitus and a generally reversible flat sensorineural hearing loss at low doses, especially in elderly patients [97].

Antiseptics

Some antiseptics used for surgical preparation are ototoxic. Povidone-iodine is safe for middle ear surgeries. However, chlorhexidine is toxic if it reaches the inner ear and should not be used, and VoSol and Gentian violet also show ototoxicity [100].

DIAGNOSIS: THE "TIMING AND TRIGGERS" WORKUP

What do targeted examinations emphasize to detect and localize the underlying dizziness/vertigo pathology?

As mentioned, the prevailing clinical model in dizziness and vertigo is being replaced by the "timing and triggers" approach to streamline the differential diagnosis, increase diagnostic accuracy, and reduce unnecessary imaging tests and misdiagnosis.

Publications have brought into focus the misdiagnosis of patients with stroke who present with isolated dizziness. The "timing and triggers" approach is shown to reduce this highly concerning problem largely resulting from [8]:

- Over-reliance on the symptom quality approach
- Lack of familiarity with key physical exam findings
- Overweighting traditional stroke risk factors for patient screening (e.g., age, vascular risk factors) and not considering stroke in younger patients
- Over-reliance on CT

The "timing and triggers" approach departs from the Drachman-Hart model by de-emphasizing patient descriptions of symptom quality, dropping presyncope and lightheadedness as dizziness and vertigo classes, and limiting use of the vague term "lightheadedness" [2; 7]. The term "dizziness" is used as a generic descriptor for disturbed balance or spatial orientation, vertigo, lightheaded, spinning, rocking, and others.

Accurate diagnosis is an essential precondition for effective treatment of dizziness and vertigo, best ensured by defining the rapidity of onset, the context, associated symptoms, intermittent or persistent nature of dizziness, and triggers of intermittent symptoms during patient history-taking. This is called the "timing and triggers" diagnostic workup. The workup is structured using the algorithm Triage-TiTrATE-Test [8; 37; 101]:

- Triage: Identify dangerous causes by noting the presence of prominent associated symptoms, abnormal vital signs, altered mental status, or ancillary test results.
- Timing: In the history of presenting illness, classify the pattern of dizziness attacks as episodic, acute, or chronic in duration.
- Triggers: In the history and review of systems, seek an underlying pathophysiologic mechanism by searching for obvious triggers or exposures.
- Targeted exam: Differentiate benign from dangerous causes within a timing-trigger category by using specific exam findings, emphasizing a targeted eye movement exam.
- Test: Choose the best laboratory or imaging test when clinically relevant uncertainty remains about a dangerous cause that has not been ruled out.

The timing and triggers history of the TiTrATE algorithm divides patients into six vestibular syndrome categories [8; 37]:

- Acute vestibular syndrome (AVS)
  - Postexposure (traumatic/toxic) (t-AVS)
  - Spontaneous (s-AVS)
- Episodic vestibular syndrome (EVS)
  - Triggered (t-EVS)
  - Spontaneous (s-EVS)
- Chronic vestibular syndrome (CVS)
  - Context-specific (t-CVS)
  - Spontaneous (s-CVS)

In this context, "vestibular" refers to vestibular symptoms and not etiology. Vestibular symptoms include vertigo, dizziness, nausea, vomiting, and nystagmus [49].

The large differential diagnosis of potential dizziness etiologies is daunting to many clinicians. Triage-TiTrATE-Test greatly streamlines this process such that every forward step eliminates potential etiologies, substantially narrows the range, and by the final step, an accurate diagnosis is already evident or confirmed by referral for specialized testing [8]. This differential diagnosis process has been referred to as a funnel approach [37].

TRIAGE

Some patients with a primary symptom of dizziness have obvious associated symptoms (e.g., gastrointestinal bleeding) or context (e.g., new antihypertensive medications, anticonvulsant toxicity), abnormal vital signs, altered mental status, and/or ancillary test results that usually point to a likely diagnosis. These potential medication, toxicity, metabolic, cardiac, or psychiatric etiologies of dizziness are examined and patients are treated or referred for further evaluation as needed [10; 37].

Other dizziness, medical, and major neurologic etiologies lack prominent associated features, but can be ruled out by assessing [20]:

- Neurologic history
- Recent viral or bacterial infection
- Patient medication list
- Social history for alcohol and substance use
- Psychiatric history

 Copyright © 2019 NetCE

Important associated symptoms to note include headache, hearing loss, tinnitus, nausea and vomiting, impaired vision, focal weakness, and difficulty walking. The severity of impairment should be assessed by asking about impact on work, driving, and recreational and social functioning [11].

Review of systems should seek symptoms of causative disorders, including upper respiratory infection symptoms (inner ear disorders); chest pain and palpitations (cardiovascular disease); dyspnea (pulmonary disease); dark stools (anemia from GI blood loss); and weight change and heat or cold intolerance (thyroid disease) [11]. Past medical history should note recent head trauma (usually obvious by history), migraine, diabetes, heart or lung disease, and regular or daily drug and alcohol use. Identify all current medications, including recent changes in drugs, dosages, or both [11].

After major medical and other etiologies are ruled out, patients with dizziness or vertigo, with or without associated headache, otologic, autonomic, or balance symptoms, should receive a timing and triggers evaluation [37].

TIMING

Timing refers to the onset, duration, and evolution of the dizziness attacks. Narrow the differential diagnosis by classifying the pattern of dizziness attacks as episodic, acute, or chronic in duration by defining the following [102]:

- Onset of dizziness attacks: Sudden or gradual and ill-defined
- Duration of dizziness attacks (minimal and maximal): Seconds to minutes, several minutes to hours, or several hours to days
- Evolution of dizziness attacks:
  - Episodic dizziness lasting seconds to minutes, several minutes to hours, or several hours to days
  - Acute with symptoms lasting days to weeks
  - Persisting symptoms more than three months (chronic)

TRIGGERS

Almost all patients with vertigo feel worse with head movements. The critical distinction is whether head movements trigger (symptoms appear only when provoked by movements) or exacerbate (movements worsen pre-movement vertigo) symptoms [8; 20].

Head movement usually exacerbates dizziness/vertigo of any vestibular cause (benign or dangerous, central or peripheral), but the worsened dizziness is often conflated with a triggered peripheral cause, potentially missing a serious or life-threatening central etiology [6; 8; 37].

Explicitly assess for the following symptom-triggering circumstances and note whether symptoms are triggered, exacerbated, or improved [15; 102]:

- Rolling over in bed, looking up, changing head position relative to gravity
- Turning the head to the side
- Any head movement
- When standing up or walking
- When supine or recumbent
- Vibration or loud sounds
- Seeing objects in motion

Assessment of triggers establishes the distinctions between positional (change of head orientation with respect to gravity), head motion-induced (head motion regardless of direction), and orthostatic position changes. Obligate triggers are specific triggers that consistently cause dizziness [8].

TARGETED EXAMS

Eye Movement Assessments

At this point in the workup, the patient is placed into one of six vestibular syndromes after some possible etiologies were ruled out during the patient history. The differential diagnosis does not extend beyond possible etiologies within the vestibular syndrome, which substantially narrows the range.

The next task is to differentiate dangerous central mimics from benign causes in acute and episodic vestibular syndromes and to diagnose BPPV by identifying the affected canal. This involves the use of targeted examinations, also called "bedside examinations," which emphasize the assessment of eye movements to detect and localize the underlying pathology of dizziness. The accuracy of eye movement assessment is superior to CT or MRI imaging in differentiating serious CNS from benign causation. Healthcare costs are also reduced by eliminating (in many but not all cases) expensive but unhelpful brain imaging.

Nystagmus is a repetitive, involuntary movement of the eyes, and nystagmus assessment is a core component of the diagnostic workup. Whether spontaneous or triggered, the characteristics of nystagmus help to localize the pathology and suggest a diagnosis. The nystagmus is tested first, because some disorders are diagnosed solely by the nystagmus characteristics [10; 20; 48; 103].

The vestibulo-ocular reflex keeps vision focused on a target during head movement. When looking to one side, the labyrinth on that side signals the head-turn, and the eyes automatically move in the opposite direction to maintain fixed gaze. The vestibulo-ocular reflex maintains gaze for continued reading while turning the head alternately to each side [103; 104]. Vestibulo-ocular reflex assessment is used in the diagnosis of vestibular disorders, because vestibular dysfunction causes inappropriate activation of the vestibulo-ocular reflex that manifests in nystagmus [16].

With vestibular disturbance, when the head is rapidly turned toward the affected side, the eyes move with the head and visual fixed gaze is broken, followed by a refixation ("catch-up") saccade back to the original visual target [104]. This is nystagmus.

In peripheral or central vestibular disorders, understanding the simple "rules" of nystagmus allows rapid, confident diagnoses. With peripheral causes of nystagmus, the fast-phase direction is away from the affected side (of canal/vestibular nerve), and this direction remains constant, regardless of gaze direction. The pattern is primarily horizontal with a torsional component—never purely torsional or vertical. In central nystagmus, the fast-phase varies with the direction with gaze (i.e., right-beating on rightward gaze, then left-beating on leftward gaze). The pattern is any direction, but primarily torsional or vertical.

HINTS is an acronym for three ocular motor tests—the head impulse test (HIT), gaze testing for nystagmus, and alternate cover test for skew deviation—that are combined to differentiate central from peripheral causes of dizziness. Nystagmus is a key observed response. Normal visual fixation can suppress mild nystagmus, but Frenzel lenses worn by the patient block visual fixation and magnify examiner view of eye movements [8; 10; 20]. When conducting the HIT, have the patient fixate his/her gaze on a midline target (e.g., the examiner's nose), then rapidly rotate his/her head 20 degrees to the right or left, bring head back to midline, then rotate to the other side. The presence of a corrective saccade is "positive" for abnormal vestibulo-ocular reflex, which generally indicates a peripheral vestibular process. Gaze that remains locked on the midline target is normal. A normal HIT in patients with AVS is highly suspicious for stroke, but HIT is only useful in patients with AVS and nystagmus. In patients with dizziness (with urosepsis or dehydration) without nystagmus, a normal HIT is a misleading false-positive for stroke.

Gaze testing for nystagmus consists of having the patient look straight ahead ("neutral" or "primary" gaze) and observing for eye movements. Patients whose eyes drift leftward and snap back horizontally to the right have right-beating horizontal nystagmus. Next, look for "gaze-evoked" nystagmus by having the patient look to the right and then to the left, each for several seconds; observe for nystagmus and direction of its fast-beating component. Two patterns suggest stroke or other central cause:

- Dominantly vertical or torsional nystagmus in any gaze position
- Dominantly horizontal nystagmus that changes direction in different gaze positions, termed bilateral or gaze-evoked nystagmus

However, the most common pattern in patients with AVS and stroke is direction-fixed horizontal nystagmus, an acute vestibular neuritis mimic that requires further testing.

Skew deviation is a vertical misalignment of the eyes due to imbalance in gravity-sensing vestibular pathways. Alternate eye cover testing checks for ability to maintain vertical alignment of the eyes. Have the patient gaze directly on a midline target (e.g., the examiner's nose), then cover one eye, and the other, alternating back and forth every one to two seconds.

Skew is shown by slight upward vertical correction on one side, and downward on the other side, appearing the moment the eye is uncovered. Horizontal movements are irrelevant; no vertical misalignment equals no skew. This test is very specific for central etiologies.

The timing-and-trigger syndrome should be identified before targeting the exam, because the same clinical feature can predict a benign condition in one syndrome and a dangerous condition in another syndrome [6; 37].

ACUTE VESTIBULAR SYNDROME

AVS is defined by acute-onset, persistent dizziness lasting days to weeks, sometimes with lingering sequelae. The temporal evolution at onset and progression during the first week is more important diagnostically than total illness duration. Many patients have an early peak in symptom severity, rapid symptom improvement over the first week, and gradual recovery over weeks to months. Unusual cases resolve in less than 48 to 72 hours [37].

Triggered AVS

For diagnostic purposes, AVS is classified into acquired (postexposure/triggered) and spontaneous forms. Triggers in t-AVS refer to behavior or exposures that precipitate dizziness. Patients with AVS typically experience worsening of dizziness (exacerbation) with head movement. This feature can be confusing or misleading, as for example when triggered dizziness in a patient with vestibular neuritis or stroke is misdiagnosed as BPPV [8].

 Copyright © 2019 NetCE

Triggered AVS results from trauma or toxic exposure and is typically diagnosed largely based on exposure history, which is usually obvious. The most common causes are blunt head injury or ingestion of prescribed or illicit drugs affecting the brainstem, cerebellum, or peripheral vestibular apparatus. Carbon monoxide exposure and acute toxicity is a rare but important consideration [37].

Most patients experience a single, acute attack resolving gradually over days to weeks following the exposure. Depending on the nature of trauma or toxin, other symptoms (e.g., headache, altered mental status) may predominate. Rotatory vertigo, spontaneous nystagmus (when looking straight ahead), and head-motion intolerance may be absent or unimpressive if the pathologic effects are bilateral and relatively symmetric (as with most toxins) [37].

Head Injury

Blunt head trauma, blast injuries, whiplash, or barotrauma may lead to direct vestibular nerve injury, labyrinthine concussion, or mechanical disruption of inner ear membranes to result in an AVS presentation. Basal skull fracture and traumatic vertebral artery dissection should always be considered. TBI may cause post-concussion syndrome, typically with a combination of dizziness, headache, fatigue, and minor cognitive impairment, with dizziness the most common symptom in the first two post-injury weeks [37].

Drug Side Effects/Toxicity

Anticonvulsant side effects or toxicity are a frequent cause of dizziness and vertigo seen in the ED. As mentioned, aminoglycoside toxicity is an established cause of acute bilateral vestibular failure. Gentamicin can cause profound, permanent loss of vestibular function with relatively spared hearing; toxicity may occur after just a single antibiotic dose. Patients usually show gait unsteadiness and oscillopsia (bouncing vision) while walking [37].

Spontaneous AVS

Within the first 48 hours of onset, how is posterior circulation stroke most accurately differentiated from a peripheral dizziness cause?

Spontaneous AVS is defined as acute onset of persistent dizziness and vertigo associated with nausea or vomiting, gait instability, nystagmus, or head motion intolerance. A focused physical exam is often diagnostic, because patients are usually symptomatic at presentation [8]. Prototype causes include vestibular neuritis and labyrinthitis [10]. Possible dangerous causes include posterior circulation stroke of the cerebellum or brainstem (the most frequent), bacterial labyrinthitis, and labyrinthine stroke (much less frequent) [8; 37].

Peripheral causes of s-AVS are more common, but central causes are not infrequent and can be fatal if missed, especially with vertebro-basilar ischemia [19]. This would not be as concerning if patients with posterior circulation TIA or stroke presented with classical focal neurologic signs along with the vestibular symptoms of AVS, as the diagnosis would be straightforward [57; 105]. However, this is often not the case.

The 1975 National Institutes of Health (NIH) recommendation that isolated dizziness or vertigo not be considered a TIA persists as a standard teaching [106]. This has contributed to missed diagnoses of TIA and stroke, because many patients with posterior circulation TIA or stroke present with isolated dizziness or vertigo without focal neurologic signs [37; 105; 107]. Patients with s-AVS presenting to the ED with dizziness are at high risk (25%) for stroke. Of nearly 800,000 annual strokes in the United States, 18% are strokes in the posterior fossa (within the brainstem or cerebellum) and up to 70% present with dizziness [8; 19].

An estimated 45,000 to 75,000 patients with stroke are misdiagnosed annually. Roughly 28% to 59% of cerebellar strokes are misdiagnosed in the ED, and isolated dizziness is a risk factor for this misdiagnosis. Posterior circulation strokes are missed more than twice as often as anterior circulation strokes, and cerebellar strokes are four times more likely to be misdiagnosed than stroke misdiagnosis overall. These misdiagnosed patients suffer higher mortality and disability at follow-up [10; 108; 109; 110].

CT is widely used but ineffective to rule out ischemic stroke in s-AVS; MRI with diffusion-weighted imaging (MRI-DWI) is markedly superior. However, within the first 48 hours of symptom onset, MRI-DWI is falsely negative in 12% to 18% of patients with AVS and 53% of patients with small brainstem strokes. Posterior circulation strokes are five times more likely to be falsely negative than anterior circulation strokes. Indiscriminate CT angiography also has very low utility (1.3%) [8; 52; 111].

In the first 48 hours, physical examination outperforms MRI. If the initial physical examination suggests stroke, a negative MRI result should not be interpreted as excluding stroke. Delayed MRI (three to seven days post-onset) may be required to confirm the presence of a new infarct [8]. Posterior circulation stroke should be differentiated from benign peripheral vestibular disorder (***Table 1***) [8; 10; 19]. Nearly all patients with AVS due to a peripheral cause exhibit nystagmus, which may be inhibited if benzodiazepines/other vestibular suppressants are taken before the exam. When possible, assess for nystagmus before medications to manage symptoms are administered [8; 10].

TESTING TO DIFFERENTIATE POSTERIOR CIRCULATION STROKE FROM BENIGN PERIPHERAL VESTIBULAR DISORDER

HINTS is performed in sequence. Test nystagmus first; HINTS is validated only in patients with nystagmus, and gaze testing is non-intrusive (i.e., head movement unnecessary).

- Gaze testing: Is there a central pattern of nystagmus?
- Alternate cover test: Is skew deviation present?
- HIT: Is the head impulse test result negative?

Patients with s-AVS and worrisome nystagmus, skew deviation, or bilateral normal HIT have a presumed stroke and should be admitted to a hospital. If all three tests seem reassuring, perform a targeted neurologic exam to determine if there are any CNS signs. This involves testing for:

- 4D symptoms:
  - Diplopia (double vision)
  - Dysphagia (difficulty swallowing)
  - Dysarthria (difficulty with speech)
  - Dysmetria (lack of coordination)
- The cranial nerves for hearing
- Anisocoria (unequal pupil size)
- Facial loss of pain or temperature sensation
- Cerebellar function for limb ataxia.

The next step is gait testing to determine if the patient can walk unassisted.

If the answer to any of these questions is yes, the cause is presumed central and treated as stroke. If the answer to all questions is no, the cause is presumed peripheral. All answers must be no in order to exclude stroke because none is sufficiently sensitive individually.

Source: [8; 10; 19] *Table 1*

EPISODIC VESTIBULAR SYNDROME

Whether intermittent dizziness is triggered or spontaneous, the duration of dizziness episodes (seconds, minutes, hours) is more important than total illness duration. EVS excludes relapsing and remitting symptoms lasting weeks at a time [37].

Triggered EVS

Triggered EVS is characterized by brief episodes of dizziness lasting seconds to minutes (depending on etiology), precipitated by an obligate trigger. Common triggers are changes in head position or body posture, as when rising from a seated or lying position, tipping the head back to wash one's hair, or rolling over in bed. Uncommon triggers include loud sounds and the Valsalva maneuver. Patients with nausea or vomiting may overestimate the episode duration, but this can usually be clarified by careful history-taking [8].

As mentioned, clinicians should distinguish triggers from exacerbating features [37]. Prototype t-EVS causes are BPPV and orthostatic hypotension; less commonly, it is caused by superior canal dehiscence syndrome [8]. Possible dangerous causes include central paroxysmal positional vertigo and serious causes of orthostatic hypotension, such as internal bleeding. Patients with panic or anxiety disorders may also complain of episodic vertigo, lightheadedness, or dizziness during panic attacks that are triggered or spontaneous. Studies show a high prevalence of vestibular dysfunction for these patients [112].

Episodic positional symptoms are common to all causes of t-EVS, differentiated by targeted history and exams. BPPV is identified by maneuvers that reproduce dizziness combined with an observed pattern of nystagmus. Orthostatic hypotension is diagnosed by observing a significant fall in blood pressure upon sitting and standing. Dangerous t-EVS mimics are identified by careful attention to the corresponding signs and symptoms that differentiate these benign conditions from potentially more serious disorders [37]. Positional triggers, such as rolling over in bed or reclining, are common in BPPV but should not occur in orthostatic hypotension [8]. Unlike head position changes in BPPV, the vertigo and oscillopsia attacks in superior canal dehiscence syndrome are triggered by pressure-related changes of the external auditory canals (e.g., loud sounds, Valsalva maneuver) [22].

 Copyright © 2019 NetCE

The nystagmus characteristics of BPPV and central paroxysmal positional vertigo are distinct. Atypical nystagmus (downbeat or horizontal) is suggestive of central paroxysmal positional vertigo, and pure vertical (up- or downbeating) nystagmus should be considered of central origin until proven otherwise [8; 23]. Central mimics of BPPV less often involve strokes and more often involve posterior fossa neoplasm, hemorrhage, or demyelination recognized by association with other abnormalities [104; 113].

Central paroxysmal positional vertigo also includes common, benign causes, such as alcohol or sedative intoxication. Such patients are more apt to complain of continuous, persistent dizziness exacerbated (not triggered) by position change, often readily diagnosed based on context and other signs of intoxication [8; 37].

In general, BPPV is not associated with vertiginous episodes provoked simply by head and body movements in general, but by sudden positional changes relative to gravity. Moreover, unprovoked (spontaneous) episodes while immobile or the constant sensation of unsteadiness also suggest a diagnosis other than BPPV [22].

BPPV

Within any (semicircular) canal, BPPV is caused by abnormal stimulation of the cupula by otoconia that are free-floating (canalolithiasis) or have attached to the cupula (cupulolithiasis) [114]. With head motion in the plane of the affected canal, cupula stimulation produces error signaling that triggers eye movement patterns (nystagmus) specific to the afflicted canal [22]. BPPV should be differentiated from other causes of imbalance, dizziness, and vertigo. Patients should also be assessed for factors that modify management, including impaired mobility or balance, CNS disorders, lack of home support, and increased risk for falling. In patients meeting BPPV diagnostic criteria, it is not necessary to obtain radiography or order vestibular testing in the absence of signs/symptoms inconsistent with BPPV [22].

Provoked nystagmus is used clinically to diagnose BPPV by positioning the head to spatially align the plane of the affected canal with gravity. Gravity challenge moves otolithic debris in the canal, inducing excitation and resultant nystagmus. This identifies the afflicted canal, determines the canal-specific therapy, and distinguishes BPPV from central causes of vertigo [15; 24; 40; 114].

Head movement tests are canal-specific. Because posterior canal BPPV is the most common type, the Dix-Hallpike maneuver is used first. For this maneuver, the patient is moved quickly from sitting upright with head turned 45° in the direction of involved ear, to supine position with head still turned 45° and neck extended 20° off the end of the exam table with the affected ear down [21; 22].

Before initiating physical maneuvers that involve head rotation, the neck should be evaluated to determine if the procedure should be modified or avoided. The Dix-Hallpike maneuver should be performed with caution or avoided in patients with a current or past neck or back injury, surgery, or painful condition [24; 114].

A diagnosis of BPPV affecting the posterior canal (pc-BPPV) is confirmed by vertigo with torsional (rotatory), upbeating (toward the forehead) nystagmus, with onset 5 to 20 seconds after completion of the Dix-Hallpike maneuver (latency) and duration less than 60 seconds. Provoked nystagmus that lasts longer than 60 seconds with no or brief latency identifies cupulolithiasis [21; 22]. If the initial maneuver is negative, it should be repeated with the opposite ear down.

Before performing the Dix-Hallpike maneuver, the patient should be advised that sudden, intense vertigo or nausea is possible but should subside within 60 seconds. The sequential steps and expected results of the maneuver should be explained, orienting the patient to the supine position and location of the head and providing reassurance that the head and body will be supported and guided safely and securely through the maneuver [21; 22].

There are two types of BPPV affecting the lateral canal (lc-BPPV)—geotropic or apogeotropic—with two types of direction-changing positional nystagmus [22; 40]. When BPPV is suspected and the Dix-Hallpike maneuver is negative, the supine roll test should be used to assess for lc-BPPV. The supine roll test provokes a linear, horizontal nystagmus in patients with lc-BPPV. In cases of lc-BPPV caused by canalolithiasis, the nystagmus beats to the ear under the head (i.e., higher intensity on the affected side). If the condition results from cupulolithiasis, the nystagmus beats to the upward ear (i.e., higher intensity on the non-affected side).

According to the American Academy of Otolaryngology, if the patient has a history compatible with BPPV and the Dix-Hallpike test exhibits horizontal or no nystagmus, the clinician should perform, or refer to a clinician who can perform, a supine roll test to assess for lateral semicircular canal BPPV.

(http://journals.sagepub.com/doi/pdf/10.1177/0194599816689667. Last accessed September 18, 2018.)

Strength of Recommendation: Recommendation (Benefits exceed the harms, but the quality of evidence is not as high)

The Dix-Hallpike maneuver also provokes vertigo and nystagmus in BPPV affecting the anterior canal (ac-BPPV), which shows downbeating nystagmus, sometimes with a torsional component, toward the affected ear. Downbeating positional nystagmus may reflect brainstem or cerebellar lesion, which should be ruled out [21; 40]. BPPV can also mimic orthostatic hypotension by producing dizziness on arising and often goes undiagnosed in the elderly.

Serious Causes of Orthostatic Hypotension

As noted, vertigo is a common but under-appreciated symptom in orthostatic hypotension. Older patients taking antihypertensives can show incidental orthostatic hypotension. Orthostatic dizziness and hypotension are not always related; orthostatic dizziness without systemic orthostatic hypotension may indicate hemodynamic TIA or intracranial hypotension [8].

Serious causes of orthostatic hypotension include fluid loss from bleeding, vomiting, diarrhea, and excessive urination/sweating. Occult internal bleeding is the primary dangerous concern [2]. Concomitant chest, back, abdominal, or pelvic pain suggests an intrathoracic or intra-abdominal emergency [37]. Myocardial infarction, occult sepsis, adrenal insufficiency, or diabetic ketoacidosis may present with severe orthostatic hypotension without other overt signs [8].

Spontaneous EVS

s-EVS is marked by recurrent, spontaneous episodes of dizziness that range in duration from seconds to days, with most lasting minutes to hours. Spells sometimes occur up to several times per day, but they are usually less frequent and can be separated by months or even years, depending on etiology [8].

Unlike t-EVS, dizziness episodes in s-EVS cannot be provoked and diagnostic evaluation relies almost entirely on patient history [37]. Vestibular migraine is the most common cause of s-EVS, with a population prevalence of roughly 1% [37]. The classical Ménière disease symptom triad of episodic vertigo, unilateral tinnitus and aural fullness, and reversible sensorineural hearing loss is initially present in only 25% of patients. Patients with suspected Ménière disease should generally be referred to an otolaryngologist, but care should be taken to avoid missing TIA mimics with audio-vestibular symptoms [37].

Reflex (vasovagal) syncope is also a common cause. In reflex syncope, episodes of near-syncope without loss of consciousness substantially outnumber true syncope. Patients usually have prodromal symptoms for 3 to 30 minutes, most commonly dizziness (70% to 75% of cases) that can manifest in vertigo. Diagnosis is based on clinical history, exclusion of dangerous mimics (especially cardiac arrhythmia), and confirmation (if needed) by formal head-up tilt table testing [8; 37].

s-EVS has been reported in panic attacks; episodes begin rapidly, usually peak within 10 minutes, and are accompanied by additional autonomic, cognitive, and perceptual symptoms. Panic attacks can be precipitated by situational stress, such as airplane travel, but often occur spontaneously [115]. Panic attack mimics include ictal panic attacks from temporal lobe epilepsy that usually last seconds with altered mental status, hypoglycemia, cardiac arrhythmias, and basilar TIA, which can produce dizziness and neurologic and autonomic features [8].

Another cause of s-EVS is vestibular paroxysmia, a condition that should be considered when the patient reports 10 or more spontaneous vertigo attacks per day lasting less than one minute (sometimes mere seconds). These attacks respond to a carbamazepine or oxcarbazepine trial [45].

The most common dangerous causes of s-EVS are vertebrobasilar TIA and cardiac arrhythmias. Less commonly, episodes have been observed with other cerebrovascular (e.g., subarachnoid hemorrhage), cardiorespiratory (e.g., unstable angina, pulmonary embolus), and endocrine (e.g., hypoglycemia) disorders. Carbon monoxide exposure is a rare serious cause [37].

Vestibular symptoms associated with s-EVS cannot be reproduced by bedside examination, and patients may be asymptomatic by the time they present to outpatient care. The history is used to distinguish vestibular migraine from TIA or other causes. Diagnosis of benign s-EVS causes can be clear-cut in typical cases, but as mentioned, classical features of vestibular migraine, vasovagal syncope, Ménière disease, or panic attacks are often absent [37].

Isolated attacks of spontaneous dizziness are the most common symptom of an imminent posterior circulation TIA and are frequent in the days to weeks preceding posterior circulation stroke [8; 37]. TIA presenting with isolated dizziness is easily missed; 90% of patients who seek medical attention for transient dizziness that preceded vertebrobasilar stroke are initially misdiagnosed [107]. Dizziness is the most common presenting symptom of basilar artery occlusion and vertebral artery dissection. Prompt diagnosis is critical; 5% of patients with TIA suffer a stroke within 48 hours, but the risk is much greater with posterior circulation TIA. Prompt treatment lowers stroke risk after TIA by 80% [8; 116; 117].

The clinical presentation of vestibular migraine is highly variable. The duration of attacks ranges from seconds to days. Nystagmus (peripheral or central), headache, and nausea, vomiting, photophobia, phonophobia or visual auras can be present or absent during an attack. Hearing loss or tinnitus can occur, mimicking Ménière disease [8].

 Copyright © 2019 NetCE

Vestibular migraine is diagnosed by clinical findings of recurrent migraine headache episodes: five or more episodes characterized by moderate-to-severe vestibular symptoms; ≥50% of episodes have pulsating, impairing headache; photo- or phonophobia; and/or visual aura [49].

The prevalence of migraine syndrome is high in patients with Ménière disease, and when such patients present with attacks of s-EVS, the diagnostic attribution may seem difficult. The presence of low frequency hearing loss favors the diagnosis of Ménière disease [19; 49].

Cardiac arrhythmia should be suspected when syncope or exertion is the precipitating factor for the onset of dizziness. Clinical features may increase or decrease the odds of a dangerous cardiac cause, but cardiac specialist testing is often required for diagnostic confirmation [8; 37].

CHRONIC VESTIBULAR SYNDROME

Triggered CVS

Central compensatory mechanisms can ameliorate vestibular symptoms over time, but to an unpredictable extent, and lasting vestibular compensation does not develop or incompletely develops. Thus, some vestibular syndromes become chronic, with persistent dizziness or unsteadiness lasting months to years, with oscillopsia, nystagmus, and/or gait disturbance. CVS develops from poorly compensated unilateral or bilateral vestibulopathy or cerebellar degeneration [118]. Other etiologies include PPPD, autoimmune or neoplastic disease, central vestibular syndromes with downbeat or upbeat nystagmus, and dizziness due to isolated causes [119]. In t-CVS, dizziness or vertigo is provoked by head movement (as in uncompensated vestibular loss), medication side effects, and/or anxiety, depression, or other psychiatric conditions [118].

Bilateral vestibulopathy is a CVS characterized by unsteadiness when walking or standing that worsens in darkness, on uneven ground, or during head motion. Patients may describe head or body movement-induced blurred vision or oscillopsia. Symptoms usually remit when sitting or lying down. Bilateral vestibulo-ocular reflex function is significantly impaired or absent in bilateral vestibulopathy and is assessed using the HIT, video-HIT, or other tests [41].

As discussed, PPPD is a newly defined CVS that unifies key features of chronic subjective dizziness, phobic postural vertigo, and related disorders. Patients with PPPD often develop gait disorder, anxiety, avoidance behaviors, and severe disability [120].

A PPPD diagnosis requires dizziness, unsteadiness, or nonspinning vertigo present on most days for at least three months, exacerbated by posture, movement, and/or moving/complex visual stimuli. Symptoms are precipitated by any condition that causes vertigo, unsteadiness, dizziness, or problems with balance and cause significant distress or impairment [62].

In addition to timing and triggers, the diagnostic approach should also capture the dynamic features of patient history to uncover the nuances of psychologic distress, maladaptive coping, and differential diagnosis. Patients who fulfill diagnostic criteria for PPPD after a TBI or whiplash should receive the diagnosis. The presence of other injury sequelae determines additional diagnoses [62].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Bárány Society, the differential diagnosis of PPPD includes chronic sequelae of acute precipitants, recurrent attacks of episodic precipitants, ongoing manifestations of chronic precipitants, other chronic vestibular syndromes, medical or psychiatric disorders that produce persistent unsteadiness or dizziness, and adverse effects of regularly consumed prescription or non-prescription medications.

(https://content.iospress.com/articles/journal-of-vestibular-research/ves622. Last accessed September 18, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Spontaneous Chronic Vestibular Syndrome

s-CVS conditions include chronic dizziness or vertigo associated with nystagmus, blurred vision, or impaired visual acuity from oscillopsia, originating from cerebellar or brainstem degeneration or atrophy [121]. Other central etiologies of s-CVS include cervical vertigo and Chiari malformations [118]. Several cerebellar syndromes due to neurodegenerative and hereditary diseases can lead to ataxia and postural instability associated with cerebellar oculomotor disorders (e.g., downbeat nystagmus, gaze-evoked nystagmus) [121].

Episodic ataxia type 2, the most frequent inherited cerebellar ataxia syndrome, is characterized by recurrent attacks of dizziness and ataxia lasting several hours, often elicited by physical activity, alcohol consumption, or stress. More than 90% of patients with episodic ataxia type 2 have oculomotor disorders such as downbeat nystagmus [118].

The vertigo symptoms are usually associated with degenerative cervical spine disease and may resemble BPPV due to proprioceptive abnormalities related to cervical spine dysfunction. However, cervical vertigo may be triggered by rotating the head relative to the body while upright, as opposed to the vertigo triggered by changes in head position relative to gravity in BPPV [22; 122].

CLINICAL MANAGEMENT

Returning to the funnel analogy, a range of possible dizziness and vertigo etiologies (e.g., orthostatic hypotension, vasovagal syncope, head injury, medication side effects/toxicity, posterior circulation TIA/stroke, central paroxysmal positional vertigo, and cardiac arrhythmias) would be excluded or diagnosed. Certain patients would be treated, and others referred to specialists or admitted to an ED. This would include all etiologies categorized as t-AVS.

After vestibular disorders have been differentiated and diagnosed, treatment selection can be divided into approaches that focus on symptom control, those specific to the underlying vestibular etiology, and those aimed at promoting recovery [123]. Therapeutic approaches broadly used across vestibular etiologies are discussed first, followed by treatments specific to acute, episodic, and chronic vestibular syndromes.

COMMON PHARMACOTHERAPIES

Most pharmacotherapies for dizziness or vertigo related to peripheral or central vestibular, cerebellar, or oculomotor disorders fall into one of seven groups, or the 7 As [61]:

- Antiemetics
- Anti-inflammatory
- Anti-Ménière
- Anti-migraine
- Antidepressants
- Anticonvulsants
- Aminopyridines

Patients with severe nausea or vomiting greatly prefer non-oral administration [123]. As such, vestibular suppressants are usually administered in non-oral routes initially for rapid symptom control, followed by oral medications.

Vestibular Suppressant Medications

Which drug is one of the most effective agents for preventing motion sickness?

As discussed, dizziness, vertigo, disequilibrium, and associated symptoms can arise from diverse central or peripheral disturbances of vestibular function. By suppressing vestibular sensory input, vestibular suppressant medications can reduce conflicting sensory input, control undesirable perceptions, and diminish patient distress [13].

Many distressing vestibular-related symptoms are mediated by the vomiting center in the medulla. The vomiting center is activated through neurotransmitter release involving vestibular and CNS (histamine, acetylcholine), visceral (gut) (dopamine, serotonin), and chemoreceptor trigger zone (dopamine, serotonin) pathways [124]. These pathways are therapeutic targets of most vestibular suppressants, which are effectively used for symptomatic control in nearly all AVS or EVS subtypes, regardless of underlying etiology. These medications are variously effective for controlling dizziness, vertigo, motion sickness, associated symptoms (e.g., nausea, vomiting, diarrhea), and patient distress or anxiety during episodes, which can be severe [22; 178].

Drug classes and agents commonly used as vestibular suppressants include antihistamines, benzodiazepines, scopolamine, dopamine antagonists, and ondansetron (***Table 2***). Antihistamines (e.g., meclizine, diphenhydramine, dimenhydrinate) block the release of histamine and acetylcholine and are especially beneficial in vestibular-mediated nausea, vomiting, and motion sickness. Side effects include sedation, confusion, dry mouth, and urinary retention. Meclizine is preferred because it has minimal anticholinergic effects, causes less sedation, and is effective in the treatment of vertigo due to labyrinth dysfunction. It is also the drug of choice in pregnancy [123].

Benzodiazepines (e.g., diazepam, clonazepam, lorazepam) potentiate the inhibitory effects of the gamma-amino butyric acid system to produce anxiolytic, sedative, muscle-relaxant, and anticonvulsant effects. Benzodiazepines can be highly effective in vertigo unresponsive to antihistamines and for calming intensely distressed patients, but they are sedating and mainly used when antihistamines are inadequate [123].

Scopolamine is a belladonna alkaloid that blocks CNS neurotransmission of acetylcholine and is one of the most effective agents for preventing motion sickness. Scopolamine is also effective for vestibular-mediated nausea/vomiting and is better tolerated as a transdermal patch than when taken orally. Common side effects are sedation, constipation, dry mouth, and urinary retention [114; 124].

Dopamine antagonists (e.g., metoclopramide, domperidone, promethazine, prochlorperazine) block dopamine stimulation in the intestines and chemoreceptor trigger zone, limiting emetic input to the medullary vomiting center. Promethazine and prochlorperazine also inhibit central muscarinic and histamine receptors, which contributes to their antiemetic and sedative properties [124].

Ondansetron inhibits serotonin-5HT3 receptors in the small bowel, vagal nerve, and chemoreceptor trigger zone, suppressing serotonergic activation of the vomiting center to alleviate nausea and vomiting. Adverse effects are uncommon but can include headache, diarrhea, and fatigue [124].

 Copyright © 2019 NetCE

VESTIBULAR SUPPRESSANT MEDICATIONS	
Medication	**Dosage and Route**
Antihistamine Agents	
Diphenhydramine	50 mg PO twice daily 10–50 mg IM or IV
Meclizine	25–50 mg PO three to four times per day
Promethazine	12.5–50 mg PO every four to six hours 50 mg RS four times per day 10–50 mg IM or IV
Benzodiazepines	
Lorazepam	0.5–2 mg PO two to three times per day
Diazepam	2–5 mg PO three to four times per day
Clonazepam	0.25–1 mg PO two to three times per day
Antiemetic Agents	
Metoclopramide	10–20 mg PO every four to six hours 10–20 mg IM or IV
Prochlorperazine	10–20 mg PO every four to six hours 25 mg RS every six hours 5–10 mg IM or IV
Domperidone	10–20 mg PO every six to eight hours
Ondansetron	8 mg PO every 6 to 12 hours 4 mg SL, IM, or IV
Anti-Motion Sickness	
Scopolamine	1 TD patch (1.5 mg) every three days
IM = intramuscular; IV = intravenous; PO = oral; RS = rectal suppository; SL = sublingual; TD = transdermal.	
Source: [15; 22; 119; 123; 125]	*Table 2*

Extrapyramidal symptoms, including irreversible tardive dyskinesia (an involuntary movement disorder), are a potential risk with all central dopamine antagonists. Extended use (duration of 12 or more weeks) increases the risk of tardive dyskinesia [126]. However, dopamine antagonists are considered safe for use as acute therapy and are usually reserved for patients with severe vomiting [123].

In peripheral vestibular disorders, all vestibular suppressants can interfere with central compensation, and their use is recommended to not exceed three days [15; 22; 125]. The goal is for patients to rapidly receive specialist care, but patients may not get an immediate appointment and remain highly symptomatic. In this context, vestibular suppressants should continue for symptom control until optimized treatment is initiated by a specialist [119].

Vestibular suppressants can cause drowsiness and interfere with driving. In particular, the use of benzodiazepines is a significant risk factor for falls; this risk increases with polypharmacy, common in the elderly [15; 22]. Antihistamines carry added risks of impaired cognitive functioning, gastrointestinal motility, and vision in elderly patients [22]. Some patients can develop psychologic dependence to benzodiazepines and have difficulty discontinuing the medication [119].

Betahistine

First approved for use in Europe in the 1970s, betahistine has been prescribed to more than 100 million patients with vestibular disorders and is the first-line treatment of Ménière disease in Germany. Betahistine is not approved by the U.S. Food and Drug Administration, but it may be obtained through compounding pharmacies in the United States with a prescription [15; 127]. It reduces vestibular symptoms but seems to differ from vestibular suppressants by promoting vestibular compensation. Histamine regulates sensory coding in the peripheral vestibular system. Betahistine (dihydrochloride or dimesylate), a structural analogue of histamine, is a potent histamine H3 receptor antagonist and a weak histamine H1 receptor agonist [15]. Betahistine reduces the frequency and severity of vertigo, nausea, and vomiting in diverse unilateral vestibular etiologies. Central and peripheral histamine receptor activity is a presumed mechanism [127; 128; 129].

Betahistine dose-dependently increases vestibulo-cochlear blood flow, increases central and vestibular system histamine turnover, decreases peripheral vestibular system input, and reduces histamine-induced excitation in vestibular cells through local H3 receptor blockade. These mechanisms are thought to improve vestibular compensation, reduce functional asymmetry of vestibular organs, and improve labyrinth microcirculation by rebalancing the production and resorption of endolymphatic fluid [127; 128; 129]. In this course, all discussions of betahistine refer to betahistine dihydrochloride, unless otherwise stated.

Antidepressant Drugs

Monoamines are the neurochemicals serotonin, norepinephrine, and dopamine. Dysregulated monoamine neurotransmission is implicated in anxiety disorders and depression. A bi-directional relationship between impaired monoamine neurotransmission and vestibular signaling dysfunction is suggested, with asymmetric vestibular system release of serotonin, norepinephrine, or dopamine linked to vestibular migraine and other dizziness/vertigo etiologies [51; 61; 119].

Antidepressant drugs include SSRIs (e.g., fluoxetine, escitalopram), serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine), and tricyclic antidepressants (e.g., nortriptyline, imipramine, amitriptyline). They modulate serotonin, norepinephrine, and dopamine neural pathways (with varying specificities) and are first-line treatments for anxiety disorders and depression. These agents are increasingly recommended for use in some vestibular-related disorders [51; 119; 130].

Aminopyridines

Aminopyridines are potassium-channel blockers, established as pharmacotherapy for cerebellar diseases that include downbeat nystagmus, upbeat nystagmus, central positional nystagmus, episodic ataxia type 2, and gait disorders in cerebellar ataxia [61].

Aminopyridines used in these disorders are 3,4-diaminopyridine (3,4-DAP) and 4-aminopyridine (4-AP). 4-AP crosses the blood-brain barrier more easily and is superior to 3,4-DAP in some cases. Both drugs are well-tolerated and without major side effects apart from nausea, transient paresthesia, or headache [121].

QT Interval Prolongation

Some vestibular disorder pharmacotherapies may interact with other medications to risk QT interval prolongation [119]. A prolonged QT interval is a symptom of disordered myocardial repolarization that increases the risk of potentially life-threatening ventricular tachycardia (i.e., torsades de pointes) [131]. A complete list of medications that prolong the QT interval is available at https://www.crediblemeds.org.

VESTIBULAR REHABILITATION

Vestibular rehabilitation, another therapeutic modality broadly used across dizziness and vertigo etiologies, is a specific physical therapy for patients with peripheral or central vestibular disorders. Vestibular rehabilitation reduces symptoms and improves functioning by promoting CNS compensation through exercise-based strategies [132; 133].

Following an acute peripheral vestibular event, clinical recovery occurs in advance of improved peripheral vestibular function. This suggests that most of the early recovery and a substantial portion of total recovery derives from central compensation (long-term changes in neuronal responses to head movements) that is multisensory and is the primary target of vestibular rehabilitation. Early rehabilitation (during a critical period of adaptation and compensation) may be more effective than late intervention. As such, vestibular rehabilitation should begin shortly after symptom onset [132; 134].

Patients typically receive supervised therapy one to two times per week and are taught daily home exercises. The average duration of therapy is 6 to 12 weeks for patients with peripheral vestibular disorder and longer for patients with central vestibular disorder or mobility-impairing comorbidities [44; 133].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Physical Therapy Association concludes that clinicians may prescribe a home exercise program of gaze stability exercises consisting of a minimum of three times per day for a total of at least 12 minutes per day for patients with acute/subacute vestibular hypofunction and at least 20 minutes per day for patients with chronic vestibular hypofunction.

(https://www.asha.org/articlesummary.aspx?id=8589969232. Last accessed September 18, 2018.)

Strength of Recommendation: D (Expert opinion from the clinical experience of the guideline development team)

General Components

What do habituation exercises work to reduce?

Vestibular rehabilitation uses several approaches to reduce symptoms and impairment and to promote function in patients with dizziness, postural instability, and gaze instability. Visual-vestibular interaction (adaptation) exercises strengthen the vestibulo-ocular reflex and gaze stability to promote central compensation for reduced vestibular input, improving gaze instability, balance, and dizziness [44; 132].

 Copyright © 2019 NetCE

Strategic substitution exercises promote the use of sensory stimuli and spatial cues from vision and proprioception to substitute for loss of vestibular inputs. Cervico-ocular reflex input is strengthened to reduce spatial uncertainty, and alternative spatial cues can improve balance and walking [44; 132].

Balance and gait training under challenging sensory and dynamic conditions facilitates visual and somatosensory cues to offset vestibular hypofunction. Equipment to augment training includes gaming technology, optokinetic drums, and virtual reality [44].

Habituation exercises reduce visual motion sensitivity (e.g., visual vertigo, space and motion discomfort) through systematic exposure to noxious stimuli evoking mild, temporary symptoms. Approaches include optokinetic stimuli and virtual reality for immersion in repetitive moving and visually challenging environments [44; 132].

Vestibular rehabilitation can help counteract the negative effects of deconditioning, common in vestibular patients, to avoid symptom provocation [44]. Psychologic deconditioning can progress to PPPD (phobic postural vertigo) to become the greatest obstacle to recovery. After a vestibular event, elderly patients can develop fear of falling, avoidance behavior, and indefinite mobility limitation without vestibular rehabilitation [74].

Based on strong evidence and a preponderance of benefit over harm, patients with acute, subacute, or chronic unilateral or bilateral vestibular hypofunction should be offered vestibular rehabilitation [44]. Without head movements, saccadic or smooth-pursuit exercises should not be used alone as gaze stability exercises.

Acute Peripheral Vertigo

For cases of acute peripheral vertigo, vestibular rehabilitation begins with the patient focusing on an object with a blank background, then moving the head slowly (to avoid severe nausea) to the right and left, and then up/down. This is done two to three times per day for several minutes, and the patient is encouraged to increase the speed as tolerated [132].

Chronic Peripheral Vestibular Hypofunction

The vestibular rehabilitation approach for chronic peripheral vestibular hypofunction is more aggressive, with increasingly more difficult tasks while keeping symptoms manageable. Tasks include eye and head movements while standing, walking forward, walking backward, and standing or walking on compliant or uneven surfaces [132].

Bilateral Vestibular Loss

Central adaptation is much less likely with bilateral vestibular loss than in unilateral loss, but vestibular rehabilitation can promote strategic substitution through strengthening saccadic eye movements and optimizing the efficacy of neck stretch receptors. Vestibulo-ocular exercises are initiated when residual vestibular function is a possibility. Improved balance and gait speed help offset the bilateral loss [135]. Education on fall prevention is critical, because these patients have an especially high fall risk, compounded by darkness and uneven surfaces [132].

Central Vertigo

Recovery of vestibular function in patients with central vertigo is limited because pathologic involvement of central vestibular structures restricts compensation, and improvement takes longer than with peripheral vestibular dysfunction [133]. For these patients, vestibular rehabilitation emphasizes gait and balance activities, along with eye and head movements. Adaptive methods to perform activities of daily function are often taught. If nausea is limiting, antiemetic medications used in conjunction with vestibular rehabilitation may improve participation and final outcomes [132].

ANXIETY AND DIZZINESS

The demonstrable interconnectivity between threat/anxiety, vestibular, visual, and somatosensory systems, and the interactions between anxiety disorders and vestibular morbidity point to the importance of a multimodality treatment approach for patients with anxiety and dizziness [71].

Studies have followed patients with dizziness over time and made several important findings [62; 71]. A highly anxious response to the acute dizziness/vertigo of new-onset vestibular neuritis or BPPV predicts continued dizziness 3, 6, and 12 months later. This initial psychologic response has a far greater impact on long-term outcomes than measurable vestibular dysfunction at baseline or follow-up. Patients with emerging symptoms of PPPD who receive cognitive-behavioral therapy within eight weeks of onset have marked reductions in dizziness and avoidance of provocative situations six months later. A highly anxious response to a precipitating event may be the pivotal initiating pathophysiologic process in PPPD (the leading cause of long-term vestibular disability), and early symptom-specific interventions might counter this effect.

Patients with poor recovery from acute vestibular neuritis have higher rates of visual dependence, autonomic arousal, anxiety, and fear of vestibular symptoms [136; 137]. Poor recovery is also unrelated to vestibular function, but significantly related to acute visual dependence and failure of sensory integration mechanisms to down-regulate visual contribution to central compensation processes. These data highlight the importance of [136; 137]:

- Early identification of abnormal visual dependence and concurrent anxiety
- Early treatment to improve long-term outcomes by reducing visual dependence with sensory re-weighting strategies
- Combining pharmacotherapy and cognitive therapies to reduce anxiety and autonomic arousal

In vestibular patients, successful treatment outcomes require the simultaneous assessment of vestibular, psychiatric (anxiety), and functional (phobic vertigo) disorders. Only when identified can they be addressed by systematically applied treatment that incorporates patient education, vestibular rehabilitation, cognitive-behavioral therapies, and medications to control morbidity and increase the potential for sustained remission [72].

SPONTANEOUS ACUTE VESTIBULAR SYNDROMES

Acute Unilateral Vestibulopathy/Vestibular Neuritis

This acute, spontaneous, peripheral vestibular disorder is characterized by the rapid onset of severe vertigo with nausea, vomiting, and gait instability. The symptoms can be severe and disabling in the short term; patients may need to be hospitalized for intravenous fluids and medications [125; 138]. Panic disorder has been found to develop in 10% of patients followed for two years after the initial acute vestibular neuritis episode [139].

Vertigo, nausea, and vomiting can be treated with a combination of vestibular suppressants, not exceeding seven days to avoid disrupting CNS adaptation and compensation [15; 125]. The vestibular nerve is selectively vulnerable to inflammation-related swelling and entrapment by its pathway in a narrow, bony canal [35]. Oral corticosteroids may help reduce the severity of vestibular neuritis if initiated in the first few days. The recommended agents are [15; 119]:

- Methylprednisolone initiated at 100 mg/day and then reduced by 20 mg every fourth day, OR
- Prednisone 60 mg/day for one week

When acute symptoms subside, patients should begin vestibular rehabilitation to promote CNS adaptation and sensory re-weighting [15; 125].

Labyrinthitis

A presumed viral acute labyrinthitis is reasonable to treat with corticosteroid therapy, such as a 10-day course of prednisone with 60 mg/daily on days 1 through 5, reduced to 10 mg/daily on days 6 through 9, and 5 mg on day 10. Some evidence suggests corticosteroid therapy may hasten recovery but does not change the long-term prognosis [138]. Patients with bacterial labyrinthitis should be referred to an ENT specialist.

Herpes Zoster Oticus

Patients with herpes zoster oticus should be treated with corticosteroids and a high-dose oral antiviral (acyclovir, famciclovir, or valacyclovir) when reactivation of latent varicella zoster virus is suspected. Carefully look for painful vesicles on the external ear and within the back of the external ear canal. Even in the absence of visible vesicles, treatment with an antiviral agent is probably prudent with significant localized ear pain and normal tympanic membrane [15].

TRIGGERED EPISODIC VESTIBULAR SYNDROMES

Benign Paroxysmal Positional Vertigo

Canalith repositioning procedures (CRPs) are the first-line therapy option and the most effective treatment for BPPV for patients with prolonged symptoms and/or frequent recurrences. Vestibular suppressants are generally avoided, though a brief course of an antihistamine (e.g., meclazine) may be indicated for initial symptom control. This may be all that is needed for patients with mild, self-limited symptoms and infrequent recurrences. Rarely, BPPV can be refractory to CRPs and require surgical occlusion of the affected semicircular canal [15].

Outcome assessment within one month of initial observation or treatment is necessary to document symptom resolution or persistence. Patients with persistent symptoms should be evaluated for treatment failure. Referral to a specialist is recommended to identify unresolved BPPV and/or an underlying peripheral or central vestibular disorder.

In general, CRPs move the patient through a sequence of head position changes that use gravity to move otolith debris (including the pathologic trigger) out of the affected canal and back into the vestibule [22]. CRPs used in canalolithiasis or cupulolithiasis appear similar [22]. These procedures should only be performed after the affected canal is identified by diagnostic positioning techniques. Patients should be informed that dizziness, vertigo, or a sense of falling can develop during a CRP. Patients who had severe nausea or vomiting with the Dix-Hallpike should receive antiemetics 30 to 60 minutes before the procedure [22; 119].

Posterior Canal BPPV

What is the preferred canalith repositioning procedure in posterior canal BPPV?

CRP is strongly recommended as initial therapy for pc-BPPV [22]. The Epley maneuver is the preferred CRP for pc-BPPV and has more than 20 years of evidential support. Meta-analyses have found that, compared with sham or control groups, the Epley led to significantly greater rates of complete vertigo resolution and conversion from a positive to a negative Dix-Hallpike. After 12 months, the Epley was superior to sham maneuver in conversion to negative Dix-Hallpike and perceived disability [22; 140].

 Copyright © 2019 NetCE

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Otolaryngology recommends clinicians should treat, or refer to a clinician who can treat, patients with posterior canal BPPV with a canalith repositioning procedure.

(http://journals.sagepub.com/doi/pdf/10.1177/0194599816689667. Last accessed September 18, 2018.)

Strength of Recommendation: Strong recommendation (Benefits of the recommended approach clearly exceed the harms and that the quality of the supporting evidence is high)

The Semont maneuver uses inertial and gravitational forces to move patients briskly down into a side-lying position and then through a rapid 180° arc. In this manner, the Semont repositions free-floating debris from the posterior canal into the vestibule or breaks off canalith from adherence to the cupula [119].

The Semont and Epley maneuvers are comparably effective in pc-BPPV [22]. With speed of rotation critical for a successful Semont, and adequate neck extension and flexibility required for a successful Epley, patient features such as obesity and neck mobility can guide CRP selection [21]. The Semont is a suggested alternative to the Epley for patients with back problems [119].

Lateral Canal BPPV

Compared with apogeotropic lc-BPPV, the geotropic form is the best-researched and most clinically responsive form. The most frequently used repositioning approaches in lc-BPPV are [21; 22; 40]:

- Gradual rotations around the longitudinal axis of the body toward the nonaffected ear
- Lying for 12 hours overnight on the nonaffected ear (for geotropic) or on the affected ear (for apogeotropic)
- The Gufoni maneuver, which moves the patient from sitting to lying sideways with the head turned downward, holding, and repeating

The Gufoni maneuver can effectively treat canalolithiasis or cupulolithiasis lc-BPPV and has the advantage of eliminating the need to determine the involved form [40; 141]. An alternative is to first convert cupulolithiasis of the lateral canal to canalolithiasis by shaking the head after bending it 90° forward into the vertical plane [40].

Anterior Canal BPPV

The Gufoni maneuver or a reverse Epley maneuver has demonstrated symptom resolution in more than 75% of patients with ac-BPPV [142].

Vestibular Suppressant Treatment

Routine use of vestibular suppressants is not recommended in BPPV, as they may interfere with central compensation and obscure Dix-Hallpike findings. None are as effective as CRPs and cannot be used as CRP substitutes [15; 22].

In some patients, acute/short-term pharmacotherapy can be indicated. Anxiety and BPPV often co-occur; anxiety levels of patients with panic disorder and agoraphobia diagnosed with BPPV remained significantly elevated 14 days after CRP [143]. Thus, benzodiazepines have a role in patients with significant anxiety or who are too anxious to proceed with CRP [15; 22].

Dimenhydrinate, scopolamine, or diazepam may be required in severely symptomatic patients before CRP, patients who become severely symptomatic after CRP, or those who refuse CRP. Patients exceptionally prone to motion sickness should receive meclizine [15; 22; 114]. CRP plus betahistine more effectively reduced vertigo symptoms than CRP alone [144]. If prescribed, clinicians should educate patients that vestibular suppressants can increase risks of cognitive impairment, falls, drug interactions, and machinery or driving accidents [22].

BPPV and CNS Disorders

Aside from migraine, BPPV in patients with pre-existing central neurologic disorders is rarely addressed in the literature. In one study of 93 patients with BPPV, 31.2% had a central neurologic disorder, with cerebrovascular disease and migraine the most common. The efficacy of repositioning therapy was excellent for BPPV with or without a pre-existing central neurologic disorder [145].

Post-CRP Residual Dizziness

Residual dizziness following successful repositioning is common in patients with BPPV, described as continuous or intermittent imbalance, lightheadedness, or unsteadiness without positional vertigo. The duration of vertigo before CRP is linked to residual dizziness and incomplete central adaptation. Residual dizziness is significantly associated with anxiety disorders, and subjects with high anxiety show more durable and disabling dizziness even after the resolution of acute vertigo in absence of otolithic or vestibular dysfunction [128; 146].

Anxiety is highly prevalent in elderly patients with BPPV, and the adverse impact of residual dizziness on psychologic, social, and daily functioning can be severe. Early recognition and treatment of BPPV and comorbid anxiety is recommended to decrease the incidence of residual dizziness [128].

Refractory BPPV

If BPPV remains refractory despite a correct diagnosis and competently performed repositioning maneuvers, surgery may be indicated. The two surgical options are partial neurectomy of the vestibular nerve (singular nerve) or occlusion of the affected (mainly posterior) semicircular canal. Of the two, posterior canal occlusion is favored based on symptom reduction and complications [147].

Superior Canal Dehiscence Syndrome

In superior canal dehiscence syndrome, sound- or pressure-induced dizziness with auditory symptoms of autophony, hyperacusis, or tinnitus results from a bony dehiscence of the superior semicircular canal. Surgical repair of the canal is the recommended treatment [119].

SPONTANEOUS EPISODIC VESTIBULAR SYNDROMES

For patients with vestibular migraine or Ménière disease, vertigo attacks are unpredictable and difficult to control or avoid. The unpredictable, distressing experience may elevate patient anxiety over the next attack sufficiently to induce a secondary panic-like disorder, substantially adding to the psychologic burden [51].

Migraine and anxiety disorders share common genetic and environmental risk factors, and an interaction between migraine and anxiety is established. Auditory center, limbic system, and vestibular system interconnections may account for high rates of anxiety in patients with persistent tinnitus, fluctuating hearing loss, and vertigo symptoms in vestibular migraine or Ménière disease [51; 148].

Ménière Disease and Endolymphatic Hydrops

The episodic vertigo, hearing loss, and tinnitus in Ménière disease is associated with endolymphatic hydrops in the labyrinthine system of the affected ear [125]. Ménière disease should be viewed and managed as a chronic condition, and treatment is tiered by disease stage and severity [149]. Acute symptomatic relief does not address the underlying pathophysiology, and the clinical goal is to minimize recurrent vertigo attacks and hearing symptoms to prevent new or additional damage to vestibular structures [150].

First Tier

Patients with Ménière disease are vulnerable to dietary and environmental factors that can impact hearing and balance. Triggers for Ménière disease may include high salt intake, caffeine, alcohol, nicotine, stress, monosodium glutamate, and allergies. Patients who identify and avoid triggers may greatly reduce their Ménière disease symptoms [150]. Therefore, lifestyle modification is the cornerstone of first-tier treatment. Caffeine and nicotine are vasoconstrictors that may reduce microvascular flow in the labyrinthine system. Alcohol also causes fluid and electrolyte shifts that can stress a fragile ear. Smoking cessation and limiting daily intake to one caffeinated or alcoholic beverage are typically recommended [150].

When dietary and environmental changes fail to control the episodes, combinations of diuretic and as-needed vestibular suppressant/antiemetic agents are effective to control vertigo episodes in many patients, but do not protect hearing loss. Off-label use of sublingual lorazepam (0.5–1 mg up to four times per day) is anecdotally effective in achieving relief from acute vertigo attacks [150].

Betahistine is a conservative treatment option widely used in Europe for Ménière disease. It is believed to decrease symptoms by improving microcirculation in the inner ear and re-balancing endolymph production with resorption [151]. In one study, patients with mixed vestibular etiologies including Ménière disease received betahistine 48 mg/day. The decrease in average vertigo attacks per month from baseline to 60 days on betahistine persisted unchanged at 60 days off betahistine, which may suggest durable vestibular compensation [129]. As mentioned, demonstrating a treatment effect separate from spontaneous remission is difficult in Ménière disease and other s-EVS disorders.

Based on clinical experience with long-term treatment in patients with Ménière disease, long-term, high-dose betahistine is the recommended therapy, initiated at 48 mg three times per day [40; 61]. If symptom alleviation is insufficient after three months, the dose can be increased up to 480 mg/day [119; 152]. As noted, betahistine can be obtained at compounding pharmacies in the United States with a prescription [15].

Second Tier

Intratympanic injection (ITI) of corticosteroids is suggested for patients with Ménière disease-related disabling vertigo attacks despite conservative treatments, as the complication rates are low and side effects minimal. ITI of 0.4–1.0 mL high-dose dexamethasone solution (12 mg/mL) can improve vertigo symptoms and patient functioning, which may remain durable over 6 to 24 months [119]. However, patients may require repeated injections to maintain efficacy that can wane over time, and intratympanic gentamicin may be more effective [150].

 Copyright © 2019 NetCE

Third Tier

Intratympanic gentamicin, a vestibulotoxic antibiotic, is a favored approach for Ménière disease refractory to less invasive options. Gentamicin induces unilateral vestibular loss to facilitate central compensation, reduce Ménière disease symptoms, and improve overall function [97; 153]. Meta-analyses of published clinical trials found 92.7% of patients achieved complete or substantial vertigo control and 74.7% achieved complete vertigo control with intratympanic gentamicin [98; 154].

ITI of gentamicin is ototoxic in some patients and has mainly been reserved for patients with Ménière disease and pre-existing hearing loss. To offset this limitation, a newer technique injects a minimal dose of gentamicin (0.5–0.75 mL of a 40 mg/mL solution) into the middle ear. A single injection provided good vertigo control over four years in 76% of patients; 15% to 20% required a second injection [150].

ITI gentamicin (2.0 mL of 40.0 mg/mL solution; up to two injections) was superior to ITI dexamethasone (4 mg/mL, three injections over seven days) in achieving complete vertigo control (81.0% vs. 43%) and complete or substantial vertigo control (93.5% vs. 61%). Significant hearing loss (>10 dB) developed in 13% of patients taking gentamicin [150; 155].

Intractable Bilateral Ménière Disease

Ménière disease may become bilateral in 15% to 20% of patients, usually within the first several years of onset. Bilateral involvement limits some vestibular ablation options, because treating both ears can result in bilateral vestibular loss [15]. Treating one side may not relieve vertigo, and interventional treatment can cause permanent hearing loss in a patient already at risk of hearing loss in both ears [125].

Options for intractable Ménière disease include endolymphatic mastoid shunt procedures, vestibular neurectomy, or labyrinthectomy, the latter used only in patients already deaf in the affected ear. Ablative surgical procedures are mainly reserved for ITI gentamicin failure. Because the development of Ménière disease is multifactorial, no single approach to therapy is expected to become the standard for all patients [147].

Vestibular Migraine

Treatment efficacy for vestibular migraine is not well-studied, partially because the disorder was only defined in 2013 [156]. Established treatments for migraine and/or vertigo are primarily recommended as abortive or prophylactic therapies for migraine symptoms in vestibular migraine. These medications may improve both headache and vertigo symptoms but can be hit or miss, and patients may need several different trials to find an individualized therapy [156; 157].

Symptomatic Treatment of Acute Episodes

Acute attacks of vestibular migraine are treated with vestibular suppressants that include benzodiazepines (e.g., clonazepam, lorazepam), antiemetics (e.g., promethazine), antihistamines (e.g., meclizine, dimenhydrinate), and anticholinergic agents (e.g., scopolamine) [157]. Patients with excessive nausea or vomiting may prefer non-oral (e.g., IV, nasal spray, suppositories, subcutaneous injections) routes [158].

Abortive Treatment

Acute migraine treatment with triptans may offer benefit for patients with vestibular migraine. Sumatriptan was particularly efficacious in improving vertigo; rizatriptan helped prevent motion sickness symptoms. Zolmitriptan probably has little benefit in vestibular migraine [157].

Prophylactic Treatment

Treatment with migraine prophylactic medication may be needed when symptoms are frequent or severe and interfere with quality of life [15]. The indications for prophylactic therapy in vestibular migraine mirror those in migraine, which consider the frequency, duration, and disabling nature of attacks [119]. If caffeine and other triggers play a role in inciting episodes, they should be avoided when possible, as avoidance may enhance the efficacy of prophylactic therapy in vestibular migraine [49; 157].

Medications evaluated for prophylactic efficacy in vestibular migraine include antiepileptic drugs (e.g., topiramate, valproate/valproic acid, lamotrigine), beta-adrenergic blockers (e.g., propranolol, metoprolol sustained-release, bisoprolol), calcium channel blockers (e.g., flunarizine, verapamil extended-release, cinnarizine), and antidepressants (e.g., venlafaxine, nortriptyline, imipramine, amitriptyline). Prophylactic recommendations have been based on available evidence, attack frequency, and clinical profile (***Table 3***).

Vestibular Migraine and Anxiety

Patients with vestibular migraine are more anxious than patients with non-vestibular migraine [162]. Anxiety is so prevalent in vestibular migraine, migraine, and vestibular disorders that a new disorder—migraine-anxiety-related dizziness—was proposed to define the association [49].

The recommended pharmacotherapy for vestibular patients with prominent anxiety, panic attacks, or depression and less prominent nausea is [15]:

- Venlafaxine 75 mg/day, OR
- A tricyclic antidepressant (e.g., nortriptyline, imipramine, amitriptyline) 50–75 mg/day

PROPHYLACTIC PHARMACOTHERAPY FOR VESTIBULAR MIGRAINE	
Characteristic	**Recommended Agent(s)**
By Available Evidence	
High-quality evidence of efficacy	Topiramate 25–100 mg/day Valproate 300–900 mg/day Metoprolol sustained-release 50–200 mg/day
Moderate-quality evidence of efficacy	Propranolol 40–240 mg/day Flunarizine 5–10 mg/day
Low-to-moderate-quality evidence of efficacy	Amitriptyline 50–100 mg/day Verapamil extended-release 120–360 mg/day Cinnarizine 37.5–75 mg/day
Lowest-quality evidence of efficacy	Acetazolamide 250–750 mg/day
By Attack Frequency	
Three or more attacks per month or long-lasting/disabling attacks	First-line: Propranolol 80–240 mg/day, metoprolol 50–200 mg/day, or bisoprolol 5–10 mg/day Second-line: Flunarizine 5–10 mg/day Third-line: Topiramate 25–100 mg/day or valproic acid 500–600 mg/day
Fifteen migraine attacks or more than eight migraine headaches per month for longer than three months	First-line: Topiramate 25–100 mg/day Second-line: A trial of onabotulinum toxin type A (155 MU) is reasonable but unlikely to improve vestibular symptoms
By Clinical Profile	
Prominent nausea and/or headaches and less prominent or minimal anxiety	Verapamil 120–240 mg/day (well-tolerated medication with good efficacy) Alternative: Topiramate 50–200 mg/day (often effective)
Prominent vertigo or dizziness, less frequent migraine headache	Lamotrigine 25–100 mg/day to reduce the frequency of vertigo episodes; less effective in reducing headache frequency
Severe vestibular migraine	Combination of two or three migraine prophylactic medications from different drug classes Consider zonisamide or acetazolamide
Source: [15; 119; 158; 159; 160; 161]	*Table 3*

The established efficacy of venlafaxine in anxiety disorder treatment suggests a potential advantage over other vestibular migraine prophylaxis. One study evaluated patients with vestibular migraine randomized to venlafaxine (37.5 mg/day), flunarizine (10 mg/day), or valproic acid (1,000 mg/day) for three months [163]. Significant decreases in precipitating physical factors and functional consequences of vestibular migraine were noted with all three medications. Improvements in emotional consequences of vestibular migraine (with venlafaxine only), vertigo attack severity (with venlafaxine and flunarizine but not valproic acid), and vertigo attack frequency (with venlafaxine and valproic acid but not flunarizine) were also noted. This suggests venlafaxine more effectively reduced emotional distress and anticipatory anxiety related to vestibular migraine attacks, as well as attack frequency and severity [163].

Other Treatment Options

Betahistine plus flunarizine leads to greater improvements in vertigo frequency and severity than betahistine alone. Decreases in headache frequency and severity are comparable [164].

Vestibular rehabilitation is effective, with improved symptoms and disability in patients with vestibular migraine as add-on treatment to medical therapy or as stand-alone treatment [49; 157].

Vestibular Paroxysmia

With vestibular paroxysmia, the characteristic brevity (seconds up to a few minutes, very seldom many hours) and frequently of recurring vertigo attacks makes the differential diagnosis generally straightforward [46]. The frequent vertigo attacks respond to carbamazepine (200–800 mg/day) or oxcarbazepine (300–900 mg/day), even in the lower dose range. Both drugs are recommended to start with a low dose, slowly progressing to higher doses as necessary [119].

 Copyright © 2019 NetCE

Second-Line Therapies for Carbamazepine/ Oxcarbazepine Intolerance

Alternative drug options include phenytoin, gabapentin, valproate, lamotrigine, topiramate, and baclofen or other non-antiepileptic drugs used in trigeminal neuralgia [46]. Treatment should start with low doses. Options include [119]:

- Phenytoin 100 mg once daily, increased up to three times per day
- Gabapentin 300 mg once daily, increased to three times daily over four to seven days and further increased with insufficient symptom relief (up to a maximum 1,800 mg)
- Valproate dosing proportional to body weight (start with 10 mg per kg body weight, increasing the dose every three days up to 20 mg/kg)

Antiepileptic medications can themselves elicit dizziness and should be prescribed cautiously, ideally by specialists who can differentiate possible side effects from dizziness or vertigo sensations per se [119].

Refractory Vestibular Paroxysmia

Surgical microvascular decompression of the 8th cranial nerve is used for medically intractable cases or in rare cases with non-vascular compression of the 8th nerve by a tumor or cyst [46].

CHRONIC VESTIBULAR SYNDROMES

Context-Specific (Triggered) CVS

Most t-CVS syndromes have been defined too recently for consistently effective therapies to surface. There is some evidence for the treatment of bilateral vestibulopathy, PPPD, depersonalization and derealization disorder, and mal de débarquement syndrome.

Bilateral Vestibulopathy

The primary cause of bilateral vestibulopathy is aminoglycoside ototoxicity, typically gentamicin or streptomycin. In these cases, the ototoxic medication should be stopped or switched to a non-ototoxic drug. Other underlying causes of bilateral vestibulopathy include autoimmune processes, local or systemic infectious/inflammatory processes, bacterial or viral meningitis, bilateral Ménière disease, head trauma, neoplasms, or malformations. The cause should be identified and resolved or symptomatically managed [119].

Vestibular rehabilitation improves dynamic visual acuity, diminishes oscillopsia, and lessens asymmetry of vestibulo-ocular function by promoting adaptation and substitution using vision and proprioceptive cues to stabilize gait and mobility [165]. Vestibular rehabilitation is strongly recommended for patients with bilateral vestibulopathy [15; 119].

Persistent Postural Perceptual Dizziness

Cognitive-behavioral therapy, possibly combined with an SNRI such as venlafaxine or duloxetine, is strongly recommended for patients with PPPD. Patients should be encouraged to not stop taking the antidepressant too early; four to five weeks is required to assess effectiveness [15; 119]. Vestibular rehabilitation can help address phobic avoidance behavior.

Depersonalization and Derealization Disorder

Patients with depersonalization and derealization disorder have benefited from SSRIs, benzodiazepines, lamotrigine, opioid antagonists, and CNS stimulants, probably from targeting other mental disorders commonly associated with or precipitated by the disorder [80].

Mal de Débarquement Syndrome

There is no established treatment for mal de débarquement syndrome, but an uncontrolled trial suggests that inducement of re-adaptation of the vestibulo-ocular reflex may result in improvement. In this approach, patients are exposed periodically to a rocking that mimics the pace and direction of their perceived sway while in a full-field optokinetic stimulus [15; 166].

Spontaneous CVS

Central Vestibular and Cerebellar Syndromes

The American Academy of Neurology has made the following treatment recommendations for cerebellar syndromes associated with nystagmus, vertigo, and ataxia [167]:

- Episodic ataxia type 2: 4-AP 15 mg/day
- Spinocerebellar ataxia or ataxia of mixed etiology: Riluzole
- Spinocerebellar ataxia type 3: Valproic acid 1,200 mg/day
- Spinocerebellar degeneration: Thyrotropin-releasing hormone over 14 days
- Degenerative ataxias: Inpatient rehabilitation (four weeks) to improve ataxia and function, transcranial magnetic stimulation to improve cerebellar motor signs

In episodic ataxia type 2, other treatment recommendations include [15; 119]:

- Acetazolamide 375–1,500 mg/day
- Dalfampridine sustained-release 10 mg PO once or twice per day

Cervicogenic Vertigo

With cervical vertigo, treatment options include manual therapy, muscle relaxant or anti-inflammatory medication, and tailored vestibular rehabilitation. With significant nerve compression that cannot be treated conservatively, interventional approaches remain a therapeutic option [119].

Post-Traumatic Vertigo

In patients with post-traumatic vertigo, the primary diagnosis should be treated. With BPPV present, CRP plus vestibular rehabilitation is the recommended approach. For patients with brainstem or labyrinthine concussion, use vestibular rehabilitation. Vestibular suppressants may be added in cases of labyrinthine concussion [22].

DIZZINESS AND FALLS PREVENTION IN OLDER PATIENTS

Vestibular dysfunction in older adults places them at substantially increased risk for what?

Dizziness and imbalance in older adults deserves specific attention. Among older adults (i.e., age older than 65 years), falls are the leading cause of disability, institutionalization, and premature mortality from injury and the fifth leading cause of death. Fear of falling, also called post-fall anxiety syndrome, is a well-recognized syndrome in older adults [168; 169; 170]. In 2015, the estimated cost of fall-related injuries in older adults in the United States was $50 billion [171].

As such, vestibular dysfunction is critical to identify in older adults. Dizziness is highly prevalent (up to 38%) in older patients, and symptomatic dizziness or vertigo substantially increases the risk for falls [172; 173].

During 2001–2004, an estimated 35.4% of adult Americans had vestibular dysfunction requiring medical attention. The prevalence of balance impairment and vestibular dysfunction increases with age—the rate is 75% among persons older than 70 years and 85% among persons 80 years of age or older. Persons with vestibular disorders have an eight-fold increase in risk of falling and resultant morbidity/mortality. Uncompensated vestibular hypofunction results in postural instability, visual blurring with head movement, and subjective complaints of dizziness and/or imbalance [44].

RISK FACTORS FOR FALLS IN THE ELDERLY

Falls typically result when age-related and environmental (e.g., unfamiliar surroundings, unsafe walking surface) risk factors intersect. Gait and balance impairment are the most consistent risk factors, followed by medications (e.g., benzodiazepines, antidepressants) and polypharmacy [174]. Older patients may have multiple risk factors, including vestibular dysfunction, cerebrovascular disease, cervical spine disorders, physical deconditioning, and postural hypotension. Visual impairment is common and promotes multisensory deficit [173; 175].

Postural control and balance rely on sensory input from proprioceptive and vestibular systems. Age-related changes in these systems impair postural control and increase the risk of falls; they include loss of proprioceptive sensitivity in the lower extremities and loss of labyrinthine hair cells, vestibular ganglion cells, and nerve fibers in the vestibular system [174]. Compounding the loss of proprioceptive and vestibular function are age-related changes in the CNS, including neuronal loss and neurotransmitter depletion, causing further impairments in postural control [174].

ASSESSMENT OF FALLS RISK

A targeted history and physical exam can identify patients at risk for falling. All older patients, especially patients with a dizziness/vertigo diagnosis, should be asked at least once yearly about falls [174]. Questions for initial screening of falls risk include [22]:

- Have you had a fall in the past year? How many times? Were you injured?
- Do you feel unsteady when standing or walking?
- Do you worry about falling?

With positive response, the clinician can perform a more detailed assessment or refer the patient to a specialist [22]. Treatment should be directed at the most readily modifiable fall risk factor(s) [173].

Clinicians should counsel patients and their families on the risk of falls with any balance, dizziness, or vestibular disorder, especially the frail elderly, who are more susceptible to serious injury from falling. Counseling should occur during the initial diagnosis and can include assessment of home safety, activity restrictions, and the need for home supervision until symptoms resolve. Healthcare providers should also ask about dizziness while driving, which may require intervention to prevent patient and public injury or fatality [22; 173; 176].

 Copyright © 2019 NetCE

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such an important aspect of the care of patients with dizziness/vertigo, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient or caregiver understanding. 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.

In this multicultural landscape, interpreters are 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 diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

Knowledge advances are transforming the clinical care of patients with dizziness and vertigo. A paradigm-changing classification system and diagnostic algorithm for dizziness and vertigo affords greater diagnostic ease and accuracy for clinicians. An expanded understanding of the vestibular system highlights the relationship of anxiety to vestibular dysfunction. The differentiation of potentially dangerous cerebrovascular mimics of benign vertigo and dizziness enhances early detection and rapid intervention. The important contribution of vestibular dysfunction to risk for falls in the elderly has been clarified, as falls are a leading cause of disability and death from injury in this population. Despite the demonstrated efficacy of repositioning therapy for the management of BPPV and the ease with which this can be used in the primary care setting, patients with BPPV frequently experience delayed diagnosis, unnecessary testing, and non-recommended treatment. Thus, continuing education has an important role in helping to ensure that clinicians and their patients benefit from current concepts, tools of evaluation, and strategies for managing dizziness and vertigo.

RESOURCES

Vestibular Disorders Association (VeDA)
https://vestibular.org

Fall Prevention Center of Excellence
http://stopfalls.org

David E. Newman-Toker, MD, PhD
Johns Hopkins Medicine

HINTS Video
https://collections.lib.utah.edu/details?id=177180

Dix-Hallpike Maneuver Video
https://collections.lib.utah.edu/details?id=177177

Supine Head Roll Video
https://collections.lib.utah.edu/details?id=177185

Customer Information/Evaluation insert located between pages 96–97.

Palliative Care and Pain Management at the End of Life

Includes 10 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for all members of the interprofessional team, including nurse practitioners, nurses, physicians, physician assistants, pharmacists, pharmacy technicians, social workers, marriage and family therapists, and other members seeking to enhance their knowledge of palliative care.

Course Objective
The purpose of this course is to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and a discussion of the challenges, benefits, and strategies of optimum palliative care at the end of life.

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

1. Describe how the definition of palliative care has evolved.
2. Define the structure of palliative care delivery, including models of care and the inter-disciplinary healthcare team.
3. List the benefits of palliative care at the end of life.
4. Anticipate the barriers to optimum delivery of palliative care through hospice.
5. Effectively engage the components of communication and decision making for end-of-life care.
6. Identify the common concerns and symptoms at the end of life for patients with life-limiting diseases.
7. Discuss the barriers to effective relief of pain at the end of life.
8. Assess pain accurately through use of clinical tools and other strategies.
9. Select appropriate pharmacologic and/or nonpharmacologic therapies to manage pain in patients during the end-of-life period.
10. Assess and manage the most common symptoms (other than pain) experienced by patients during the end-of-life period.
11. Evaluate the psychosocial needs of patients at the end of life and their families and provide appropriate treatment or referral.
12. Recognize and address the spiritual needs of patients at the end of life and provide appropriate treatment or referral.
13. Develop a strategy for providing care to patients and their families over the last days and hours of life.
14. Support appropriate grief and mourning.
15. Explain the specific challenges and ethical considerations in delivering optimum palliative care to older patients, children, and patients in critical care settings.

Faculty
Lori L. Alexander, MTPW, ELS, MWC, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the American Medical Writers Association (AMWA) Journal, the peer-review journal representing the largest association of medical communicators in the United States. Ms. Alexander earned a Master's degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

Faculty Disclosure
Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

A full Works Cited list is available online at www.NetCE.com. ***Mention of commercial products does not indicate endorsement.***

 Copyright © 2019 NetCE

Accreditations & Approvals

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Designations of Credit

NetCE designates this continuing education activity for 15 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 15 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 10 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 11/21/2021); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2019); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

How to Receive Credit

- Read the following course.
- Complete the Evaluation.
- Return your Customer Information/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/GIA19**.
- A full Works Cited list is available online at www.NetCE.com.

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 concept of palliative care has garnered much attention since the term was first used in the late 1960s to refer to a holistic approach to patient-centered care, with a focus on enhancing the quality of life for patients living with serious illness and their families. As currently practiced, palliative care is interdisciplinary team care designed to engage the expertise of providers from different clinical disciplines. The purpose of palliative care is to alleviate suffering and provide comfort; to this end, the primary goals are relief of pain and other distressing symptoms, effective communication with the patient and family in order to establish patient-centered goals of care, attentiveness to psychologic and spiritual needs, and support for family members. With its roots in hospice care, the term "palliative care" has long been used interchangeably with "end-of-life care." However, in contrast to hospice, the initiation of palliative care is not contingent upon the expectation that the patient has less than six months to live or that disease-directed therapy has run its course. Across all specialties, the emphasis now is on the integration of palliative care into the ongoing management strategy for any patient with a serious, life-threatening illness, regardless of age. Hospice care is palliative care provided in the last weeks and months of life, when disease-directed or curative treatment has been exhausted or deemed no longer to be of benefit [1].

Palliative care at the end of life is delivered most effectively through hospice. Palliative care/hospice was once primarily confined to the cancer setting because of the evident and often rapid health decline to death with this disease. Hospice extended to the acquired immunodeficiency syndrome (AIDS) setting for the same reason. Ongoing advances in medicine have changed these once-lethal diseases into chronic conditions, shifting the trajectory of illness and leaving a growing number of patients in need of palliative care for longer periods of time. Similarly, individuals with other life-limiting diseases, such as heart failure, chronic obstructive pulmonary disease (COPD), end-stage renal disease, and dementia, are in need of similar care. Thus, a growing number of individuals could benefit from palliative care. However, palliative/hospice care is underutilized in the United States for a variety of reasons, and many patients experience an unnecessary degree of physical and psychologic suffering at the end of life [1;13].

Both clinician- and patient-related factors contribute to the underuse of palliative/hospice care. In addition, evidence-based guidelines are lacking for end-of-life care for many noncancer life-threatening conditions. More research on the prevalence and severity of symptoms and functional status in patients with life-limiting diseases, as well as the efficacy of interventions is needed to generate these much-needed guidelines.

This course is designed to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and associated clinical issues and a discussion of the benefits and barriers to optimum palliative care at the end of life. Central to this discussion is an emphasis on the importance of talking to patients about the value of palliative care, of clearly presenting the prognosis and appropriate treatment options and goals, and of ensuring that advance planning is completed. The majority of the course focuses on the assessment and management of the most common end-of-life needs, with particular attention to pain, the most prevalent, as well as the most distressing, physical symptom. Psychosocial and spiritual needs of the patient and family are also discussed. Palliative care presents unique challenges for some patient populations, most notably older patients, children/adolescents, and patients receiving critical care. An overview of the most important issues specific to these settings is provided.

CONCEPT OF PALLIATIVE CARE

EVOLVING DEFINITION OF PALLIATIVE CARE

What are challenges of defining palliative care?

The term "palliative care" was first used by Balfour Mount, a Canada-trained physician and visiting professor at St. Christopher's Hospice, the first program of its kind. Dr. Mount subsequently established a palliative care program at Royal Victoria Hospital in Montreal, the first such program to be integrated in an academic teaching hospital [2]. Since that time, many attempts have been made to craft a definition of palliative care that represents its unique focus and goals. The challenge in defining palliative care has been encompassing all that such care refers to while specifying the timing of it (***Table 1***) [3; 4; 5; 6; 7]. The timing of palliative care remains an important point of discussion. As a result of its roots in hospice care, the term "palliative care" has often been considered to be synonymous with "end-of-life care." However, the current emphasis is to integrate palliative care earlier in the overall continuum of care (***Figure 1***) [5; 8].

As the definition of palliative care has evolved, end-of-life care has become one aspect of palliative care. The time period assigned to "end of life" has not been defined, with the phrase being used to describe an individual's last months, weeks, days, or hours [9; 10]. Designating a specific time period as the "end of life" is further challenged by disease trajectories that differ depending on the underlying life-limiting disease, a problem discussed in detail later in this course.

EFFORTS TO ENHANCE PALLIATIVE CARE AT THE END OF LIFE

Since the establishment of the first hospice in the United States in 1974, many initiatives have been undertaken to enhance the quality of care given at the end of life. The lack of progress in relieving end-of-life suffering was highlighted with the publication of findings from the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) [11; 12]. The results of this landmark study indicated that in-hospital deaths were characterized by prolonged suffering, uncontrolled pain, and caregiver hardship. In response, the Institute of Medicine (IOM) commissioned a report on the quality of care at the end of life, and the authors of this report, *Approaching Death: Improving Care at the End of Life*, noted that too many patients "suffer needlessly" at the end of life and emphasized the need for better training of healthcare professionals and reform of outdated laws that inhibited the use of pain-relieving drugs [13]. A subsequent IOM report pointed out the need for enhanced pediatric palliative care [14]. Several initiatives have been developed to address the deficiencies in the quality of pallia-

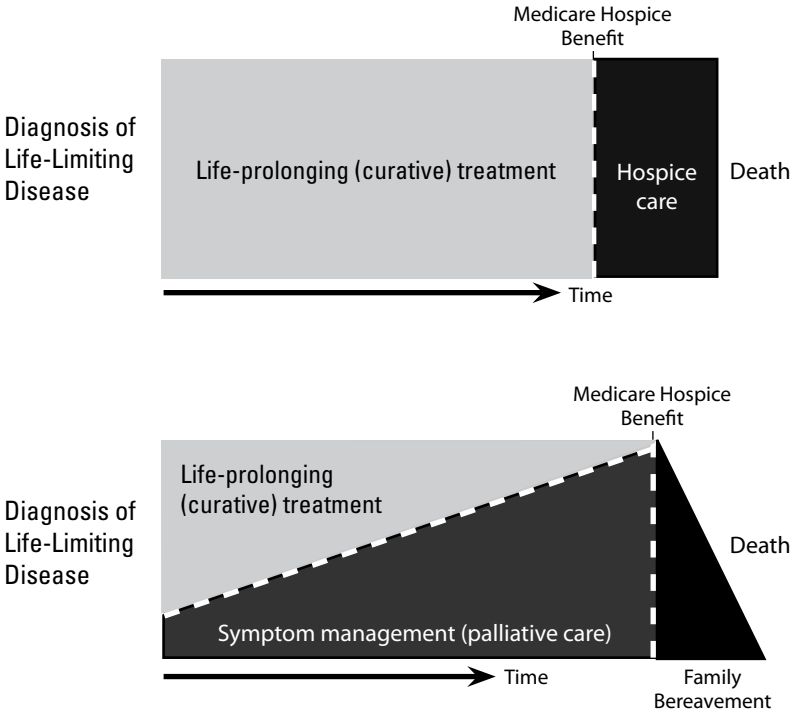
 Copyright © 2019 NetCE

EVOLVING DEFINITION OF PALLIATIVE CARE		
Year	**Source and Definition**	**Comments**
1990	World Health Organization (WHO): "…The active total care of patients whose disease is not responsive to curative treatment."	Does not apply exclusively to palliative care
1993	*The Oxford Textbook of Palliative Medicine*: "The study and management of patients with active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is the quality of life."	Lacks essential aspects, such as support provided to families, as well as specificity about timing
2004	National Consensus Project: "The goal of palliative care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies…" Palliative care expands traditional disease-model medical treatments to include the goals of enhancing quality of life for patient and family, optimizing function, helping with decision making, and providing opportunities for personal growth. As such, it can be delivered concurrently with life-prolonging care or as the main focus of care.	First definition to reflect integration of palliative care earlier into the disease continuum
2007	WHO (revision): "An approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual."	Improvement over original WHO definition, but expansion of palliative care throughout the continuum of care not explicit
2009	American Society of Clinical Oncology: "Palliative cancer care is the integration into cancer care of therapies to address the multiple issues that cause suffering for patients and their families and have an impact on the quality of their lives. Palliative cancer care aims to give patients and their families the capacity to realize their full potential, when their cancer is curable as well as when the end of life is near."	Defines palliative care for patients with cancer, but definition can be applied to palliative care in all settings
2013	National Consensus Project: "Palliative care means patient and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social, and spiritual needs and to facilitate patient autonomy, access to information, and choice."	Characterization of palliative care in the United States, as defined by the U.S. Department of Health and Human Services and the National Quality Forum
Source: [3; 4; 5; 6; 7]		*Table 1*

tive care; to optimize the use of hospice; to help the lay public better understand the meaning of palliative care and hospice and their benefits; and to enhance the knowledge, skills, and attitudes of healthcare professionals. Five organizations—the American Academy of Hospice and Palliative Medicine (AAHPM), the Center to Advance Palliative Care (CAPC), the Hospice and Palliative Nurses Association, the Last Acts Partnership, and the National Hospice and Palliative Care Organization (NHPCO)—joined forces in the National Consensus Project for Quality Palliative Care Consortium and published clinical practice guidelines to help reduce the variation in palliative care programs and enhance continuity of care across healthcare settings [5]. The National Quality Forum (NQF) built on these guidelines when it proposed a national framework for palliative and hospice care [15].

Other efforts included the first core curriculum in hospice and palliative care, created by the AAHPM; the development of the Education in Palliative and End-of-Life Care (EPEC) Project (https://www.bioethics.northwestern.edu/programs/epec); and the subsequent development of the EPEC-Oncology (EPEC-O) curriculum and the End-of-Life Nursing Education Consortium Project (https://www.aacnnursing.org/ELNEC).

EVOLUTION OF THE PALLIATIVE CARE MODEL



Source: [8] *Figure 1*

COMPONENTS OF HIGH-QUALITY PALLIATIVE CARE

What are the priorities for patients with a life-limiting illness receiving palliative care?

Because palliative care focuses on the physical and psychosocial needs of the patient and his or her family, the patient's and family's perspectives are vital considerations in developing high-quality palliative care programs. An early survey of patients with life-limiting diseases identified five priorities for palliative care: receiving adequate treatment for pain and other symptoms, avoiding inappropriate prolongation of life, obtaining a sense of control, relieving burden, and strengthening relationships with loved ones [16]. In another study, a spectrum of individuals involved with end-of-life care (physicians, nurses, social workers, chaplains, hospice volunteers, patients, and recently bereaved family members) echoed these findings, with the following factors being noted as integral to a "good death:" pain and symptom management, clear decision making, preparation for death, completion, contributing to others, and affirmation of the whole person [17].

The priorities set by patients and healthcare professionals were considered carefully in the structuring of clinical practice guidelines for high-quality palliative care developed by the National Consensus Project for Quality Palliative Care. These guidelines are organized according to eight domains [5]:

- Structure and processes of care
- Physical aspects
- Psychologic and psychiatric aspects
- Social aspects
- Spiritual, religious, and existential aspects
- Cultural aspects
- Care of the patient nearing the end of life
- Ethical and legal aspects

In its publication, the NQF sets forth 39 guidelines based on these eight domains (***Table 2***) [5].

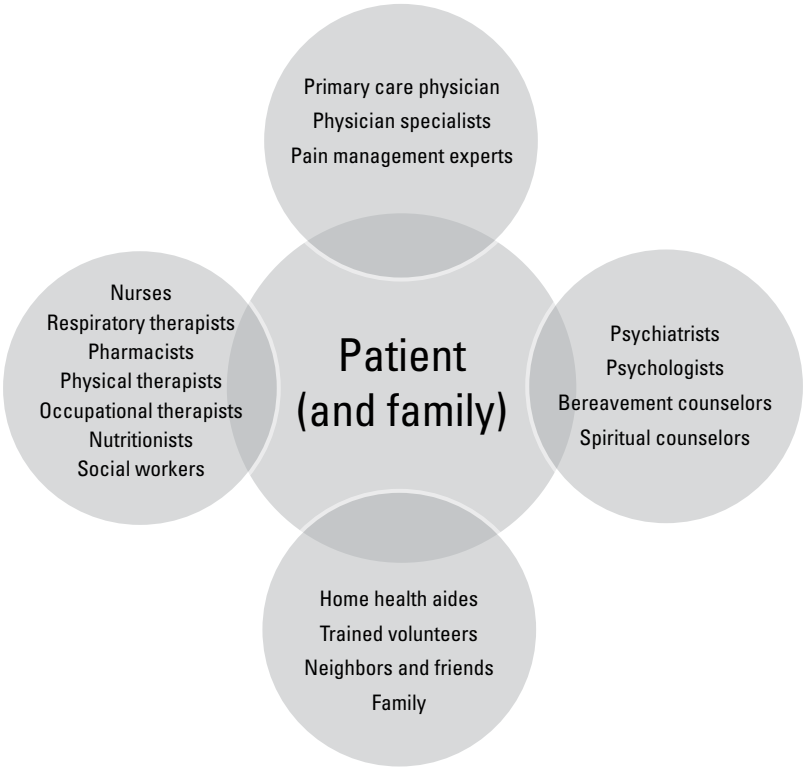
 Copyright © 2019 NetCE

GUIDELINES FOR PALLIATIVE AND HOSPICE CARE

1. Since palliative care is holistic in nature, it is provided by a team of physicians, advanced practice registered nurses, physician assistants, nurses, social workers, chaplains, and others based on need.
2. An interdisciplinary comprehensive assessment of the patient and family forms the basis for the development of an individualized patient and family palliative care plan.
3. In collaboration with the patient and family, the IDT develops, implements, and updates the care plan to anticipate, prevent, and treat physical, psychological, social, and spiritual needs.
4. The IDT has defined processes to ensure access, quality, and continuity of care, especially during transitions of care.
5. Palliative care is provided in any care setting, including private residences, assisted living facilities, rehabilitation, skilled and intermediate care facilities, acute and long-term care hospitals, clinics, hospice residences, correctional facilities, and homeless shelters.
6. Education, training, and professional development are available to the IDT.
7. Care is coordinated and characterized as the right care at the right time throughout the course of an individual's disease(s) or condition. The IDT recognizes that transitions of care occur within care settings, between care settings, and between care providers. Care transitions are anticipated, planned, and coordinated to ensure patient goals are achieved.
8. Providing palliative care to patients with a serious illness and their families has an emotional impact, therefore the IDT creates an environment of resilience, self-care, and mutual support.
9. In its commitment to continuous quality improvement (CQI), the IDT develops, implements, and maintains a data-driven process focused on patient- and family-centered outcomes using established quality improvement methodologies.
10. Recognizing limitations in reimbursement for interdisciplinary palliative care, the IDT endeavors to secure funding for long-term sustainability and growth.
11. The palliative care interdisciplinary team (IDT) endeavors to relieve suffering and improve quality of life, as defined by the patient and family, through the safe and timely reduction of the physical symptoms and functional impairment associated with serious illness.
12. The IDT assesses physical symptoms and their impact on well-being, quality of life, and functional status.
13. Interdisciplinary care plans to address physical symptoms, maximize functional status, and enhance quality of life are developed in the context of the patient's goals of care, disease, prognosis, functional limitations, culture, and care setting. An essential component of palliative care is ongoing management of physical symptoms, anticipating changes in health status, and monitoring of potential risk factors associated with the disease and side effects due to treatment regimens.
14. The palliative care team provides written and verbal recommendations for monitoring and managing physical symptoms.
15. The IDT includes a social worker with the knowledge and skills to assess and support mental health issues, provide emotional support, and address emotional distress and quality of life for patients and families experiencing the expected responses to serious illness. The IDT has the training to assess and support those with mental health disorders, either directly, in consultation, or through referral to specialist level psychological and/or psychiatric care.
16. The IDT screens for, assesses, and documents psychological and psychiatric aspects of care based upon the best available evidence to maximize patient and family coping and quality of life.
17. The IDT manages and/or supports psychological and psychiatric aspects of patient and family care including emotional, psychosocial, or existential distress related to the experience of serious illness, as well as identified mental health disorders. Psychological and psychiatric services are provided either directly, in consultation, or through referral to other providers.
18. The IDT provides recommendations for monitoring and managing long-term and emerging psychological and psychiatric responses and mental health concerns.
19. The palliative care IDT has the skills and resources to identify and address, either directly or in collaboration with other service providers, the social factors that affect patient and family quality of life and well-being.
20. The IDT screens for and assesses patient and family social supports, social relationships, resources, and care environment based on the best available evidence to maximize coping and quality of life.
21. In partnership with the patient, family, and other providers, the IDT develops a care plan for social services and supports in alignment with the patient's condition, goals, social environment, culture, and setting to maximize patient and family coping and quality of life across all care settings.
22. A palliative care plan addresses the ongoing social aspects of patient and family care, in alignment with their goals and provides recommendations to all clinicians involved in ongoing care.
23. Patient and family spiritual beliefs and practices are assessed and respected. Palliative care professionals acknowledge their own spirituality as part of their professional role and are provided with education and support to address each patient's and family's spirituality.
24. The spiritual assessment process has three distinct components—spiritual screening, spiritual history, and a full spiritual assessment. The spiritual screening is conducted with every patient and family to identify spiritual needs and/or distress. The history and assessment identify the spiritual background, preferences, and related beliefs, values, rituals, and practices of the patient and family. Symptoms, such as spiritual distress and spiritual strengths and resources, are identified and documented.
25. The IDT addresses the spiritual needs of the patient and family.
26. Patient and family spiritual care needs can change as the goals of care change or patients move across settings of care.
27. The IDT delivers care that respects patient and family cultural beliefs, values, traditional practices, language, and communication preferences and builds upon the unique strengths of the patient and family. Members of the IDT work to increase awareness of their own biases and seek opportunities to learn about the provision of culturally sensitive care. The care team ensures that its environment, policies, procedures, and practices are culturally respectful.
28. The IDT ensures that patient and family preferred language and style of communication are supported and facilitated in all interactions.
29. The IDT uses evidence-based practices when screening and assessing patient and family cultural preferences regarding health care practices, customs, beliefs and values, Llevel of health literacy, and preferred language.
30. A culturally sensitive plan of care is developed and discussed with the patient and/or family. This plan reflects the degree to which patients and families wish to be included as partners in decision-making regarding their care. When hosting meetings to discuss and develop the plan, the IDT ensures that patient and family linguistic needs are met.
31. The IDT includes professionals with training in end-of-life care, including assessment and management of symptoms, communicating with patients and families about signs and symptoms of approaching death, transitions of care, and grief and bereavement. The IDT has established structures and processes to ensure appropriate care for patients and families when the end of life is imminent.
32. The IDT assesses physical, psychological, social, and spiritual needs, as well as patient and family preferences for setting of care, treatment decisions, and wishes during and immediately following death. Discussions with the family focus on honoring patient wishes and attending to family fears and concerns about the end of life. The IDT prepares and supports family caregivers throughout the dying process, taking into account the spiritual and cultural background and preferences of the patient and family.
33. In collaboration with the patient and family and other clinicians, the IDT develops, implements, and updates (as needed) a care plan to anticipate, prevent, and treat physical, psychological, social, and spiritual symptoms. The care plan addresses the focus on end-of-life care and treatments to meet the physical, emotional, social, and spiritual needs of patients and families. All treatment is provided in a culturally and developmentally appropriate manner.
34. During the dying process, patient and family needs are respected and supported. Post-death care is delivered in a manner that honors patient and family cultural and spiritual beliefs, values, and practices.
35. Bereavement support is available to the family and care team, either directly or through referral. The IDT identifies or provides resources, including grief counseling, spiritual support, or peer support, specific to the assessed needs. Prepared in advance of the patient's death, the bereavement care plan is activated after the death of the patient and addresses immediate and longer-term needs.
36. The core ethical principles of autonomy, substituted judgment, beneficence, justice, and nonmaleficence underpin the provision of palliative care.
37. The provision of palliative care occurs in accordance with federal, state, and local regulations and laws, as well as current accepted standards of care and professional practice.
38. The patient's preferences and goals for medical care are elicited using core ethical principles and documented.
39. Within the limits of applicable state and federal laws, current accepted standards of medical care, and professional standards of practice, person-centered goals form the basis for the plan of care and decisions related to providing, forgoing, and discontinuing treatments.

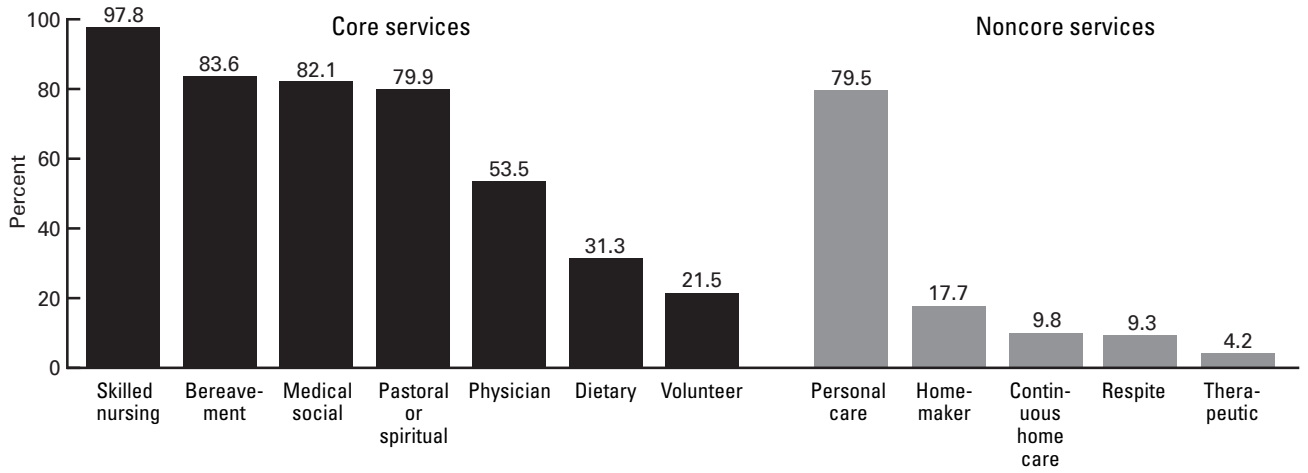
Source: [5] Reprinted with permission from National Consensus Project for Quality Palliative Care Consortium Organizations. Clinical Practice Guidelines for Quality Palliative Care. 4th ed. Pittsburgh, PA: National Consensus Project; 2018. *Table 2*

MEMBERS OF THE PALLIATIVE CARE TEAM



Source: [15; 25; 26; 27] *Figure 2*

SERVICES PROVIDED DURING HOSPICE CARE



Source: [30] Reprinted from Caffrey C, Sengupta M, Moss A, Harris-Kojetin L, Valverde R. Home health care and discharged hospice care patients: United States, 2000 and 2007. Natl Health Stat Report. 2011;(38):1-27. *Figure 3*

 Copyright © 2019 NetCE

Models of Care

Palliative care service is rendered through several different models, including hospital-based inpatient programs, outpatient clinics (based in hospitals or private practices), and combined consultation services and inpatient programs. Hospice programs may provide a consultative service but generally assume direct responsibility for end-of-life palliative care rendered at home, hospital, of other hospice resident facility [15]. The Joint Commission began offering an advanced certification program for palliative care in September 2011 [18]. In an effort to enhance access to end-of-life care, models of care are being adapted for a variety of specific settings, such as rural communities, correctional facilities, long-term care facilities, children's hospitals, and intensive care units [19; 20; 21; 22; 23; 24].

Healthcare Team

The delivery of comprehensive palliative care relies on a team of skilled providers with experience and training in the principles of palliative care (***Figure 2***). The team may be organized around a primary care clinician or a palliative care specialist who functions as consultant or principal provider [15; 25; 26; 27]. Palliative care interventions have been shown to significantly improve patient outcomes, although the data are stronger for patients with cancer than for life-limiting diseases overall [28; 29]. This is illustrated by results of a randomized controlled trial of early palliative care provided as an adjunct to standard oncologic care for patients with metastatic non-small cell lung cancer. In this study, involving 151 subjects enrolled from a single academic practice, patients in the intervention group were seen by a palliative care clinician regularly (once or more per month) for 12 weeks; in comparison to the group receiving only standard care, the intervention (palliative care) group had a measurably better quality of life, lower rate of depression, and improved survival by 2.7 months [51].

The composition of a hospice care team is essentially the same as for a standard palliative care team. The primary service provided during hospice care is skilled nursing care and management of distressing symptoms, followed by bereavement services and medical social services (***Figure 3***) [30]. Clinical specialists (e.g., oncologists, cardiologists, pulmonologists) also become members of a palliative care team when they are involved with the care of their patients during the end of life. Family physicians and general internists typically provide primary palliative care; this level of care requires skill in core palliative care competencies (such as basic symptom assessment and management and knowledge of psychosocial and community services) [5; 7].

The composition of the healthcare team and the roles of its members may differ across palliative care settings, and roles and responsibilities should be clear and well documented to help members work effectively as a team. Team members' roles should also be communicated to the patient and the family.

The primary care physician is usually responsible for referral to palliative care through hospice when the patient has a non-cancer diagnosis. In general, the primary care physician becomes the attending physician, assuming primary responsibility for the patient [31; 32]. The primary care physician should be prepared to relinquish some autonomy in order to work effectively with the interdisciplinary team [31]. Home-based hospice care is organized around a team that includes the attending physician, registered nurse, social worker, and counselor. These team members are necessary for Medicare reimbursement [33]. The attending physician collaborates with other members of the hospice team to manage symptoms and fulfills other basic obligations, such as admission orders, medication prescriptions and refills, certification of hospice eligibility, and signing of the death certificate [32].

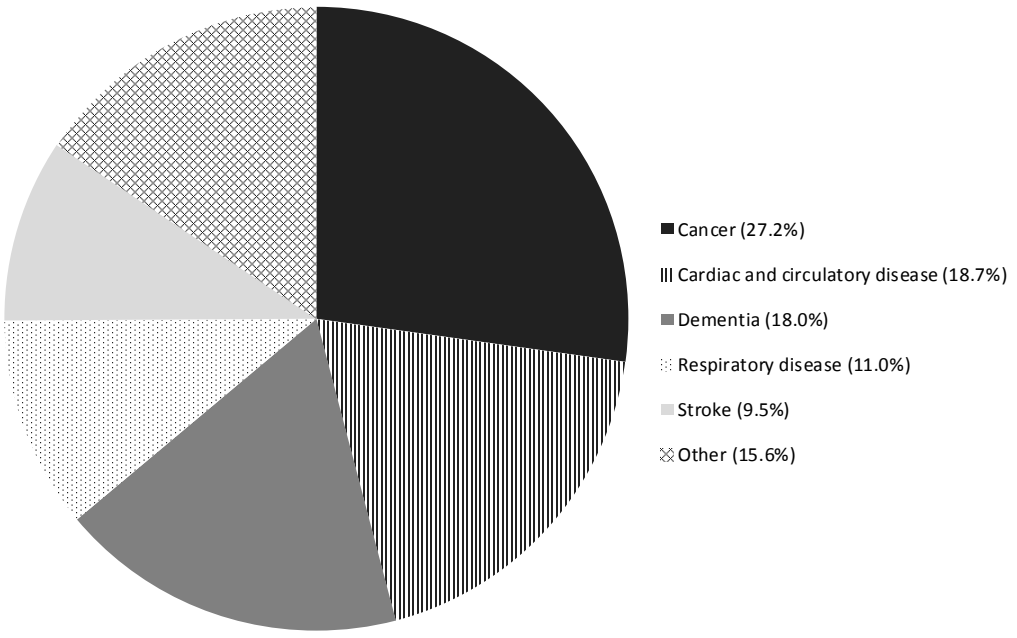
High-quality palliative care also requires special expertise in honest, compassionate communication. In addition to enhancing the patient's and family's experience, these skills help to establish trust and overcome barriers to adequate care and relief of symptoms. Several communication tasks are especially important: conveying accurate prognostic information while maintaining hope, eliciting information about symptoms, decision making about curative and palliative treatments, handling emotions, and dealing with requests from patients and families who have unrealistic goals [34; 35; 36]. The challenges of communicating effectively are discussed later in this course.

USE OF PALLIATIVE CARE AND HOSPICE SERVICES

Despite the increasing use of hospice, palliative care and hospice are underutilized services. The NHPCO estimated that 48% of all Medicare decedents in 2017 occurred under hospice care [1]. Hospice use varies according to several demographic factors. Patients treated in hospice are primarily women, although the gap has been closing, with 58.6% of the 2017 hospice population being female [1]. Studies have also consistently shown that white individuals are more likely to use hospice than individuals in minority populations [37; 38; 39; 40]. According to statistics compiled by the NHPCO, 86.5% of individuals in hospice in 2017 were white; 8.3% were black; 1.2% were Asian, Hawaiian, or other Pacific Islander; and 0.4% were American Indian or Alaskan Native; approximately 2.1% were of Hispanic ethnicity [1].

The lower rates of hospice use in minority populations have been attributed to many factors, including beliefs about health care, death, and end-of-life care; lack of awareness of hospice services; mistrust of the healthcare system; cultural differences in healthcare decision making and in disclosure of illness to the patient; lack of insurance; lack of healthcare professionals' cultural competency; lower referral rates by health care professionals; and the hospice caregiver requirement [39; 41; 42; 43].

DISTRIBUTION OF DIAGNOSES IN HOSPICE CARE, 2017



Source: [1] *Figure 4*

Most Common Diagnoses

Cancer and human immunodeficiency virus (HIV)/AIDS were once the predominant diseases in hospice and palliative care programs, but as treatments for these diseases have improved, the number of individuals with the diseases in hospice programs has decreased while the number of individuals with chronic, progressive diseases has increased. Cancer still accounts for the highest proportion of a single disease entity (27.2%) in the hospice population [1]. In 2017, the four noncancer diseases that represented the highest percentages of hospice use were cardiac and circulatory disease, stroke, dementia (including Alzheimer disease), and respiratory disease (***Figure 4***) [1].

BENEFITS OF PALLIATIVE CARE AT THE END OF LIFE

The greatest increase in survival during hospice has been associated with which disease?

Most of the studies designed to determine the benefits of palliative care/hospice at the end of life have centered on patients with cancer. However, an increasing number of researchers are focusing on palliative care interventions for patients with other life-limiting diseases. The field of palliative care/hospice research has grown considerably in the past decade, but reliable meta-analyses of palliative care studies have been limited because of variations in methodology and in the focus and extent of services [44]. Increasingly, studies are confirming the benefits of palliative care/hospice in terms of quality of life, satisfaction with care, and end-of-life outcomes, as well as cost-effectiveness.

A systematic review indicated weak evidence of benefit for palliative care/hospice. The results did demonstrate significant benefit of specialized palliative care interventions in four of 13 studies in which quality of life was assessed and in one of 14 studies in which symptom management was assessed [29]. However, the authors of the review noted that most of the studies lacked the statistical power to provide conclusive results, and the quality-of-life measures evaluated were not specific for patients at the end of life [29]. Other research has shown that palliative care intervention was associated with significantly better quality of life and greater patient and/or family caregiver satisfaction [44; 45; 46]. Data to support benefit in reducing patients' physical and psychologic symptoms have been lacking [44]. Such symptoms were significantly improved when patients received care delivered by palliative care specialists [28].

Surveys of patients' family members also demonstrate the value of palliative care. The Family Assessment of Treatment at the End of Life (FATE) survey was developed to evaluate family members' perceptions of their loved one's end-of-life care in the Veterans Administration (VA) healthcare system. FATE consists of nine domains: well-being and dignity,

 Copyright © 2019 NetCE

information and communication, respect for treatment preferences, emotional and spiritual support, management of symptoms, choice of inpatient facility, care around the time of death, access to VA services, and access to VA benefits after the patient's death. Using the assessment tool, researchers found that palliative care and hospice services were associated with significantly higher overall scores compared with usual care [47].

In addition to the benefits realized by patients, palliative care is beneficial for patients' family members as well. According to a survey of bereaved family members, a significantly higher proportion of respondents had their emotional or spiritual needs met when the patient received palliative care (compared with "usual care") [48]. Palliative care was also seen to improve family member coping skills and the ability to manage the inevitable tasks associated with terminal illness; that is, more family members knew what to expect when the patient was dying, felt competent to participate in the care of the dying person, and felt confident in knowing what to do when the patient died [48]. Other studies have shown benefit for caregivers through positive effects on caregiver burden, anxiety, satisfaction, and the ability to "move on" more easily after the patient's death [45; 49].

The most surprising finding is the apparent survival advantage conferred by palliative and hospice care. One study showed that hospice care extended survival for many patients within a population of 4,493 patients with one of five types of cancer (lung, breast, prostate, pancreatic, or colorectal cancer) or heart failure [50]. For the population as a whole, survival was a mean of 29 days longer for patients who had hospice care than for those who did not. With respect to the specific diseases, heart failure was associated with the greatest increase in survival (81 days), followed by lung cancer (39 days), colorectal cancer (33 days), and pancreatic cancer (21 days) [50]. There was no survival benefit for patients with breast or prostate cancer. In a study of patients with metastatic non-small cell lung cancer, patients who received early palliative care (within three weeks after enrollment in the study) lived significantly longer than those who received standard oncologic care only (11.6 months vs. 8.9 months) [51]. In the same study, the quality of life and symptoms of depression were also significantly better for the cohort of patients who received early palliative care. Similarly, a retrospective study found a slight survival advantage to hospice care among older individuals (>65 years) with advanced lung cancer [52]. These observations prompted the American Society of Clinical Oncology (ASCO) to publish a Provisional Clinical Opinion in which it states that concurrent palliative care and standard oncologic care should be offered to people with metastatic non-small cell lung cancer at the time of initial diagnosis [53]. The ASCO Opinion also notes that although the evidence of survival benefit is not as strong for other types of cancer, the same approach should be considered for any patient with metastatic cancer and/or high symptom burden [53]. The 2013 ACCP guideline for the diagnosis and management of lung cancer also recommends that "palliative care combined with standard oncology care be introduced early in the treatment course" for patients with late-stage (i.e., stage IV) lung cancer and/or a high symptom burden [237].

The cost of care at the end of life is a controversial issue because of the disproportionate costs incurred for care within the last two years of life and the wide variation in costs related to the aggressiveness of care across healthcare facilities [54]. The simple act of discussing end-of-life issues can help patients and families better understand options, leading to reduced costs. In a study of 603 patients with advanced cancer, costs in the last week of life were approximately $1,000 lower for patients who had end-of-life discussions with their healthcare providers compared with patients who did not have such conversations [55].

Several studies have documented the cost-effectiveness of hospice care. A meta-analysis published in 1996 showed that hospice care reduced healthcare costs by as much as 40% during the last month of life and 17% over the last six months [56]. A later study demonstrated little difference in costs at the end of life, with the exception of costs for patients with cancer, which were 13% to 20% lower for those who had received hospice care than for those who had not [57]. In a study of 298 patients with end-stage organ failure diseases, in-home hospice care significantly reduced healthcare costs by decreasing the number of hospitalizations and emergency department visits [45]. The strongest evidence of cost savings is found in a 2007 study in which hospice use reduced Medicare costs during the last year of life by an average of $2,309 per hospice user [58]. As was found earlier, the cost savings were greater for patients with cancer than for those with other diagnoses [58]. The greatest cost reduction (about $7,000) was associated with a primary diagnosis of cancer and length of stay of 58 to 103 days [58]. The maximum cost savings was much lower (approximately $3,500) for other life-limiting diagnoses but with a similar length of stay (50 to 108 days) [58].

Palliative care consultations also reduce costs. A review of data for Medicaid beneficiaries (with a variety of life-limiting diagnoses) at four hospitals in New York showed that hospital costs were an average of $6,900 lower during a given admission for patients who received palliative care than for those who received usual care [59]. The reduction in costs was greater ($7,563) for patients who died in the hospital compared with those who were discharged alive [59].

CHALLENGES TO OPTIMUM DELIVERY OF PALLIATIVE CARE AT THE END OF LIFE

What are barriers to the optimum use of palliative care at the end of life?

Despite the many benefits of palliative care and hospice, referrals are usually not timely and often are not made at all [60; 61; 62; 63; 64; 65]. Many challenges contribute to the low rate of optimum end-of-life care.

Among the most important barriers to the optimum use of palliative care at the end of life are the lack of well-trained healthcare professionals; reimbursement policies; difficulty in determining accurate prognoses; and attitudes of patients, families, and clinicians.

Lack of Well-Trained Healthcare Professionals

Medical school and residency training programs emphasize disease recognition, diagnostic assessment, and treatment and management strategies that have restorative power, prolong life, and prevent death. The role of palliative care traditionally has not been sufficiently addressed [66]. Students who have participated in mandatory courses in palliative medicine have noted that they are better prepared to care for dying patients [67]. Efforts to enhance education have resulted in the development of more than 100 primary care residency programs that offer palliative medicine as part of the curriculum and 72 postgraduate medical fellowship programs in palliative care [68; 69]. In addition, hospital-based palliative care programs have integrated the eight NCP domains into graduate courses and residencies for physicians and registered nurses, and certifications in palliative care have become available for physicians, nurses, and social workers [5]. Between 1996 and 2006, more than 2,100 physicians obtained certification in hospice and palliative medicine from the American Board of Hospice and Palliative Medicine [489]. In 2006, subspecialty certification in hospice and palliative medicine was established for 10 Boards within the American Board of Medical Specialties. The first exam was held in 2008, and 1,274 physicians earned certification in hospice and palliative medicine. In the intervening 10 years the number of physicians who have earned certification though the American Board of Medical Specialties has increased fivefold, with physicians in internal medicine and family medicine accounting for 88% of the total (***Table 3***) [70].

Initiatives to enhance the knowledge and skills of nurses have included graduate nursing programs in palliative care, instructional resources for nursing educators, communication skills training for nurses, and educational programs for home care professionals, as well national certifications [5; 71]. More than 18,000 nurses are Board-certified in hospice and palliative nursing [72].

NUMBER OF PHYSICIANS CERTIFIED IN SUBSPECIALTY OF HOSPICE AND PALLIATIVE MEDICINE, 2016

American Board Specialty	No. of Physicians
Internal medicine	4,200
Family medicine	1,723
Pediatrics	234
Anesthesiology	117
Emergency medicine	112
Psychiatry and neurology	110
Surgery	69
Radiology	67
Obstetrics and gynecology	48
Physical medicine and rehabilitation	46
Total	**6,726**

Source: [70] *Table 3*

Reimbursement Policies

Medicare reimbursement for hospice care became available when the Medicare Hospice Benefit was established in 1982, and reimbursement through private health insurances soon followed [33]. Reimbursement for hospice enabled more people with life-limiting disease to receive palliative care at home and in hospice units: the number of hospices in the United States has increased steadily, from 158 Medicare-certified hospices in 1985 to more than 4,382 in 2016 [1]. Despite the positive impact of the Medicare Hospice Benefit, the benefit has impeded timely referral because of its policy disallowing concurrent hospice care and life-prolonging treatment (***Table 4***). The eligibility requirements of the benefit explicitly state that the focus of hospice "is on comfort, not on curing an illness," and in order to receive reimbursement for hospice services, patients must sign a statement that they will forego curative treatment [33]. This requirement frightens some patients or their families, who subsequently view hospice as "giving up." Furthermore, the restriction does not account for palliative treatments that serve the dual purpose of alleviating symptoms while prolonging life. For example, therapeutic regimens and measures designed to optimally treat heart failure are the same as those used for palliative care of patients with heart failure [73]. At present, there are no Medicare regulations that specify which treatments are considered palliative, and this lack of clarity has led to variation in what treatments individual hospice programs offer.

 Copyright © 2019 NetCE

MEDICARE HOSPICE BENEFIT	
Variables	**Criteria**
Benefits (covered services)	Services of physicians; nurses; social workers; dietary counselors; physical, occupational, language, and speech therapists; hospice aides and homemakers; grief and loss counselors Medications for symptom control (small co-payment may be necessary) Medical equipment and supplies Short-term inpatient or respite care (small co-payment may be necessary)
Nonreimbursable services	Care in an emergency department or inpatient facility, or ambulance transportation, unless arranged by hospice medical team Care from a provider not arranged by the hospice medical team Room and board Prescription drugs, other than for pain relief or symptom control Curative treatment
Period of care	Two 90-day periods, followed by unlimited number of 60-day periods
Restrictions	Signed acknowledgment that treatment (including medications) directed at curing the terminal disease cannot be carried out Certification by physician at the beginning of each period of stay that the prognosis is six months or less
Source: [33]	*Table 4*

Hospice care may be denied to patients receiving palliative chemotherapy or radiotherapy, and this may result in many people not choosing hospice. Although oncology experts have noted that radiotherapy is an important component of palliative care for many people with metastatic cancer, only 3% of people receiving hospice care receive radiation therapy; expense and the need to transport patients were the primary barriers [74; 75; 76]. Other palliative interventions, such as chemotherapy, blood transfusions, total parenteral nutrition, and intravenous medications, may not be economically feasible for small hospice units but may be possible at larger ones [77; 78; 79].

Many have suggested that the hospice model should change to allow for integration of disease-directed therapy [80; 81]. The Affordable Care Act of 2010 stipulates that the Centers for Medicare & Medicaid Services implement a three-year demonstration project to evaluate concurrent hospice care and disease-directed treatment [81]. This project represents a significant change to the eligibility criteria and, while the change has the potential to improve access to hospice care, careful assessment of the effect of concurrent treatment on use of hospice as well as on quality of life, quality of care, survival, and costs is needed [81]. Phase 2 of the project, the Medicare Care Choices Model, began January 1, 2018, and has become a five-year study involving 140 hospices and an estimated 150,000 eligible Medicare beneficiaries [490].

The Medicare Hospice Benefit criterion of a life expectancy of six months or less has also affected the timeliness of referral to hospice because of the aforementioned challenges in predicting prognosis. Many hospices were accused of fraud and were assessed financial penalties when government review found documentation of patients who received hospice care for longer than six months. As a result, many clinicians delayed hospice referral because of their lack of confidence in their ability to predict survival within six months. However, the six-month regulation has been revised, and a penalty is no longer assessed if a patient lives beyond six months if the disease runs its normal course [33].

Unfortunately, reimbursement for end-of-life care discussions is not as straightforward as for hospice care. An effort to establish government reimbursement for discussions of end-of-life care options, including hospice care and advance directives, sparked a political storm that led to the removal of the proposed reimbursement from the healthcare reform bill of 2011. Some have noted that clinicians can be reimbursed for end-of-life discussions by using time-based Evaluation and Management (E&M) codes [82]. According to E&M guidelines, these codes can be used "when counseling and/or coordination of care dominates (more than 50%) the physician/patient and/or family encounter" services [83; 84]. As of January 2016, Medicare began reimbursement for "advance care planning" discussions [491].

Difficulty in Prognostication

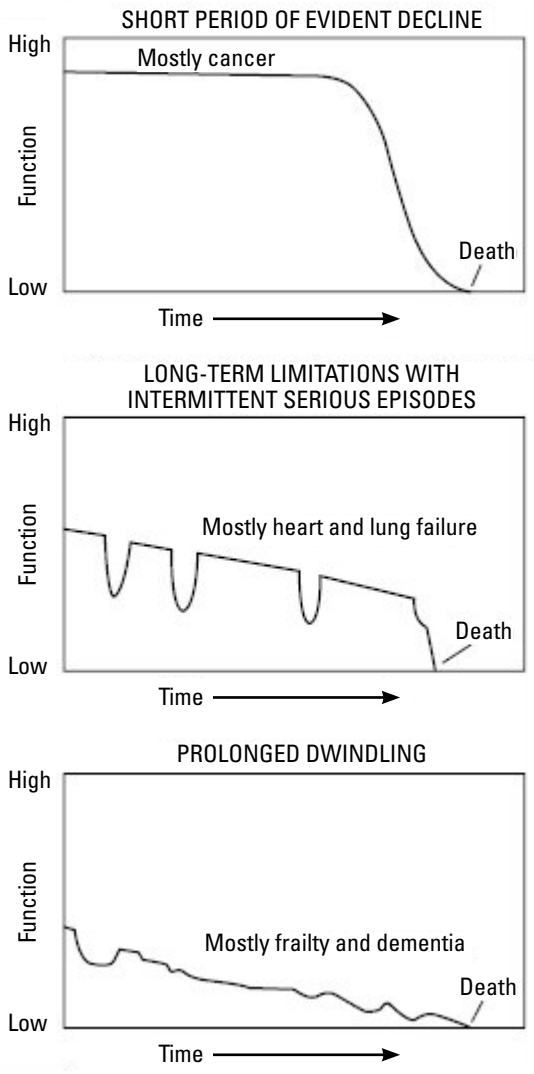
To make appropriate referrals to hospice, clinicians must be able to determine accurate prognoses, at least within the six-month timeframe required for reimbursement. However, prognostication is a complex issue and is a primary barrier to hospice use [85; 86; 87; 88; 89; 90; 91; 92]. Studies have found that physicians typically overestimate survival, and one study found that physicians overestimate prognosis both in determining it and in communicating it to the patient [93; 90; 94]. The difficulty in determining the risk of death within a specific time period not only affects the ability of clinicians to make appropriate referrals to hospice but also impedes the ability of patients and families to make necessary end-of-life decisions, with many patients not fully understanding the severity and progressive nature of the disease [95].

Several factors contribute to physicians' difficulty in prognostication, including a desire to meet the patient's needs (for a cure or prolongation of life) and a lack of reliable prognostic models [78; 94; 96]. Perhaps the most important factor contributing to prognostic difficulty is the variations in disease trajectories, which have been characterized as a short period of evident decline, long-term limitations with intermittent serious episodes, and a prolonged decline (***Figure 5***) [8; 31; 97].

How difficult it is to determine a prognosis depends on the disease trajectory. Determining a prognosis in the cancer setting was once clear-cut because of the short period of evident decline, but advances in cancer therapies have made it more difficult to estimate a prognosis. Studies have shown rates of accurate prognosis of 20%, with survival usually overestimated, up to a factor of five [90; 93]. The unpredictable course of organ-failure diseases, with its long-term limitations and acute exacerbations has always made prognostication difficult [61; 86; 98; 99]. In a survey of cardiologists, geriatricians, and internists/family practitioners, approximately 16% of respondents said they could predict death from heart failure "most of the time" or "always" [86]. Predicting survival for people with the third type of trajectory (prolonged decline) is extremely difficult because of the wide variation in progressive decline. The prognosis for dementia can range from 2 to 15 years, and the end-stage may last for 2 years or more [100; 101].

To help facilitate more timely referrals to hospice, the NHPCO established guidelines for determining the need for hospice care, and these guidelines were adopted by the Health Care Finance Administration to determine eligibility for Medicare hospice benefits [73]. Other prognostic models have been developed, such as the SUPPORT model, the Palliative Prognostic (PaP) Score, and the Palliative Prognostic Index (PPI) [11; 102; 103; 104]. Most were developed for use in the cancer setting and for hospitalized patients, and their value beyond those settings has not been validated [78; 92]. In addition, the PaP and the PIP will identify most patients who are likely to die within weeks but are much less reliable for patients who have 6 to 12 months to live [92]. A systematic review showed that the NHPCO guidelines, as well as other generic and disease-specific prognostic models, were not adequately specific or sensitive to estimate survival of at least six months for older individuals with nonmalignant life-limiting disease, especially heart failure, COPD, and end-stage liver disease [96].

TYPICAL DISEASE TRAJECTORIES AND SERVICE NEEDS OVER TIME FOR ELDERLY PATIENTS



Source: [8] Reprinted, with permission from Lynn J, Adamson DM. Living Well at the End of Life: Adapting Health Care to Serious Chronic Illness in Old Age. Santa Monica, CA: Rand; 2003. *Figure 5*

 Copyright © 2019 NetCE

COMPARISON BETWEEN PALLIATIVE CARE AND HOSPICE		
Condition	**Palliative Care**	**Hospice**
Cancer	Uncontrolled signs and symptoms due to cancer or treatment Introduced at time of diagnosis if disease terminal Introduced when disease progresses despite therapy	Any patient with metastatic or inoperable cancer
Heart disease	Stage III or IV heart failure despite optimal medical management Angina refractory to medical or interventional management Frequent emergency department visits or hospital admissions Frequent discharges from implanted defibrillators despite optimal device and antiarrhythmic management	Heart failure symptoms at rest Ejection fraction less than 20% New dysrhythmia Cardiac arrest or syncope Frequent emergency department visits for symptoms
Pulmonary disease	Oxygen-dependent, O_2 saturation less than 88% on room air Unintentional weight loss Dyspnea with minimal-to-moderate exertion Other pulmonary diagnoses (e.g., pulmonary fibrosis, pulmonary hypertension)	Dyspnea at rest Signs or symptoms of right heart failure O_2 saturation less than 88% PCO_2 greater than 50 Unintentional weight loss
Dementia	Behavioral problems Feeding problems, weight loss Caregiver stress Frequency of emergency department visits Increased safety concerns	Unable to walk, bathe, or dress self without assistance Incontinence Less than six intelligible words Frequent emergency department visits
Liver disease	Increased need for paracentesis for removal of ascitic fluid Increased confusion (hepatic encephalopathy) Symptomatic disease	International normalized ratio greater than 5 Albumin level less than 2.5 g/dL Refractory ascites Spontaneous bacterial peritonitis Jaundice Malnutrition and muscle wasting
Renal disease	Dialysis Stage IV or stage V chronic kidney disease	Not a candidate for dialysis Creatinine clearance of less than 15 mL/minute Serum creatinine level greater than 6 mg/dL
Neurologic disease	Stroke Parkinson disease Amyotrophic lateral sclerosis Multiple sclerosis	Frequent emergency department visits Albumin level less than 2.5 g/dL Unintentional weight loss Decubitus ulcers Homebound/bed confined
Source: [110]		*Table 5*

Most prognostic tools for organ-failure diseases are used to estimate the risk of dying and to select patients for treatment, not to determine when end-of-life care should be initiated. Several models have been established to determine prognosis for heart failure; the one used most often is the Seattle Heart Failure model, which represents the most comprehensive set of prognostic indicators to provide survival data for one, two, and five years [105; 106]. Newer evidence-based recommendations for estimating survival in advanced cancer have been published, as has a nomogram; however, use of the nomogram for hospice referral is limited, as it estimates survival at 15, 30, and 60 days [78; 107].

For estimating prognosis in advanced dementia—a condition with the most challenging disease trajectory—the Advanced Dementia Prognostic Tool (ADEPT) has been shown to be better than the NHPCO guidelines in identifying nursing home residents with advanced dementia at high risk of dying in six months [108]. However, the ability of ADEPT to identify these patients is modest [108]. Lastly, the Patient-Reported Outcome Mortality Prediction Tool (PROMPT) was developed to estimate six-month mortality for community-dwelling individuals 65 years or older with self-reported declining health over the past year; the model shows promise for making appropriate hospice referrals, but the model needs validation [109].

In addition to the low reliability of these models, another problem is that the clinician's prediction of survival remains integral, as it is one element in prognostic models, sometimes representing as much as half of a final score [107]. Other variables include performance status, laboratory data, and quality of life scales.

Researchers continue to evaluate prognostic variables to establish criteria for prognosis, especially disease-specific criteria. In its guidelines for palliative care, the Institute for Clinical Systems Improvement distinguished between the clinical indicators that should prompt palliative care discussions and those that should prompt hospice referral (***Table 5***) [110].

This difficulty in determining prognosis can have a negative impact on the appropriate timing of hospice referral and the degree of benefit to be derived. Although the use of hospice has increased over the past decades, the timing of referral has not changed significantly since the mid-1980s [111]. The average length of hospice care is much lower than the six months allowed by the Medicare benefit; in 2017, the average length was approximately 71 days, and the median duration (a more accurate reflection because it is not influenced by outliers) was 24 days [1]. In addition, approximately 27.9% of patients died (or were discharged) within only seven days [1]. Studies have indicated that the benefits of hospice increase as the duration of care increases, and such services as bereavement counseling, palliative care, and respite for caregivers is best when hospice care is provided for four to eight weeks, a longer period of time than the median stay [58; 112].

Longer durations of hospice services are also linked to family members' perceptions of the quality of care. According to the findings of 106,514 surveys from 631 hospices in the United States, 11% of family members thought their loved one was referred "too late" to hospice; this perception was associated with more unmet needs, higher reported concerns, and lower satisfaction [113].

In contrast to the restrictions on access to hospice, there are no restrictions on access to palliative care. Referrals for palliative care should be made on the basis of actual or anticipated needs at any time during the disease continuum; referrals should not be made on the basis of prognostic models [78; 96]. Referrals for specialist palliative care should be made when treatment goals change from curative to palliative [114; 115]. A consensus report from the Center to Advance Palliative Care provides guidance for identifying patients with a life-limiting illness who are at high risk of unmet palliative care needs [115]. The report includes criteria for referral for palliative care assessment at the time of hospital admission and during each hospital day (***Table 6***) [115]. Experts in nonmalignant life-limiting diseases are calling for earlier palliative care consultation. Such consultation before implantation of a left ventricular assist device as destination therapy is recommended, as it has been shown to improve the quality of care and advance care planning [116; 117]. Guidelines for renal and respiratory diseases note that all patients with these diseases should be offered palliative care services, and the integration of palliative care specialists into liver transplantation teams has been suggested [118; 119; 120].

Knowledge and Attitudes of Patients, Families, and Physicians

Physicians have reported that they delay discussions of palliative care and hospice because they fear the reaction of the patient and/or family [31; 32]. Negative reactions are grounded in a lack of accurate knowledge about palliative care and hospice. According to two polls conducted in 2011 (800 adults in one poll and 1,000 adults in the other), 70% to 92% of respondents were not "too" or "at all" familiar with the term palliative care [121; 122].

Enhancing the public's knowledge can improve access to palliative care: the 2011 polls showed that once palliative care was appropriately defined, 92% said they were likely (63% "very likely" and 29% "somewhat likely") to consider palliative care for a loved one who had a serious illness and 96% said that it was important for palliative (and end-of-life) care to be a top priority for the healthcare system [121; 122].

Hospice is a more familiar concept to the general population. One of the polls showed that 86% of respondents were familiar with the term hospice care, and other studies have indicated that approximately half of patients with a life-limiting illness know what hospice is [122; 123]. Although people may be familiar with the term, many believe several myths about hospice; for example, that hospice is only for old people, is only for people with cancer, is for people who do not need a high level of care, is used when there is no hope, and is expensive [124].

 Copyright © 2019 NetCE

CRITERIA FOR PALLIATIVE CARE ASSESSMENT AT THE TIME OF HOSPITAL ADMISSION AND DURING HOSPITAL STAY	
At Time of Hospital Admission	
Primary criteria[a]	*A potentially life-limiting or life-threatening condition AND* Not surprised if the patient were to die within 12 months More than one admission for same condition within several months Admission for difficult physical or psychologic symptoms Complex care requirements (e.g., functional dependency, complex home support for ventilator/antibiotics/feedings)
Secondary criteria[b]	*A potentially life-limiting or life-threatening condition AND* Admission from long-term care facility Older age, with cognitive impairment and acute hip fracture Metastatic or locally advanced incurable cancer Chronic use of home oxygen Out-of-hospital cardiac arrest Current or past use of hospice program Limited social support No history of advance care planning discussion/document
During Hospital Stay	
Primary criteria[a]	*A potentially life-limiting or life-threatening condition AND* Not surprised if the patient were to die within 12 months More than one admission for same condition within several months Stay in intensive care unit of seven days or more Lack of documentation of goals of care Disagreements or uncertainty among the patient, staff, and/or family about major medical treatment decisions, resuscitation preferences, or use of nonoral feeding or hydration
Secondary criteria[b]	*A potentially life-limiting or life-threatening condition AND* Awaiting, or deemed ineligible for, solid-organ transplantation Patient/family/surrogate emotional, spiritual, or relational distress Patient/family/surrogate request for palliative care/hospice services Patient is a potential candidate for feeding tube placement, tracheostomy, initiation of renal replacement therapy, placement of left ventricular assist device or automated implantable cardioverter-defibrillator, bone marrow transplantation (high-risk patients)
[a]Primary criteria are the minimum indicators for screening patients at risk for unmet palliative care needs. [b]Secondary criteria are more specific indicators of a high likelihood of unmet palliative care needs.	
Source: [110] Reprinted, with permission, from Weissman DE, Meier DE. Identifying patients in need of a palliative care assessment in the hospital setting: a consensus report from the Center to Advance Palliative Care. J Palliat Med. 2011;14(1):17-23. *Table 6*	

Several other factors contribute to negative feelings about hospice [77; 85; 125]:

- Denial or lack of awareness about the severity of the illness
- Not wanting to "give up"
- Fear of abandonment by the family physician
- Perception that the patient will not receive adequate medical services
- Interpretation of hospice referral as a cost-savings measure

When initiating a discussion about palliative care and hospice, clinicians should always first ask the patient if he or she has heard of either term and, if so, to describe his or her experience and knowledge [126]. Guidelines on communicating in the end-of-life setting note that clinicians must "clarify and correct misconceptions" about palliative care, especially emphasizing that such care is not limited to people who are imminently dying [114]. Clinicians should also address the factors that act as barriers to hospice by explaining that the goal of hospice is to die naturally—in the patient's own time, not sooner—and by ensuring that

patients and families are fully informed about the prognosis, understand that the physician will be available for care, and know that routine care will continue [95; 127].

Clinicians also need to evaluate their own attitudes about the use of curative therapies and hospice. Their interpretation of quality of life, a focus on longer survival rather than better quality of life, a fear of failure, and religious and cultural beliefs may influence their decision making about treatment options for patients near the end of life [128].

COMMUNICATION ISSUES

Communicating effectively about palliative care and hospice requires basic patient-physician communication skills as well as skills specific to the end-of-life setting. The importance of effective patient-clinician communication across all healthcare settings has received heightened attention over the past several years, as studies have shown a direct relationship between enhanced communication and better patient decision making, patient satisfaction, adherence to treatment, health-related quality of life, and survival [34; 66].

Basic Patient-Clinician Communication

Among the most important factors for effective communication across all healthcare settings are knowledge of the language preference of the patient and family; an awareness of the patient's and family's health literacy levels; and an understanding of and respect for the patient's and family's cultural values, beliefs, and practices (referred to as cultural competency) [129; 130; 131]. These issues are significant, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2016, more than 63.1 million Americans speak a language other than English in the home, with more than 25.4 million of them (8.5% of the population) reporting that they speak English less than "very well" [132]. Clinicians should ask their patients what language is spoken at home and what language they prefer for their medical care information, as some patients prefer their native language even though they have said they can understand and discuss medical information in English [133].When the healthcare professional and the patient speak different languages, a professional interpreter should be used. Studies have demonstrated that the use of professional interpreters rather than "ad hoc" interpreters (untrained staff members, family members, friends) facilitates a broader understanding and leads to better outcomes [134; 135]. Using a family member as a translator confuses the role of that member in the family, may involve confidentiality issues, and may lead to a modified message to protect the patient. In addition, individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [136]. Professional interpreters have recommended that clinicians can further enhance the quality of care by meeting with interpreters before discussions of bad news and by explicitly discussing with the interpreter whether strict interpretation or cultural brokering is expected [137].

Knowledge of the family's health literacy is important for achieving treatment goals and good outcomes, yet most individuals lack adequate health literacy. Studies have indicated that as many as 26% of patients have inadequate health literacy, which means they lack the ability to understand health information and make informed health decisions; an additional 20% have marginal health literacy [138; 139; 140]. Health literacy varies widely according to race/ethnicity, level of education, and gender, and clinicians are often unaware of the literacy level of their patients and family [131; 141].

Several instruments are available to test the health literacy level, and they vary in the amount of time needed to administer and the reliability in identifying low literacy. Among the most recent tools is the Newest Vital Sign (NVS), an instrument named to promote the assessment of health literacy as part of the overall routine patient evaluation [142]. The NVS takes fewer than three minutes to administer, has correlated well with more extensive literacy tests, and has performed moderately well at identifying limited literacy [131; 141]. Two questions have also been found to perform moderately well in identifying patients with inadequate or marginal literacy: "How confident are you in filling out medical forms by yourself?" and "How often do you have someone help you read health information?" [131]. Clinicians should adapt their discussions and educational resources to the patient's and family's identified health literacy level and degree of language proficiency and should also provide culturally appropriate and translated educational materials when possible.

Cultural competency is essential for addressing healthcare disparities among minority groups [129]. Clinicians should ask the patient about his or her cultural beliefs, especial those related to health and dying and should be sensitive to those beliefs [143]. In addition, information sharing and the role of decision maker vary across cultures, and the healthcare team must understand the family dynamics with respect to decision making [114]. Clinicians should not make assumptions about the preferences of the patient or family on the basis of cultural beliefs. Even within a single culture or ethnicity, the level of information desired, preferences for treatment, role of other family members in decision making, and goals of care differ among patients and families [39; 114]. Clinicians should ask their patients about these issues, as well as other family and social factors and religious or spiritual views [39].

 Copyright © 2019 NetCE

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement asserts that a cultural assessment should be an integral component of every palliative care plan. (https://www.icsi.org/_asset/k056ab/PalliativeCare.pdf. Last accessed October 24, 2018.)

Level of Evidence/Strength of Recommendation: Low-Quality Evidence, Strong Recommendation

Communication in the End-of-Life Setting

What clinician-related factors contribute to the low rate of end-of-life discussion?

Patients and families have noted that communication about end-of-life care is one of the most important skills for clinicians to have [144]. Experts in end-of-life communication note that physicians have an obligation to discuss medical, psychosocial, and spiritual needs with seriously ill patients in a timely and sensitive manner [145]. In addition, communication guidelines developed by an Australian and New Zealand Expert Advisory Group recommend "all patients with advanced progressive life-limiting illnesses be given the opportunity to discuss prognosis…and end-of-life issues" [114].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement recommends that palliative care discussions should be included wherever a patient with a life-limiting illness presents, including the intensive care unit and the emergency department. (https://www.icsi.org/_asset/k056ab/PalliativeCare.pdf. Last accessed October 24, 2018.)

Level of Evidence/Strength of Recommendation: Low-Quality Evidence, Strong Recommendation

Although the topic is emotionally and intellectually overwhelming for patients and families, they want information. In a systematic review (46 studies), Parker et al. found that patients with advanced life-limiting illnesses and their families have a high level of information needs at all stages of disease [146]. That study and others have shown that the end-of-life issues of most importance to patients are [61; 146]:

- Disease process
- Prognosis for survival for quality of life
- Likely symptoms and how they will be managed
- Treatment options and how they will affect quality of life and duration life
- What dying might be like
- Advance care planning

Most patients want some discussion of end-of-life issues (including hospice care) at the time a life-limiting illness is diagnosed or shortly thereafter [61; 146].

Although many physicians say they avoid discussing end-of-life issues because they are afraid the conversation will destroy the patient's hope, the discussion actually offers many benefits: it makes patients fully informed and thus better able to make decisions about treatment options and care goals; provides patients with an opportunity to achieve closure on life and family issues; allows patients to handle practical matters; and enables patients to carry out advance care planning [34; 78; 145; 147]. As such, the discussion empowers patients, giving them a sense of control over choices [145; 147]. Patients who discuss end-of-life issues and goals of care with their clinician also are more likely to receive care that is consistent with their preferences, to enroll in hospice, to complete advance directives, and are less likely to be intubated or to die in an intensive care unit [148; 181].

Despite these benefits, studies have consistently shown that few clinicians and patients discuss end-of-life issues or discuss them in a timely manner. Overall, about 25% to 33% of physicians have noted that they did not discuss hospice or end-of-life care with their patients who have life-limiting diseases [125]. In a multiregional study of more than 1,500 people with stage IV lung cancer, 47% had not discussed hospice within four to seven months after diagnosis [149]. Discussions are particularly lacking among people with nonmalignant life-limiting diseases, with 66% to more than 90% of patients or clinicians reporting that they had not discussed end-of-life issues [61; 123; 150; 151].

Even among clinicians who discuss end-of-life care with their patients, the timing is not optimal. Approximately 24% of physicians have noted that they provide hospice information at the time of diagnosis, the point at which this discussion is recommended [125; 152]. In a national survey of clinicians caring for people with cancer, most respondents said they would wait until treatment options had been exhausted or symptoms had occurred before discussing end-of-life issues, and many said they would have the discussion only if the patient or family raised the issue [153].

Patients and clinicians should talk about end-of-life issues early to avoid discussing the topic during the stress of exacerbated disease or imminent death. The topic can then be framed as a component of care for all patients with a life-limiting illness [61; 114]. According to published guidelines and expert recommendations, end-of-life issues should be discussed when the clinician would not be surprised if the patient died within six months to one year [5; 114; 145]. As other markers, an end-of-life discussion is generally recommended in the presence of moderate or severe COPD, during evaluation for liver transplantation, and in the presence of

stage 4 or 5 chronic kidney disease or end-stage renal disease [61; 118; 120]. The 2009 ACCF/AHA guideline for the diagnosis and management of heart failure noted that end-of-life care options should be discussed when "severe symptoms in patients with refractory end-stage heart failure persist despite application of all recommended therapies;" the 2013 ACCF/AHA guideline for the management of heart failure are less clear about the timing of such a discussion [154; 492]. The American College of Chest Physicians (ACCP) recommends discussing end-of-life care options when caring for patients with advanced lung cancer [237].

Other indications that should prompt a conversation about end-of-life care are a discussion of prognosis or of a treatment option with a low likelihood of success, a change in the patient's condition, patient and/or family requests or expectations that are inconsistent with the clinician's judgment, recent hospitalizations, and patient and/or family questions about hospice or palliative care [114; 145].

Several patient-related and clinician-related factors contribute to the low rate of end-of-life discussions or their untimeliness. Most patients will not raise the issue for many reasons: they believe the physician should raise the topic without prompting, they do not want to take up clinical time with the conversation, they prefer to focus on living rather than death, and they are uncertain about continuity of care and fear abandonment [61; 114; 145; 147]. Clinician-related factors include [78; 144; 145; 155; 156]:

- Lack of time for discussion and/or to address patient's emotional needs
- Uncertainty about prognosis
- Fear about the patient's reaction (anger, despair, fear)
- Lack of awareness and inability to elicit the concerns of patients and their families regarding prognosis
- Lack of strategies to cope with own emotions and those of patient and family
- Feeling of hopelessness or inadequacy about the lack of curative therapies (perceived as "giving up")

Perhaps the greatest barrier to end-of-life care discussions is clinicians' lack of confidence in their ability to talk about end-of-life issues, and research has confirmed a low rate of effective communication skills among clinicians, especially with respect to delivering "bad news" [61; 78; 151; 157].

The Australian/New Zealand communication guideline provides several evidence-based recommendations for discussing end-of-life issues, and other experts have offered practical guidance to help clinicians discuss bad news and end-of-life care more effectively [114; 158; 159; 160]. These guidelines and expert recommendations emphasize communication behaviors that patients and families have noted to be most important, such as expression of empathy, acknowledgment and support of emotions, honesty, willingness to listen more than talk, and encouragement of questions [78; 114; 120; 146; 144; 159].

The most commonly recommended communication approach is SPIKES, a six-step protocol that was developed for delivering bad news in the oncology setting and can be used in other settings [158; 159]:

- **S**etting (context and listening skills)
- **P**atient's perception of condition and seriousness
- **I**nvitation from patient to give information
- **K**nowledge—explaining medical facts
- **E**xplore emotions and empathize as patient responds
- **S**trategy and summary

In establishing the setting, the clinician should ask the patient if he or she wishes to have a family member present for the conversation and should ensure that the discussion takes place in privacy [61; 159]. The clinician should also introduce himself or herself to the patient and any others present [159]. With SPIKES, the setting also involves listening skills—the use of open-ended questions, clarification of points, and avoidance of distractions [159].

Bad news—even when delivered clearly and compassionately—can affect the ability of patients and family members to understand and retain information. To minimize misinterpretation, clinicians should use simple (jargon-free) language and open-ended questions and ask follow-up questions that include the patient's own words [114; 159]. Clinicians should also check often to make sure the patient and/or family understands, as research has shown that clinicians tend to overestimate their patients' understanding of end-of-life issues [161]. The discussion should focus on the importance of relieving symptoms and enhancing the quality of life, to avoid having the patient and/or family think that the clinician is "giving up" or abandoning the patient [39; 114]. Clinicians should also provide educational resources in a variety of formats (print, Web-based, video, etc.) to address different learning styles.

It was once thought that the ability to communicate effectively was innate and thus could not be taught [159]. However, multiday communication skills training programs have enhanced the skills and behaviors of beginning and experienced physicians and nurses. These programs have improved clinicians' use of more focused questions and open questions, expression of empathy, and appropriate responses to cues [162; 163]. Patient-related interventions have also helped to enhance end-of-life discussions. A structured list of questions and the use of individualized feedback forms regarding end-of-life preferences have led more patients to ask their physicians about end-of-life care [164; 165].

 Copyright © 2019 NetCE

Discussing Prognosis

The vast majority of patients say that they want to know their prognosis, and most clinicians believe that patients and families should be told the truth about the prognosis [119; 123; 147]. However, discussions of prognosis are lacking among clinicians and patients with life-limiting diseases. Across studies and surveys, fewer than half of patients have had a truthful discussion of prognosis [78; 105; 147]. Many physicians have said they discuss prognosis only when asked by the patient or family [78].

In discussing prognosis, clinicians tend to be overly optimistic, and, although most clinicians believe that they should be truthful, they sometimes withhold the truth, often at the request of a family member [155]. Honesty about the prognosis, with acknowledgment of inherent uncertainty, is needed because patients who are aware of their prognosis are more likely to choose hospice rather than aggressive treatment and to carry out advance directives [30; 78; 166]. Conversely, patients who are not fully aware of their prognosis tend to overestimate their life expectancy, which can influence decision making about treatment options [126].

As with other end-of-life issues, the prognosis should be discussed when the clinician would not be surprised if the patient died within six months to one year [5; 114; 145]. For patients with cancer, it is recommended that the prognosis be discussed within one month after a new diagnosis of advanced cancer is made [156]. A guideline from the Renal Physicians Association notes that prognosis should be fully discussed with all patients who have stage 4 or 5 chronic kidney disease or end-stage renal disease [118]. A discussion about prognosis is also recommended before the initiation of such treatments as implantation of a left ventricular assist device, dialysis, and ventilator support [119; 147; 167; 168; 169].

Clinicians should carefully prepare for the discussion of prognosis by reviewing the patient's medical record and talking to other healthcare professionals involved in the care of the patient [114]. Because there is variation among patients with regard to their desire for information, clinicians should follow the "ask-tell-ask" approach: ask the patient if he or she is willing to discuss prognosis; if yes, discuss the prognosis and then ask the patient to confirm his or her understanding [61; 159]. When discussing prognosis, quantitative estimates are more understandable for patients and family than qualitative ones (such as "poor"), and general timeframes for survival should be given [61; 78; 159; 170]. In addition, clinicians should emphasize that prognosis is determined by looking at large groups of patients and that it is harder to predict survival for an individual [61; 118; 126; 156]. The discussion of prognosis is often not documented in the patient's record but should be [114].

Discussing Treatment Options and Goals

Treatment options and goals of care are other topics that are often avoided in the end-of-life setting. A discussion of the survival benefit of palliative chemotherapy is frequently vague or absent from discussions of treatment options for patients with cancer [171]. In another example, approximately 60% to 95% of physicians involved with the care of patients with heart failure have two or fewer conversations about deactivation of implantable cardioverter defibrillators, and the discussions are usually within the last few days of life [86; 172].

Deciding when curative therapy should end is difficult because of the advances made in treatment and life-prolonging technology and the unpredictable course of disease, especially for organ-failure diseases. These factors have led many patients, as well as some clinicians, to have unrealistic expectations for survival [51; 173]. Unrealistic expectations are a major contributor to an increased use of aggressive treatment at the end of life. Among more than 900 patients with cancer, those who thought they would live for at least six months were more likely to choose curative therapy than "comfort care" compared with patients who thought there was at least a 10% chance they would not survive for six months [174].

Many studies have demonstrated high rates of aggressive treatment within the last months to weeks of life, with increased rates of hospital admissions, stays in an intensive care unit, use of medical resources, and use of chemotherapy. Goodman et al. found that patients with severe chronic disease near the end of life spent a disproportionate number of days in an intensive care unit and received care from multiple physicians; more than half of the patients saw 10 or more physicians within the last six months of life [54]. Similarly, Sheffield et al. found high rates of admission to the intensive care unit among nearly 23,000 patients with pancreatic cancer, and Unroe et al. found that 80% of more than 229,000 people with heart failure were hospitalized in the last six months of life [175; 176]. In the cancer setting, several researchers have reported increased rates of chemotherapy in the last two to four weeks of life [175; 177; 178]. However, studies to evaluate the benefit of high-intensity treatment near the end of life have consistently found that such treatment offers no survival benefit, decreases the quality of life, and delays the use of hospice [54; 77; 179; 180].

Before discussing treatment options, the clinician should talk to the patient to gauge his or her level of understanding of the disease and prognosis and to explore the quality-of-life factors that are most important [182]. The clinician should frame the conversation to focus on active interventions rather than the end of curative therapy; should focus on the overall care goals; and should discuss options within the context of these goals (that is, does the patient wish to enroll in hospice, enroll in a phase I trial, or be present at a family

event?) [78; 114]. The discussion should include an explanation of the likelihood of achieving the patient's goals with each option and a comparison of the risks, benefits, and costs of each option, noting the overall lack of benefit of aggressive treatment [183; 184]. It is also important to allow the patient and family enough time to express emotion and concerns and to ask questions [114; 159; 185]. Because frequent exacerbations in organ-failure diseases are usually predictive of a more rapid decline, hospitalizations for disease exacerbation should prompt discussions about changes in prognosis and treatment goals and advance care planning [98; 186; 187]. Admission to the hospital or intensive care unit should also prompt a discussion of goals and preferences with patients with cancer; this conversation should be documented within 48 hours after admission [156]. The ACCP recommends a discussion of the pros and cons of life-sustaining treatment when caring for patients with advanced lung cancer [237].

When the patient, family, and/or healthcare team do not agree on the benefit/utility of interventions, the clinician should consider consulting with social workers or pastoral care services to help with conflict resolution [183]. In addition, the clinician should explain to patients that the likelihood of insurance coverage for a treatment is low if it is not medically indicated [184].

Clinical guidelines have begun to address the use of aggressive treatment at the end of life. The ACCF/AHA guideline on the management of heart failure notes that it is not appropriate to carry out aggressive procedures in the last several months of life if they do not contribute to recovery or improve quality of life (including intubation and implantation of a cardiac defibrillator) [105]. In addition, discussion of device deactivation for patients with refractory heart failure is recommended [492]. The Renal Physicians Association recommends forgoing dialysis for patients with chronic kidney disease or end-stage renal disease who have "very poor prognosis" [118]. The increased use of chemotherapy near the end of life has led oncology experts to recommend more judicious use of chemotherapy. Oncologists have called for the discontinuation of chemotherapy when the chance of success is minimal, such as when disease progresses after three consecutive regimens [173; 188].

Early discussion of preferences for life-sustaining measures is especially important. It is estimated that roughly 75% of patients will be unable to participate in some or all of the decisions pertaining to their care at the end of life [189; 190]. Documentation of preferences helps to inform decision making by the physician and the patient's health care proxy (surrogate decision maker). Clinicians should encourage their patients to designate a healthcare proxy early in the course of a life-limiting disease [61; 79; 119]. Patients should be urged to clarify their wishes with their chosen health proxy, as a proxy often inaccurately predicts a patient's wishes or may have values that conflict with those of the patient [190].

Advance directives, designation of a healthcare proxy, do-not-resuscitate (DNR) orders, and living wills were developed as a way to ensure that patients received care that was consistent with their preferences and goals. Advance directives offer many benefits; they have been associated with a lower likelihood of in-hospital deaths, an increased use of hospice, and a significant reduction in costs [191]. Although early studies showed that advance directives did not always translate into patients receiving their preferred level of care, later studies have demonstrated that most patients with advance directives do receive care consistent with their preferences, especially if they want limited care (rather than "all possible" care) [190; 192].

The American College of Physicians recommends that clinicians ensure that patients with "serious illness" engage in advance care planning, including the completion of advance directives [46]. Clinicians must emphasize the value of advance directives because most patients have not completed them. An estimated 20% of the population have written advance directives, with higher rates among the older population and nursing home residents and lower rates among minority populations and those with nonmalignant life-limiting diseases (compared with people with cancer) [193; 194; 195; 196; 197]. Other guidelines recommend that advance care planning be done early in the course of disease, to help avoid potential compromise of decision-making capacity near the end of life [61; 105; 118; 119].

In preparing for a discussion about advance directives, clinicians should ask the patient if he or she wishes to have other family members present during the conversation. This is especially important for patients of some cultural backgrounds, as healthcare decisions are the responsibility of family members in many cultures [196]. Increased efforts should be aimed at obtaining advance directives from patients of minority races/ethnicities. Although the rate of advance directives is higher in the gay and lesbian community than in the general population, clinicians should emphasize the importance of these documents to gay and lesbian patients to ensure that the patient's wishes are carried out and to avoid legal consequences for the patient's partner [198].

 Copyright © 2019 NetCE

DNR orders and living wills have limitations and have been open to interpretation, which has led to the development of medical order forms based on patients' preferences. Developed at the Oregon Health & Science University, the Physicians Orders for Life-Sustaining Treatment (POLST) program is designed to ensure that a patient's preferences regarding cardiopulmonary resuscitation, scope of treatment, artificial nutrition by tube, and use of antibiotics (in some states) can be followed, regardless of where the patient receives care [199]. Nearly all states have an endorsed POLST program or one in development [199]. A POLST does not replace a traditional advance directive, and when available, an advance directive should accompany the POLST form [199]. Early studies have demonstrated that the use POLST has led to higher rates of meeting patients' preferences [200; 201].

Legal issues related to advance directives and POLSTs vary according to state, and clinicians should be familiar with the law in the state in which they practice [193].

GUIDELINES FOR PALLIATIVE CARE

The NCP consortium published an update of its *Clinical Practice Guidelines for Quality Palliative Care* in 2018, a copy of which is available online [5]. The guidelines are applicable for both specialty and primary palliative care and are organized in reference to the same eight domains used in past editions. New themes emphasized in each domain include comprehensive assessment, family caregiver support and education, care coordination, and culturally inclusive care [5]. The ICSI also provides guidelines for palliative care, including an algorithm for overall care, with details on the management of several specific symptoms [110]. Other general guidelines for palliative care have been developed by the International Association for Hospice and Palliative Care, now in its third edition [202].

Despite these resources, there is limited guidance on the treatment of specific symptoms in disease settings other than cancer. As a way to heighten awareness of the need for improved palliative care across disease settings, researchers began to document the prevalence of symptoms among groups of patients as well as compare the prevalence and severity of symptoms with those found among patients with cancer. Studies have documented that the symptom burden at the end of life for patients with life-limiting diseases is often as high as—or higher than—that for patients with cancer, and the most common symptoms are similar across disease settings (***Table 7***) [119; 197; 204; 205; 206; 207; 208].

In the wake of such studies, the American College of Physicians published a clinical practice guideline on palliative care interventions for three symptoms with the overall strongest evidence—pain, dyspnea, and depression—and evidence-based guidelines and recommendations for palliative care have been developed for respiratory diseases, heart failure, and end-stage renal disease [46; 105; 118; 119; 209; 210; 211]. These guidelines represent an important step toward enhancing palliative care, but more work is needed in many disease settings to address all aspects of palliative care. For one, definitions in palliative and supportive care are not standardized and remain a significant barrier to improvement [493].

MOST COMMON SYMPTOMS AT THE END OF LIFE ACROSS LIFE-LIMITING DISEASE SETTINGS

Overall	Fatigue Pain Dyspnea Delirium Anorexia
Cancer	Pain Fatigue Anorexia Anxiety Depression
Heart failure	Dyspnea Fatigue Pain Anxiety Sleep disturbances
COPD	Dyspnea Fatigue Xerostomia Coughing Anxiety
Renal disease	Fatigue Sleep disturbances Pain Anxiety Constipation
End-stage liver disease	Depression Sleep disturbances Fatigue Muscle cramps Cachexia
HIV/AIDS	Diarrhea Fatigue Depression Pain Delirium

Source: [119; 197; 204; 205; 206; 207; 208] *Table 7*

PHYSICAL CARE

What is the best approach for the assessment of physical symptoms at the end of life?

Among patients with life-limiting illness who receive palliative care consultation, physical symptoms are cited as causing the greatest distress [212]. Patients usually have multiple symptoms, and a mean of nine to 11 symptoms per patient has been reported [204; 205; 206; 213]. The presence of multiple symptoms can create challenges in identifying causes, as many symptoms are intricately linked with others, including symptoms in the psychosocial domain.

Several tools have been developed to assess factors in the end-of-life experience, including five tools to evaluate physical symptoms (three of which are used to assess pain), four to assess quality of life, and six to assess functional status [214]. However, a systematic review of 99 tools in these three domains plus six others (emotional and cognitive symptoms, advance care planning, continuity of care, spirituality, grief and bereavement, satisfaction and quality of care, and caregiver well-being) showed that data on the reliability and validity were lacking for most of the tools [215]. Assessment of symptoms should include comprehensive documentation of the patient's history and findings on physical examination and should be carried out at regular intervals [5]. To help ensure that patients' physical distress is alleviated, when clinicians ask patients about the presence and severity of symptoms, they should also ask which symptom is most troublesome, as patients do not often specifically state this [216].

Although asking open-ended questions about symptoms is helpful, systematic assessment of symptoms is also necessary. A study of patients in a palliative medicine program demonstrated that significantly more symptoms were identified on systematic assessment than through open-ended questioning (2,075 symptoms compared with 325) [217]. The symptoms that went unreported were not inconsequential; of those symptoms not initially volunteered by the patient, 69% were rated as "severe" and 79% were described as "distressing" [217]. Studies have demonstrated that patients are often reluctant to report worsening symptoms because of fear that they indicate progressive disease. Clinicians should describe potential symptoms to help patients and family understand which symptoms can be expected and when it is appropriate to notify a member of the healthcare team. It is important for the healthcare team to acknowledge the patient's symptoms as real and to take prompt actions to relieve them adequately. The patient's comfort should take precedence over the exact cause of the symptom. Diagnostic studies to determine the cause of symptoms should be undertaken only if the results will substantially help in directing effective treatment. The risks, benefits, costs, and options for treating an underlying cause should be discussed with the patient and family and considered within the context of the patient's culture, belief system, and expectations.

An important contribution of palliative care is the commitment to explore sources of suffering other than merely the physical aspects. Serious illness inevitably leads to an array of thoughts, feelings, fears about the future, and an erosion of capacity for work and other activities that give life meaning and purpose. Thus, in addition to pharmacologic treatment of physical symptoms, nonpharmacologic strategies are needed to augment therapy and to address the sensory, cognitive, affective, and functional components of illness [66]. The healthcare team should talk to the patient and family about priorities for pharmacologic versus nonpharmacologic treatments. Although data are limited on some nonpharmacologic interventions, many patients have benefited from these approaches. As research expands in the field of palliative care, other innovative strategies are being scientifically evaluated, and results are sometimes conflicting. Nonpharmacologic measures should be carried out in conjunction with pharmacologic management before medications fail to provide relief, as interventions, especially cognitive/behavioral techniques, are more effective when symptoms are acute and/or mild.

Once the patient's needs have been assessed, the palliative care team should work with the patient (and family) to develop priorities and goals of care [110]. Continual reassessment of symptoms and periodic review and documentation of the patient's goals and care plan are necessary to ensure that his or her needs are met [110]. It may be helpful for patients or a family member to keep a pain or symptom diary to note which measures have or have not provided relief and the duration of relief. This information will help clinicians determine the efficacy of specific therapeutic options and modify the treatment plan as necessary.

The discussion of interventions that follows focuses on the care of adults. Palliative care for children is addressed later in this course.

PAIN

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [218]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [46; 123; 183; 204; 206; 213; 218; 219; 220; 221].

 Copyright © 2019 NetCE

Issues in Effective Pain Management

What beliefs may result in a patient being afraid to take opioids?

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [222]. This reluctance is related to a variety of attitudes and beliefs [218; 222]:

- Fear of addiction to opioids
- Worry that if pain is treated early, there will be no options for treatment of future pain
- Anxiety about unpleasant side effects from pain medications
- Fear that increasing pain means that the disease is getting worse
- Desire to be a "good" patient
- Concern about the high cost of medications

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [223]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [218]. It is also helpful to note the difference between addiction and physical dependence.

There are several other ways clinicians can allay patients' fears about pain medication:

- Assure patients that the availability of pain relievers cannot be exhausted; there will always be medications if pain becomes more severe.
- Acknowledge that side effects may occur but emphasize that they can be managed promptly and safely and that some side effects will abate over time.
- Explain that pain and severity of disease are not necessarily related.

Encouraging patients to be honest about pain and other symptoms is also vital. Clinicians should ensure that patients understand that pain is multidimensional and emphasize the importance of talking to a member of the healthcare team about possible causes of pain, such as emotional or spiritual distress. The healthcare team and patient should explore psychosocial and cultural factors that may affect self-reporting of pain, such as concern about the cost of medication.

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [218; 219; 222; 224; 225; 226]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [222; 224; 226; 227]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [222; 224].

Clinicians require a clear understanding of available medications to relieve pain, including appropriate dosing, safety profiles, and side effects. If necessary, clinicians should consult with pain specialists to develop an effective approach.

Legal and Ethical Issues Related to the Treatment of Pain

Fear of license suspension for inappropriate prescribing of controlled substances is also prevalent, and a better understanding of pain medication will enable physicians to prescribe accurately, alleviating concern about regulatory oversight. Physicians must balance a fine line; on one side, strict federal regulations regarding the prescription of schedule II opioids (morphine, oxycodone, methadone, hydromorphone) raise fear of Drug Enforcement Administration investigation, criminal charges, and civil lawsuits [218; 228]. Careful documentation on the patient's medical record regarding the rationale for opioid treatment is essential [228]. On the other side, clinicians must adhere to the American Medical Association's Code of Ethics, which states that failure to treat pain is unethical. The code states, in part: "Physicians have an obligation to relieve pain and suffering and to promote the dignity and autonomy of dying patients in their care. This includes providing effective palliative treatment even though it may foreseeably hasten death" [229]. In addition, the American Medical Association Statement on End-of-Life Care states that patients should have "trustworthy assurances that physical and mental suffering will be carefully attended to and comfort measures intently secured" [230].

Physicians should consider the legal ramifications of inadequate pain management and understand the liability risks associated with both inadequate treatment and treatment in excess. The undertreatment of pain carries a risk of malpractice liability, and this risk is set to increase as the general population becomes better educated about the availability of effective approaches to pain management at the end of life. Establishing malpractice requires evidence of breach of duty and proof of injury and damages. Before the development of various guidelines for pain management, it was difficult to establish a breach of duty, as this principle is defined by nonadherence to the standard of care in a designated specialty. With such standards now in existence, expert medical testimony can be used to demonstrate that a practitioner did not meet established standards of care for pain management. Another change in the analysis of

malpractice liability involves injury and damages. Because pain management can be considered as separate from disease treatment and because untreated pain can lead to long-term physical and emotional damage, claims can be made for pain and suffering alone, without wrongful death or some other harm to the patient [231].

The proper storage and disposal of prescription pain medications should also be considered. Taking steps to ensure that medications are stored and destroyed securely and safely can help prevent unintended overdose and substance abuse. In 2010, the U.S. House of Representatives passed the Safe Disposal Drug Act, which amended the Controlled Substances Act to permit the take-back disposal of medications by authorized persons (rather than the patient with the prescription) [486]. As such, healthcare professionals may be required to dispose of drugs returned by patients in addition to drug samples that have expired or are not being dispensed. For best practice guidelines on the disposal of medications by patients or healthcare professionals, please visit the Drug Enforcement Administration Office of Diversion Control at https://www.deadiversion.usdoj.gov/drug_disposal [487].

Patients with History of Substance Abuse

The population of people with a history of substance abuse presents challenges to the effective use of pain medication, with issues related to trust, the appropriate use of pain medications, interactions between illicit drugs and treatment, and compliance with treatment. The issues differ depending on whether substance abuse is a current or past behavior.

With active substance abusers, it is difficult to know if patients' self-reports of pain are valid or are drug-seeking behaviors. It has been recommended that, as with other patients at the end of life, self-reports of pain should be believed [66; 223]. A multidisciplinary approach, involving psychiatric professionals, addiction specialists, and, perhaps, a pain specialist, is necessary. To decrease the potential for the patient to seek illicit drugs for pain, an appropriate pain management plan should be implemented and the patient should be reassured that pain can be managed effectively [66; 223]. When planning treatment, the patient's tolerance should be considered; higher doses may be needed initially, and doses can be reduced once acute pain is under control. Long-acting pain medications are preferred for active substance abusers, and the use of nonopioids and coanalgesics can help minimize the use of opioids. Setting limits as well as realistic goals is essential and requires establishing trust and rapport with the patient and caregivers.

Establishing trust is also essential for patients with former substance abuse behavior, who often must be encouraged to adhere to a pain management program because of their fears of addiction. Involving the patient's drug counselor is beneficial, and other psychologic clinicians may be helpful in assuring the patient that pain can be relieved without addiction. Recurrence of addiction is low, especially among people with cancer, but monitoring for signs of renewed abuse should be ongoing [223].

Patients who are following a methadone maintenance program may also fear effective pain management as a risk for recurrent abuse. Two approaches may be followed for these patients: they may receive an increased dose of methadone as the pain reliever or they may be given other opioids along with the same methadone dose, with the dose of the opioid titrated for effective pain relief [66; 223]. Again, involvement of the drug counselor is important.

Prevalence

The prevalence of pain at the end of life has been reported to range from 8% to 96%, occurring at higher rates among people with cancer than among adults with other life-limiting diseases [208; 232].

Etiology

Pain can be caused by a multitude of factors and is usually multidimensional, with pain frequently being exacerbated by other physical symptoms and by psychosocial factors, such as anxiety or depression [219].

Assessment

What is the most reliable indicator of pain?

As the fifth vital sign, pain should be assessed routinely, and frequent assessment has become the standard of care [219]. Pain is a subjective experience, and as such, the patient's self-report of pain is the most reliable indicator. Research has shown that pain is underestimated by healthcare professionals and overestimated by family members [219; 233]. Therefore, it is essential to obtain a pain history directly from the patient, when possible, as a first step toward determining the cause of the pain and selecting appropriate treatment strategies. When the patient is unable to communicate verbally, other strategies must be used to determine the characteristics of the pain, as will be discussed.

Questions should be asked to elicit descriptions of the pain characteristics, including its location, distribution, quality, temporal aspect, and intensity. In addition, the patient should be asked about aggravating or alleviating factors. Pain is often felt in more than one area, and physicians should attempt to discern if the pain is focal, multifocal, or generalized. Focal or multifocal pain usually indicates an underlying tissue injury or lesion, whereas generalized pain could be associated with damage to the central nervous system. Pain can also be referred, usually an indicator of visceral pain.

 Copyright © 2019 NetCE

The quality of the pain refers to the sensation experienced by the patient, and it often suggests the pathophysiology of the pain [219]. Pain that is well localized and described as aching, throbbing, sharp, or pressure-like is most likely somatic nociceptive pain. This type of pain is usually related to damage to bones and soft tissues. Diffuse pain that is described as squeezing, cramping, or gnawing is usually visceral nociceptive pain. Pain that is described as burning, tingling, shooting, or shock-like is neuropathic pain, which is generally a result of a lesion affecting the nervous system.

Temporal aspects of pain refer to its onset: acute, chronic, or "breakthrough." A recent onset characterizes acute pain, and there are accompanying signs of generalized hyperactivity of the sympathetic nervous system (diaphoresis and increased blood pressure and heart rate). Acute pain usually has an identifiable, precipitating cause, and appropriate treatment with analgesic agents will relieve the pain. When acute pain develops over several days with increasing intensity, it is said to be subacute. Episodic, or intermittent, pain occurs during defined periods of time, on a regular or irregular basis. Chronic pain is defined as pain that persists for at least three months beyond the usual course of an acute illness or injury. Such pain is not accompanied by overt pain behaviors (grimacing, moaning) or evidence of sympathetic hyperactivity.

"Breakthrough" is the term used to describe transitory exacerbations of severe pain over a baseline of moderate pain [234]. Breakthrough pain can be incident pain or pain that is precipitated by a voluntary act (such as movement or coughing), or can occur without a precipitating event. Breakthrough pain occurs in as many as 90% of people with cancer or in hospice settings and is often a consequence of inadequate pain management [218].

Documentation of pain intensity is key, as several treatment decisions depend on the intensity of the pain. For example, severe, intense pain requires urgent relief, which affects the choice of drug and the route of administration [3; 219]. The numeric rating scale is the tool used most often to assess pain; with this tool, patients rate pain on a scale of 0 to 10 [219]. Visual analogue scales (patients rate pain on a line from 0 to 10) and verbal rating scales, which enable the patient to describe the pain as "mild," "moderate," or "severe," have also been found to be effective. Some patients, however, may have difficulty rating pain using even the simple scales. In an unpublished study involving 11 adults with cancer, the Wong-Baker FACES scale, developed for use in the pediatric setting, was found to be the easiest to use among three pain assessment tools that include faces to assess pain [235].

Functional assessment is important. The healthcare team should observe the patient to see how pain limits movements and should ask the patient or family how the pain interferes with normal activities. Determining functional limitations can help enhance patient compliance in reporting pain and adhering to pain-relieving measures, as clinicians can discuss compliance in terms of achieving established functional goals [223]. The Memorial Pain Assessment Card can be used to evaluate both the severity of pain and the effect of pain on function [219; 236].

Physical examination can be valuable in determining an underlying cause of pain. Examination of painful areas can detect evidence of trauma, skin breakdown, or changes in osseous structures. Auscultation can detect abnormal breath or bowel sounds; percussion can detect fluid accumulation; and palpation can reveal tenderness. A neurologic examination should also be carried out to evaluate sensory and/or motor loss and changes in reflexes. During the examination, the clinician should watch closely for nonverbal cues that suggest pain, such as moaning, grimacing, and protective movements. These cues are especially important when examining patients who are unable to verbally communicate about pain.

Management

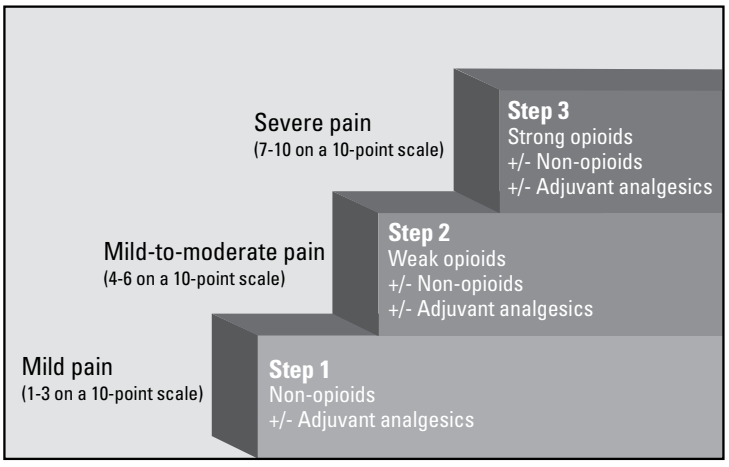
Strong evidence supports pain management approaches for people with which life-limiting disease?

Strong evidence supports pain management approaches for people with cancer, but the evidence base for management of pain in people with other life-limiting diseases is weak [46; 105; 183; 209; 211; 237]. Effective pain management involves a multidimensional approach involving pharmacologic and nonpharmacologic interventions that are individualized to the patient's specific situation [219].

Pharmacologic Interventions

The pharmacologic management of pain is best achieved with use of the WHO three-step analgesic ladder, which designates the type of analgesic agent based on the severity of pain (***Figure 6***) [238]. Step 1 of the WHO ladder involves the use of nonopioid analgesics, with or without an adjuvant (coanalgesic) agent, for mild pain (pain that is rated 1 to 3 on a 10-point scale). Step 2 treatment, recommended for moderate pain (score of 4 to 6), calls for a weak opioid, which may be used in combination with a step 1 nonopioid analgesic for unrelieved pain. Step 3 treatment is reserved for severe pain (score of 7 to 10) or pain that persists after Step 2 treatment. Strong opioids are the optimum choice of drug at Step 3. At any step, nonopioids and/or adjuvant drugs may be helpful.

THE WORLD HEALTH ORGANIZATION'S THREE-STEP LADDER OF ANALGESIA



Source: [238] *Figure 6*

The WHO ladder is also accompanied by five principles: prescribe analgesics according to the severity of pain (regardless of whether treatment at a previous step was carried out), use oral formulations (preferably), give analgesics at regular intervals around the clock (not on an as-needed basis), tailor the dose to the individual, and prescribe analgesics with attention to detail (document a treatment program) [238]. The pharmacologic treatment of pain involves the selecting the right drug(s) at the right dose, frequency, and route, and managing side effects [219]. A decision pathway was developed for use in the cancer setting and can be applied to other settings (***Figure 7***) [219].

Nonopioid analgesics, such as aspirin, acetaminophen (Tylenol), and nonsteroidal anti-inflammatory drugs (NSAIDs), are primarily used for mild pain (Step 1 of the WHO ladder) and may also be helpful as coanalgesics at Steps 2 and 3. Acetaminophen is among the safest of analgesic agents, but it has essentially no anti-inflammatory effect. Toxicity is a concern at high doses, and the maximum recommended dose is 3–4 g per day [219]. Acetaminophen should be avoided or given at lower doses in people with a history of alcohol abuse or renal or hepatic insufficiency [219].

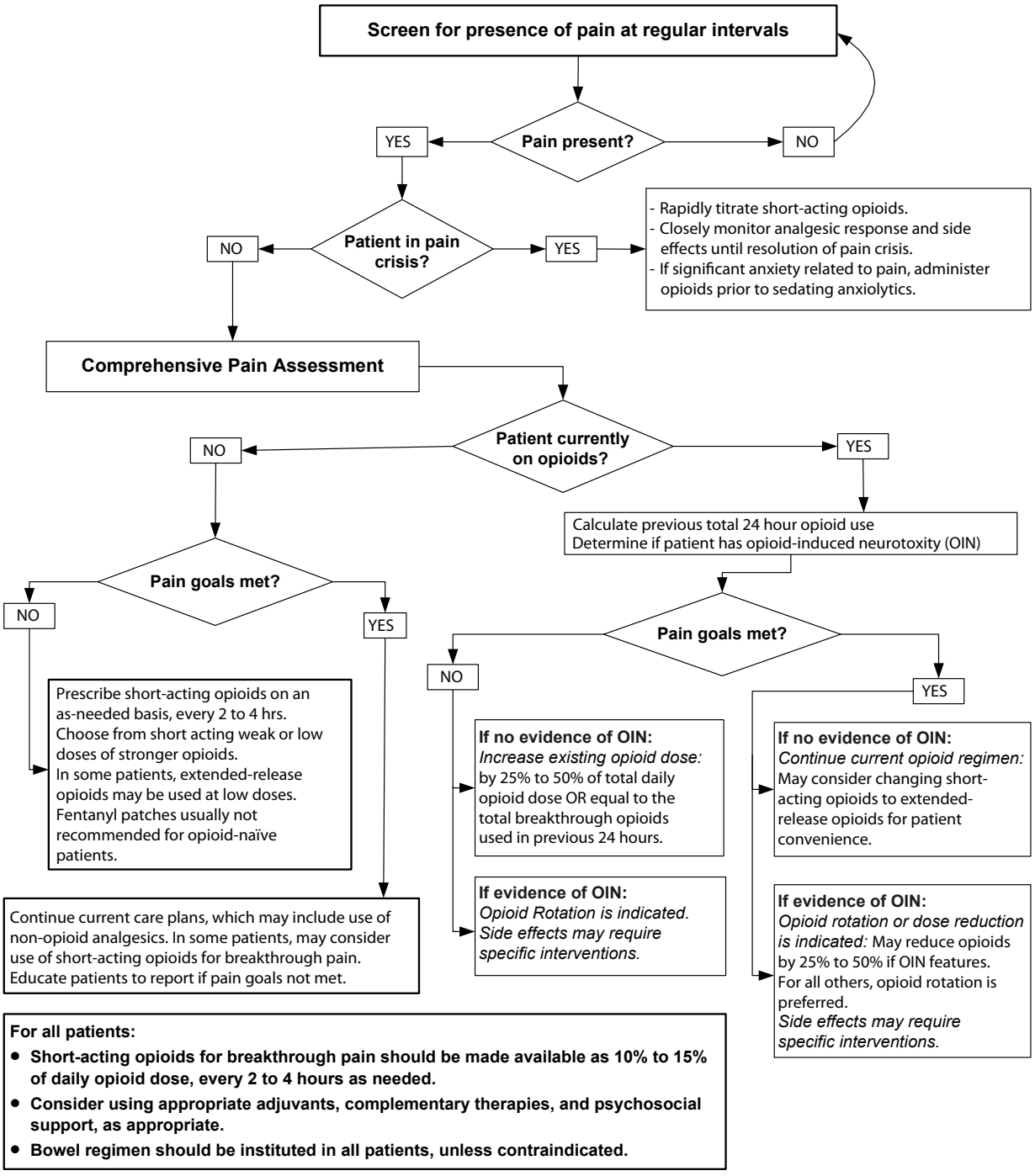
NSAIDs are most effective for pain associated with inflammation. Among the commonly used NSAIDs are ibuprofen (Motrin, Advil), naproxen (Aleve, Naprosyn), and indomethacin (Indocin). There are several classes of NSAIDs, and the response differs among patients; trials of drugs for an individual patient may be necessary to determine which drug is most effective [66]. NSAIDs inhibit platelet aggregation, increasing the risk of bleeding, and also can damage the mucosal lining of the stomach, leading to gastrointestinal bleeding. There is a ceiling effect to the nonopioid analgesics; that is, there is a dose beyond which there is no further analgesic effect. In addition, many side effects of nonopioids can be severe and may limit their use or dosing.

Moderate pain (Step 2) has often been treated with analgesic agents that are combinations of acetaminophen and an opioid, such as codeine, oxycodone, or hydrocodone. However, it is now recommended that these combination drugs be avoided, as limits on the maximum dose of acetaminophen limits the use of a combination drug [202; 219]. Individual drugs in combination is preferred, allowing for increases in the dose of the opioid without increasing the dose of the coanalgesic.

Strong opioids are used for severe pain (Step 3) [105; 183; 211; 219]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used Step 3 opioids in the United States [239]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. For an opioid-naïve patient or a patient who has been receiving low doses of a weak opioid, the initial dose of a Step 3 opioid should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled. Typical starting doses for patients who are opioid-naïve have been noted, but these doses should be used only as a guide, and the initial dose, as well as titrated dosing, should be done on an individual basis (***Table 8***). Guidelines suggest that the most appropriate dose is the one that relieves the patient's pain throughout the dosing interval without causing unmanageable side effects [183; 202; 243].

 Copyright © 2019 NetCE

DECISION PATHWAY FOR PAIN MANAGEMENT



Source: [219] Reprinted, with permission from Dalal S, Bruera E. Assessment and management of pain in the terminally ill. Prim Care Clin Office Pract. 2011;38:195-223.

Figure 7

OPIOIDS FOR THE MANAGEMENT OF PAIN IN ADULTS[a]			
Drug	**Typical Starting Dose[b]**	**Onset of Action**	**Duration of Action**
Codeine	15–60 mg	30 to 60 minutes	4 to 6 hours
Hydrocodone	2.5–10 mg	10 to 20 minutes	4 to 8 hours
Morphine, immediate release	15–30 mg	15 to 30 minutes or 5 to 10 minutes	3 to 6 hours
Oxycodone, immediate release	5–10 mg	10 to 30 minutes	3 to 4 hours
Oxymorphone, sustained release	10 mg	5 to 10 minutes	8 to 12 hours
Hydromorphone	2–4 mg	15 to 30 minutes	4 to 5 hours
Methadone	5–10 mg	30 to 60 minutes	4 to 6 hours
Tapentadol	50–100 mg	<60 minutes	4 to 6 hours
Tapentadol, extended release	50–100 mg	—	—
Fentanyl (buccal tablet)	100–200 mcg	5 to 15 minutes	2 to 4 hours
Fentanyl (transdermal patch)	25 mcg/hour (worn for 3 days)	12 to 18 hours	48 to 72 hours
Buprenorphine (transdermal patch)	5–10 mcg/hour (worn for 7 days)	—	—

[a]All information is given for oral formulations unless otherwise specified.
[b]Doses given are guidelines for opioid-naïve patients; actual doses should be determined on an individual basis.

Source: [183; 219; 240; 241; 242] *Table 8*

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [219]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [219].

Morphine is considered to be the first-line treatment for a Step 3 opioid [202]. Morphine is available in both immediate-release and sustained-release forms, and the latter form can enhance patient compliance. The sustained-release tablets should not be cut, crushed, or chewed, as this counteracts the sustained-release properties. Morphine should be avoided in patients with severe renal failure [211].

Buprenorphine (Butrans) has the general structure of morphine but differs from it in several ways [239]. The transdermal formulation of the drug was approved in 2010 for moderate-to-severe chronic pain in patients requiring an around-the-clock opioid for an extended period [219]. It may be used for people with renal impairment but is contraindicated in patients who have substantial respiratory depression [239; 240].

The sustained-release form of oxycodone (OxyContin) has been shown to be as safe and effective as morphine for cancer-related pain, and it may be associated with less common side effects, especially hallucinations and delirium [244]. Oxycodone is also available in an immediate-release form (Roxicodone). Oxycodone should be used in people with advanced chronic kidney disease only if alternative options are not available [211]. If the drug must be used, the intervals between doses should be increased, and the patient should be monitored closely [211].

Hydromorphone and fentanyl are the most potent opioids; neither drug should be given to an opioid-naïve patient. Hydromorphone, which is four times as potent as morphine, is available in immediate- and extended-release forms [494]. Fentanyl is the strongest opioid (approximately 80 times the potency of morphine) and is available as a transdermal drug-delivery system (Duragesic; Ionsys), buccal film (Onsolis), tablet (Fentora), nasal spray (Lazanda), sublingual spray (Subsys), sublingual tablet (Abstral), and lozenge (Actiq) [240; 245]. Fentanyl preparations have a more rapid onset than other opioids given nonparenterally [219]. Because of its potency, fentanyl must be used with extreme care, as deaths have been associated with its use. Physicians must emphasize to patients and their families the importance of

 Copyright © 2019 NetCE

following prescribing information closely, and members of the healthcare team should monitor the use of the drug. Fentanyl, administered subcutaneously, is the recommended choice for patients with advanced chronic kidney disease [211].

The use of methadone to relieve pain has increased substantially over the past few years, moving from a second-line or third-line drug to a first-line medication for severe pain in people with life-limiting diseases [246]. A systematic review showed that methadone had efficacy similar to that of morphine [247]. Physicians must be well educated about the pharmacologic properties of methadone, as the risk for serious adverse events, including death, is high when the drug is not administered appropriately [247; 248]. If the dose of methadone is increased too rapidly or administered too frequently, toxic accumulation of the drug can cause respiratory depression and death. Because of the unique nature of methadone, and its long and variable half-life, extreme care must be taken when titrating the drug, and frequent and careful evaluation of the patient is required. Practitioners are advised to consult with a pain or palliative care specialist if they are unfamiliar with methadone prescribing or if individual patient considerations necessitate rapid switching to or from methadone [183].

Propoxyphene (Darvon) is an opioid that is chemically similar to methadone. It is not recommended for use because of toxicity even at therapeutic doses and a lack of efficacy compared with placebo or acetaminophen [66; 223]. Similarly, meperidine (Demerol) should not be used in the palliative care setting because of limited efficacy and potential for severe toxicity. Agonist-antagonist opioids (nalbuphine [Nubain], butorphanol [Stadol], and pentazocine [Talwin]) are not recommended for use with pure opioids, as they compete with them, leading to possible withdrawal symptoms.

Tapentadol (Nucynta) is a short-acting opioid approved for moderate to severe pain in adults; an extended release formulation (Nucynta ER) was approved in 2011 for moderate-to-severe chronic pain when an around-the-clock opioid is needed [240]. The drug is associated with a lower incidence of adverse effects than other opioids, and it has been shown to be highly effective for chronic pain conditions but has not been extensively studied in cancer-related pain or the palliative care setting [249]. A 2014 study of 123 patients that had previously received long-term analgesia for cancer-related pain showed tapentadol significantly reduced pain scores and was generally well tolerated; concomitant use of pain medications was also reduced [495].

The most appropriate option for breakthrough pain is an immediate-release opioid taken in addition to the around-the-clock regimen [219]. The fentanyl buccal tablet has been shown to be effective and safe for relieving breakthrough pain in people who are opioid tolerant [183; 250; 251]. Between January 2011 and January 2012, three forms of fentanyl were approved for breakthrough pain in people with cancer: fentanyl sublingual tablet (Abstral), fentanyl nasal spray (Lazanda), and fentanyl sublingual spray (Subsys) [240]. As of 2018, the fentanyl lozenge (Actiq), buccal film (Onsolis), and buccal tablet (Fentora) are also approved for breakthrough cancer pain [494]. For each formula, the initial dose may be repeated once if pain is not relieved adequately after 30 minutes. Patients should wait at least two hours before using the sublingual tablet, buccal film, or the nasal spray for another breakthrough pain episode; the interval is four hours for the sublingual spray, lozenge, or buccal tablet [240; 494].

When pain responds poorly to escalated doses of an opioid, other approaches should be considered, including alternative routes of administration, use of alternate opioids (termed opioid rotation or opioid switching), use of adjuvant analgesics, and nonpharmacologic approaches. A process for opioid switching has been established (***Figure 8***); the first step is to calculate the equianalgesic dose of the new drug (***Table 9***) [183; 202; 219]. Additional care is needed when switching to methadone, and conversion ratios have been established (***Table 10***) [183]. Evidence suggests that the traditionally recommended equianalgesic doses for the fentanyl transdermal patch are subtherapeutic for patients with chronic cancer-related pain, and more aggressive approaches may be warranted (***Table 11***) [183; 219; 252].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement recommends that opioid rotation, especially for patients with cancer, should be considered when opioid side effects are difficult to manage or if inadequate analgesia is present.

(https://www.icsi.org/_asset/k056ab/PalliativeCare.pdf. Last accessed October 24, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Another approach that has been used for pain management in the cancer setting is combination opioid therapy, or the concurrent use of two strong opioids. The effectiveness of this approach has been evaluated in only two studies, and the combination was morphine and oxycodone or morphine with fentanyl or methadone [253]. The evidence to support a recommendation of combination opioid therapy is weak, and the side effects most likely outweigh the benefit [253].

PROCESS FOR OPIOID SWITCHING

Calculate the total dose of the current opioid(s) taken in a 24-hour period.

⇩

Calculate the equianalgesic dose of the new drug.

⇩ ⇘

If pain was effectively controlled with current drug, reduce the dose of the new drug by 25% to 50% (to allow for incomplete cross-tolerance).[a]

If pain was not effectively controlled with current drug, may begin with 100% or 125% of the equianalgesic dose.

⇩

Divide the 24-hour dose of the new opioid by the number of doses to be given over 24 hours.

⇩

Titrate liberally during first 24 hours, taking into account both pain relief and side effects.

⇩

Give 50% to 100% of the 4-hourly dose for breakthrough pain.

[a]Reduce by a greater percentage if the patient is older, frail, or has significant organ dysfunction. If changing to methadone, reduce the dose by 75%. If changing to transdermal fentanyl, do not reduce the dose and continue the current opioid for 12 to 48 hours.

Source: [183; 202; 219] *Figure 8*

OPIOID EQUIVALENT DOSES

Drug	Oral Dose	Parenteral Dose
Morphine	30 mg	10 mg
Codeine	200 mg	NA
Hydromorphone	7.5 mg	1.5 mg
Hydrocodone	30–45 mg	NA
Oxycodone	20 mg	NA
Oxymorphone	10 mg	1 mg
Methadone	20 mg	10 mg
Buprenorphine transdermal patch	5–10 mcg/hour	NA

Source: [183; 202; 219] *Table 9*

Opioids are associated with many side effects, the most notable of which is constipation, occurring in nearly 100% of patients. The universality of this side effect mandates that once extended treatment with an opioid begins, prophylactic treatment with laxatives must also be initiated. Tolerance to other side effects, such as nausea and sedation, usually develops within three to seven days. Some patients may state that they are "allergic" to an opioid. It is important for the physician to explore what the patient experienced when the drug was taken in the past, as many patients misinterpret side effects as an allergy. True allergy to an opioid is rare [219]. Opioid rotation may also be done to reduce adverse events.

 Copyright © 2019 NetCE

DOSE CONVERSION RATIOS FOR METHADONE	
Oral Morphine	**Conversion Ratio (Morphine:Oral Methadone)**
30–90 mg	4:1
91–300 mg	8:1
>300 mg	12:1
100 mcg/hour	800 mg
Source: [183]	*Table 10*

EQUIANALGESIC ORAL OPIOID DOSES FOR FENTANYL TRANSDERMAL PATCH				
Transdermal Fentanyl	**Morphine**	**Hydromorphone**	**Oxycodone**	**Codeine**
25 mcg/hour	60 mg	7.5 mg	30 mg	200 mg
50 mcg/hour	120 mg	15 mg	60 mg	400 mg
75 mcg/hour	180 mg	22.5 mg	90 mg	600 mg
100 mcg/hour	240 mg	30 mg	120 mg	800 mg
Source: [183; 219]				*Table 11*

ORAL ADJUVANT ANALGESICS			
Drug Class	**Drug**	**Typical Starting Dose**	**Usual Effective Dose**
Anticonvulsants	Gabapentin	100–300 mg once daily	300–1200 mg (2 or 3 divided doses)
	Pregabalin	25–75 mg twice daily	75–200 mg (3 divided doses)
	Carbamazepine	50–100 mg twice daily	300–600 mg twice daily
	Topiramate	25–50 mg daily	50–200 mg twice daily
	Oxcarbazepine	150–300 mg twice daily	150–600 mg twice daily
	Tiagabine	4 mg at bedtime	4–12 mg twice daily
Tricyclic antidepressants	Amitriptyline Nortriptyline Desipramine	10–25 mg at bedtime	50–150 mg at bedtime
Serotonin-norepinephrine reuptake inhibitors	Venlafaxine	37.5 mg daily	150–350 mg daily
Skeletal muscle relaxants	Baclofen	5 mg twice daily	10–20 mg 2 or 3 times daily
	Cyclobenzaprine	5 mg 3 times daily	10–20 mg 3 times daily
	Metaxalone	400 mg 3 times daily	Not defined
Corticosteroids	Dexamethasone	1–2 mg	Not defined
Source: [183; 219; 494]			*Table 12*

When opioids are prescribed, careful documentation of the patient's history, examinations, treatments, progress, and plan of care are especially important from a legal perspective. This documentation must provide evidence that the patient is functionally better off with the medication than without [66]. In addition, physicians must note evidence of any dysfunction or abuse.

Adjuvant agents are often used in conjunction with opioids and are usually considered after the use of opioids has been optimized [66]. The primary indication for these drugs is adjunctive because they can provide relief in specific situations, especially neuropathic pain. Examples of adjuvant drugs are tricyclic antidepressants, anticonvulsants, muscle relaxants, and corticosteroids (***Table 12***) [183; 219]. A systematic review found that there was limited evidence to sup-

port the use of selective serotonin reuptake inhibitors (SSRIs) for neuropathic pain, but one serotonin-norepinephrine reuptake inhibitor, venlafaxine (Effexor), was found to be effective [254].

Nonpharmacologic Interventions

Several nonpharmacologic approaches are therapeutic complements to pain-relieving medication, lessening the need for higher doses and perhaps minimizing side effects. These interventions can help decrease pain or distress that may be contributing to the pain sensation. Approaches include palliative radiotherapy, complementary/alternative methods, manipulative and body-based methods, and cognitive/behavioral techniques. The choice of a specific nonpharmacologic intervention is based on the patient's preference, which, in turn, is usually based on a successful experience in the past.

Palliative radiotherapy is effective for managing cancer-related pain, especially bone metastases [46; 255; 256]. Bone metastases are the most frequent cause of cancer-related pain; 50% to 75% of patients with bone metastases will have pain and impaired mobility [255]. External-beam radiotherapy is the mainstay of treatment for pain related to bone metastases. At least some response occurs in 70% to 80% of patients, and the median duration of pain relief has been reported to be 11 to 24 weeks [255]. It takes one to four weeks for optimal therapeutic results [255; 256].

However, palliative radiotherapy has become a controversial issue. Although the benefits of palliative radiotherapy are well documented and most hospice and oncology professionals believe that palliative radiotherapy is important, this treatment approach is offered at approximately 24% of Medicare-certified freestanding hospices, with less than 3% of hospice patients being treated [74; 75; 76]. As previously noted, reimbursement issues present a primary barrier to the use of palliative radiotherapy [74; 75; 76]. Among other barriers are short life expectancy, transportation issues, patient inconvenience, and lack of knowledge about the benefits of palliative radiotherapy in the primary care community [74; 75; 256; 257].

One study found that more than half (54%) of people use complementary/alternative medicine therapies at the end of life [258]. The most commonly used therapies are massage, music, relaxation techniques, and acupuncture [258; 259; 260; 496; 497].

Massage, which can be broadly defined as stroking, compression, or percussion, has led to significant and immediate improvement in pain in the hospice setting [261]. Both massage and vibration are primarily effective for muscle spasms related to tension or nerve injury, and massage can be carried out with simultaneous application of heat or cold. Massage may be harmful for patients with coagulation abnormalities or thrombophlebitis [223].

Focused relaxation and breathing can help decrease pain by easing muscle tension. Progressive muscle relaxation, in which patients follow a sequence of tensing and relaxing muscle groups, has enabled patients to feel more in control and to experience less pain and can also help provide distraction from pain. [223]. This technique should be avoided if the muscle tensing will be too painful.

Acupuncture typically provides pain relief 15 to 40 minutes after stimulation. Relief seems to be related to the release of endorphins and a susceptibility to hypnosis [223]. The efficacy of acupuncture for relieving pain has not been proven, as study samples have been small. However, acupuncture has been found to be of some benefit for cancer-related pain when the therapy is given in conjunction with analgesic therapy [262].

Other nonpharmacologic interventions that have been helpful for some patients but lack a strong evidence base include manipulative and body-based methods (such as application of cold or heat, and positioning), yoga, distraction, and music or art therapy. The application of cold and heat are particularly useful for localized pain and have been found to be effective for cancer-related pain caused by bone metastases or nerve involvement, as well as for prevention of breakthrough incident pain [223]. Alternating application of heat and cold can be soothing for some patients, and it is often combined with other nonpharmacologic interventions.

Cold can be applied through wraps, gel packs, ice bags, and menthol. It provides relief for pain related to skeletal muscle spasms induced by nerve injury and inflamed joints. Cold application should not be used for patients with peripheral vascular disease. Heat can be applied as dry (heating pad) or moist (hot wrap, tub of water) and should be applied for no more than 20 minutes at a time, to avoid burning the skin. Heat should not be applied to areas of decreased sensation or with inadequate vascular supply, or for patients with bleeding disorders.

Changing the patient's position in the bed or chair may help relieve pain and also helps minimize complications such as decubitus ulcers, contractures, and frozen joints. Members of the healthcare team as well as family members and other informal caregivers can help reposition the patient for comfort and also perform range-of-motion exercises. Physical and occupational therapists can recommend materials, such as cushions, pillows, mattresses, splints, or support devices.

Hatha yoga is the branch of yoga most often used in the medical context, and it has been shown to provide pain relief for patients who have osteoarthritis and carpal tunnel syndrome but it has not been studied in patients at the end of life. Yoga may help relieve pain indirectly in some patients through its effects on reducing anxiety, increasing strength and flexibility, and enhancing breathing [263]. Yoga also helps patients feel a sense of control.

 Copyright © 2019 NetCE

Methods to provide distraction from pain come in a wide variety of methods, including reciting poetry, meditating with a calm phrase, watching television or movies, playing cards, visiting with friends, or participating in crafts.

Music therapy and art therapy are also becoming more widely used as nonpharmacologic options for pain management. Listening to music has been shown to decrease the intensity of pain and reduce the amount of opioids needed, but the magnitude of the benefit was small [264]. Research suggests that art therapy contributes to a patient's sense of well-being [265]. Creating art helps patients and families to explore thoughts and fears during the end of life. An art therapist can help the creators reflect on the implications of the art work. Art therapy is especially helpful for patients who have difficulty expressing feelings with words, for physical or emotional reasons.

FATIGUE

Fatigue is a subjective feeling of tiredness, weariness, and lack of energy. Fatigue is often accompanied by a feeling of weakness (asthenia), which can be either generalized or localized. The National Comprehensive Cancer Network (NCCN) defines fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion…that is not proportional to recent activity and interferes with usual functioning" [183]. Fatigue associated with life-limiting diseases is further characterized by the disproportionate relationship to recent activity and the lack of recovery following additional sleep [266]. Persistent fatigue has a significant impact on the quality of life by negatively affecting functional status, interfering with normal activities, and contributing to emotional distress [183]. Fatigue may also cause distress for a patient's family members, who may interpret this symptom as a sign of the patient "giving up." As is the case with pain, fatigue is underreported, underdiagnosed, and undertreated [266]. Studies have indicated that approximately half of patients do not report fatigue to their healthcare team, and the primary reasons were that they did not think effective treatments were available and their physicians did not offer interventions [267].

Fatigue is often part of a cluster of symptoms that may also include pain, depression, sleep disturbances, and anxiety/depression, especially at the end of life [183; 268; 269; 270; 498]. Analysis of 25 symptoms among 922 patients with advanced cancer demonstrated seven clusters. One of those clusters, referred to as the fatigue/anorexia-cachexia cluster, was composed of easy fatigue, weakness, lack of energy, anorexia, early satiety, weight loss, dry mouth, and taste changes [271]. Fatigue has often been reported to be the symptom that causes patients the most distress [272].

Prevalence

A sense of fatigue and weakness is one of the most common symptoms near the end of life, and patients often consider this symptom to be more troublesome than pain [273; 274]. The prevalence of fatigue has been reported to range from 12% to 97% of patients with life-limiting diseases, and the prevalence is fairly consistent across disease settings [208; 266].

Etiology

Among the most common contributors to fatigue in people with advanced life-limiting diseases are medications, anemia, dehydration, direct tumor effects on energy consumption and supply, infection, metabolic disturbances, fluid and electrolyte imbalance, dyspnea, sleep apnea, depression, and loss of skeletal muscle due to cachexia [105; 183; 266].

Prevention

Ensuring adequate management of symptoms related to fatigue may help in preventing the condition. Clinicians should advise the patient to conserve energy as much as possible, to follow a normal sleep cycle, and to engage in aerobic exercise [105; 183; 266; 272].

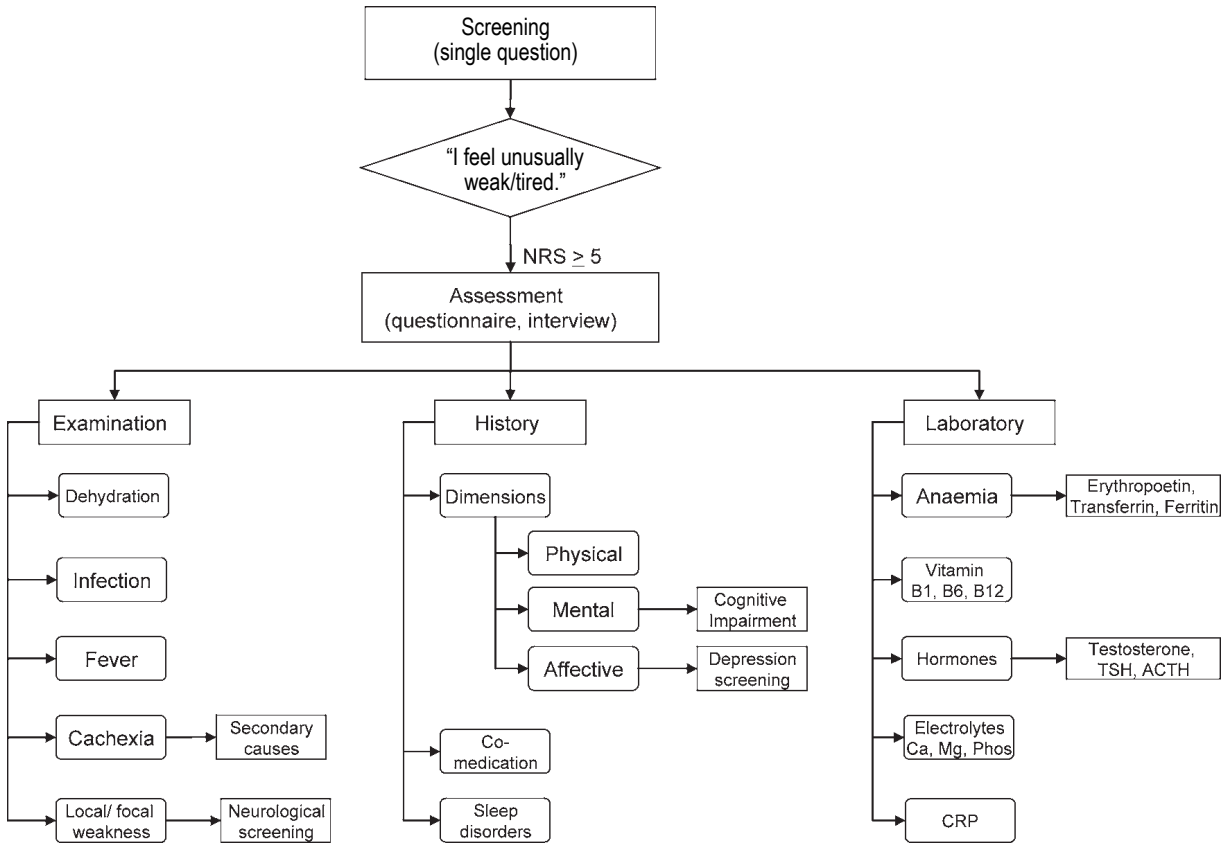
Assessment

Assessing fatigue can be a challenge, but as with pain, the patient's report of how he or she is feeling is the gold standard in the assessment. For patients who speak a language other than English, questions about fatigue should include such words and phrases as "tired," "weak," and "lack of energy," as the word "fatigue" may translate differently in some languages [266]. Several tools are available to assess fatigue, but because it usually occurs in a cluster of symptoms, many of these tools are multidimensional instruments, often involving several questions, which can be impractical [266; 498]. In assessing patients for fatigue, the clinician should ask such questions as "Do you feel unusually tired or weak?" or "How tired/weak are you?" [266].

An easy-to-use instrument is the Brief Fatigue Inventory, which includes nine items that ask the patient to rate the severity of fatigue on a scale of 0 (no fatigue) to 10 ("as bad as you can imagine") [275]. The patient is asked to consider the current level of fatigue as well as fatigue experienced within the past 24 hours and to indicate the degree to which fatigue has interfered with activities, mood, walking ability, relations with other people, and enjoyment of life.

Assessment should also include a physical examination to detect an underlying cause of fatigue, a focused history-taking, and laboratory tests, as appropriate, to rule out suspected causes (***Figure 9***) [266].

ALGORITHM FOR THE DIAGNOSIS OF FATIGUE IN PATIENTS RECEIVING PALLIATIVE CARE



ACTH = adrenocorticotropic hormone, Ca = calcium, CRP = C-reactive protein, Mg = magnesium, NRS = numerical rating scale, Phos = phosphate, TSH = thyroid-stimulating hormone.

Source: [266] Reprinted, with permission from Radbruch L, Strasser F, Elsner F, et al. Fatigue in palliative care patients—an EAPC approach. Palliat Med. 2008;22(1):13-32. *Figure 9*

Management

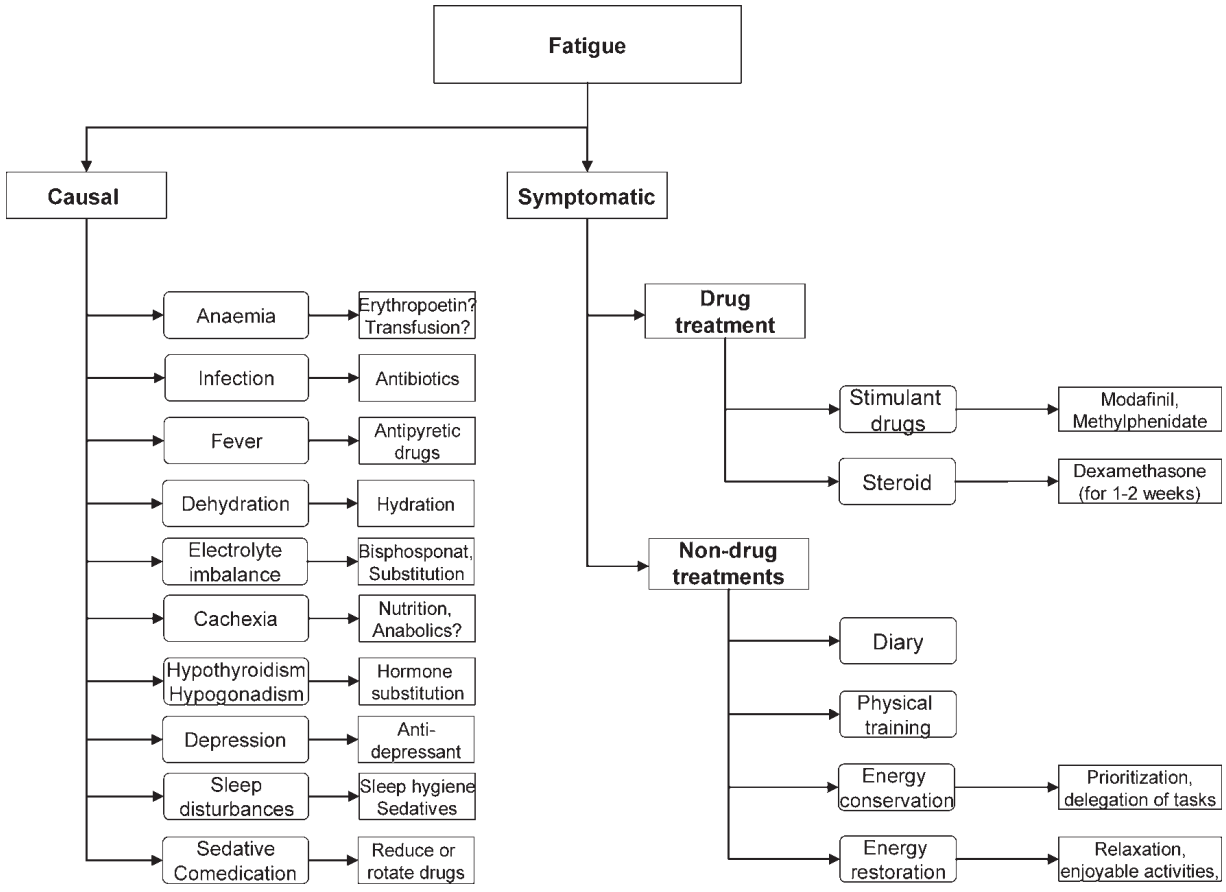
Little evidence is available to support guidelines for the management of fatigue during the end of life. Most of the research on nonpharmacologic and pharmacologic treatment options has been conducted with subjects receiving active cancer treatment or long-term follow-up care after cancer treatment. Fatigue in the palliative care setting is addressed specifically by the European Association for Palliative Care (EAPC) (all settings) and the NCCN (cancer setting) and is noted in guidelines for palliative care for advanced heart failure [105; 183; 266]. In addition, the AHRQ has addressed fatigue in the cancer setting, and systematic reviews have been done to help determine effective pharmacologic and nonpharmacologic interventions [268; 276; 277; 278; 279]. Management of fatigue should include treatment of an underlying cause, if one can be identified, but symptomatic relief should also be provided (***Figure 10***) [105; 183; 266].

When medications are the underlying cause of the fatigue, nonessential medications should be discontinued, and changing medications or the time of dosing may reduce tiredness during the day. Appropriate management of infection, cachexia, depression, and insomnia may also help reduce fatigue [266; 273]. The patient's life expectancy and preferences should be considered before carrying out treatment of an underlying cause [266]. Fatigue may provide a protective effect for patients in the last days or hours of life [266]. As such, the patient may be more comfortable without aggressive treatment of fatigue during that period [266].

The treatment of anemia as an underlying cause of fatigue (and other symptoms) is a complex issue. Many studies have provided evidence to recommend the use of erythropoiesis-stimulating agents (erythropoietin [Epogen], darbepoetin [Procrit]) for anemia in people with cancer, HIV/AIDS, chronic kidney disease, and heart failure because of benefit

 Copyright © 2019 NetCE

ALGORITHM FOR THE MANAGEMENT OF FATIGUE IN PATIENTS RECEIVING PALLIATIVE CARE



Source: [266] Reprinted, with permission from Radbruch L, Strasser F, Elsner F, et al. Fatigue in palliative care patients—an EAPC approach. Palliat Med. 2008;22(1):13-32. *Figure 10*

in increasing the hemoglobin level, improving exercise tolerance, reducing symptoms, and decreasing the need for blood transfusions [266; 276; 280; 281; 282]. However, safety concerns led the U.S. Food and Drug Administration (FDA) to require a boxed warning on the label of erythropoiesis-stimulating agents regarding the increased risk of several adverse events (death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence) among people with chronic kidney disease or cancer [240]. The FDA recommends using the lowest dose sufficient to avoid red blood cell transfusion [240]. Recommendations for these agents in these populations have been withdrawn or revised [277; 283; 284]. A 2010 systematic review and meta-analysis (11 studies, 794 subjects) demonstrated benefit of erythropoiesis-stimulating agents among people with heart failure and mild anemia (>10 g/dL) with no increase in adverse events [282].

Most patients will try to manage fatigue by resting and/or sleeping more often, and many healthcare professionals will also recommend this strategy. However, additional rest and/or sleep usually does not restore energy in patients who have fatigue related to a life-limiting disease; continued lack of exercise may even promote fatigue [266]. Regular aerobic exercise and strength training has been found to alleviate fatigue, although much of the research in this area has been conducted with cancer survivors [498]. For example, a meta-analysis (28 studies, 2,083 subjects) demonstrated a significant effect of exercise in the treatment of fatigue during and after cancer treatment [279]. Some small studies of fatigue have been done in the palliative care setting, and exercise was found to be beneficial [285; 286; 287].

Although an exercise program is recommended, decreasing activity to conserve energy is also encouraged [105; 183; 266]. Clinicians should talk to the patient and family about the importance of the patient conserving energy by adjusting daily activities to correspond to times of peak energy, setting priorities for activities, following a normal wake-sleep cycle, and using assistive devices, and delegating less important tasks [183; 266]. Encouraging adequate nutrition, stress reduction through meditation or relaxation techniques, and engagement in enjoyable activities can help restore energy [183; 266]. Counseling about setting realistic goals for activities and function may also help patients and family members adapt to new daily routines.

Pharmacologic treatment of fatigue should be undertaken only after potential causes of fatigue have been ruled out [183; 266]. The EAPC and the ASCO note that methylphenidate (Ritalin) and modafinil (Provigil) may reduce fatigue, and the NCCN recommends these two drugs as first-line options in the cancer palliative care setting [183; 266; 498]. These recommendations are based on systematic reviews showing a significant effect of methylphenidate for the treatment of fatigue in people with cancer or HIV/AIDS or for opioid-induced sedation [266; 276; 277; 278; 288]. An optimal dose of methylphenidate has not been defined, but an initial dose of 5–10 mg (given in the morning) has been used, with the dose titrated to 40–60 mg per day (given once in the morning and once at midday) [266]. Among the side effects are nervousness, jitteriness, agitation, arrhythmia, and tachycardia [266]. The initial recommended dose of modafinil is 200 mg per day [266]. Major side effects have included agitation, nervousness, sleep disturbances, nausea, and diarrhea. Since the publication of these recommendations, researchers conducting a systematic review concluded that the evidence was insufficient to recommend a specific drug for the treatment of fatigue in the palliative care setting [278]. The ASCO notes that evidence for their use is weak; others argue that an improper (too low) dose and short study duration leads to suboptimal effect in trials and that individual response to central nervous system stimulants is highly variable [498; 499].

Corticosteroids (prednisone and dexamethasone) have been used frequently to treat fatigue in the palliative care setting, but no research on their effectiveness is available [278]. These agents have provided short-term relief of fatigue and improved quality of life among people with cancer, but because of the toxicity associated with long-term use, they should be considered only at the end life or to alleviate fatigue for a well-defined goal (such as allowing the patient to attend a special event) [183; 266].

DYSPNEA

Dyspnea is a subjective sense of breathlessness (extreme shortness of breath) and ranges from experiencing breathlessness on exertion to severe shortness of breath for longer periods of time. Patients may describe dyspnea as "smothering," "suffocating," or "drowning." Dyspnea can have a substantial impact on a patient's quality of life by restricting the patient's activities as well as causing distress for both patients and their families.

Prevalence

The prevalence of dyspnea among adults with life-limiting disease ranges from 10% to 95%, with the highest rates among people with COPD, lung cancer, and heart failure, especially in the last week of life [204; 206; 208; 210; 237; 289; 290].

Etiology

Physical causes of dyspnea vary according to the life-limiting disease and/or comorbid conditions and include pleural effusion, airway obstruction, pulmonary embolism, pericardial effusion, and asthma [237]. Pain and psychologic conditions such as anxiety and depression may augment the severity or prolong the duration of dyspnea [210; 237].

Prevention

Measures to reduce anxiety can help to prevent dyspnea or reduce its severity. In addition, patients with heart failure or lung diseases should be advised to conserve energy.

Assessment

Practice guidelines recommend that clinicians regularly assess dyspnea in patients receiving end-of-life care [46; 210; 237]. Assessment should involve asking the patient to note the severity and/or distress related to dyspnea, as objective testing, such as respiratory rate, arterial blood gas levels, and pulse oximetry, do not always correlate with a patient's experience of shortness of breath [210]. Tools for patient-reported dyspnea include a modified Borg scale, a visual analog scale, or a numerical scale [210; 291]. In addition to asking about the severity of breathlessness, the clinician should ask about other symptoms, especially concurrent chest pain, and about the activities that cause dyspnea. Patients with dyspnea often modify their activities to avoid dyspnea, so the clinician should ask the patient if he or she has changed or stopped any activities because of dyspnea [237]. Because of the link between psychologic factors and dyspnea, the clinician should also evaluate the patient's psychosocial status.

Physical assessment of the patient should include evaluation of breath sounds, heart rate, respiratory rate, jugular pressure, and functional status. Testing should be done to identify a suspected underlying cause of dyspnea [119; 237].

 Copyright © 2019 NetCE

Management

The American College of Physicians, the American Thoracic Society, the Canadian Thoracic Society (endorsed by the ACCP), and the NCCN have developed evidence-based guidelines for the management of dyspnea [46; 119; 183; 210; 237; 500]. In addition, evidence-based recommendations for managing dyspnea in people with advanced heart failure are available [105]. A stepwise approach to managing dyspnea should be taken, with the first step being treatment of the underlying cause, if one can be identified [237]. Nonpharmacologic interventions should be used first; if the response is inadequate, pharmacologic interventions may be added.

Supplemental oxygen is commonly used to treat dyspnea. Strong evidence supports the use of oxygen and pulmonary rehabilitation for dyspnea, and supplemental oxygen may provide relief of dyspnea for people with advanced lung or heart disease who have hypoxemia at rest or with minimal activity [46; 183; 209; 210; 237; 500]. However, data suggest that oxygen offers no benefit to patients who do not have hypoxemia [105].

A variety of nonpharmacologic interventions have been suggested in several practice guidelines, although the evidence base varies (***Table 13***) [119; 183; 210; 500]. In a systematic review of nonpharmacologic interventions for dyspnea in people with advanced malignant and nonmalignant diseases, there was strong evidence for chest wall vibration and neuroelectrical muscle stimulation and moderate evidence for walking aids and breathing training [293]. The data were insufficient to recommend the use of a fan, music, relaxation, counseling and support, and psychotherapy [293]. A subsequent small randomized controlled trial demonstrated that a handheld fan directed at the face reduced breathlessness [292].

Opioids represent the primary recommended pharmacologic intervention for severe dyspnea in people with advanced cancer and lung disease [46; 210; 500]. A systematic review and meta-analysis (18 randomized controlled trials) demonstrated a significant positive effect of opioids on breathlessness [294]. Guidelines recommend that oral or parenteral opioids be considered for all patients with severe and unrelieved dyspnea; nebulized opioids have not had an effect when compared with placebo [46; 209; 210; 500]. Oral morphine is the most commonly prescribed opioid, but other opioids, such as diamorphine, dihydrocodeine, fentanyl, hydromorphone, and oxycodone, may be used [210]. The dose should be selected and titrated according to such factors as renal, hepatic, and pulmonary function and past use of opioids [210]. An oral dose of morphine of 2.5–10 mg every four hours as needed (1–5 mg intravenously) has been recommended for opioid-naïve patients [119; 183]. Although respiratory depression is a side effect associated with opioids, especially morphine, this effect has not been found with doses used to relieve dyspnea [119; 295]. Evidence-based recommendations for palliative care for people with heart failure note that diuretics represent the cornerstone of treatment of dyspnea [105]. Nitrates may also provide relief, and inotropes may be appropriate in select patients [105]. The recommendations also include the use of low-dose opioids [105].

NONPHARMACOLOGIC INTERVENTIONS FOR DYSPNEA RECOMMENDED IN PRACTICE GUIDELINES

Chest wall vibration
Neuroelectrical muscle stimulation
Walking aids
Breathing training
Inspiratory muscle training
Physical activity
Handheld fan directed at the face
Pursed-lip breathing
Cool compress on the forehead
Cool room
Open windows
Activity pacing
Noninvasive positive pressure ventilation
Relaxation techniques
Acupuncture/acupressure
Psychosocial support
Patient and family education

Source: [119; 183; 210; 292; 293; 500; 501] *Table 13*

Anxiolytics are often a recommended option for relief of breathlessness because of the association between anxiety and dyspnea. However, anxiolytic agents have not been found to be effective for the management of dyspnea. A systematic review published in 2010 (seven studies, 200 subjects) showed that benzodiazepines had no beneficial effect on breathlessness in people with advanced cancer or COPD [296]. Bronchodilators and systemic corticosteroids may be helpful in relieving dyspnea in people with lung cancer and underlying obstructive airway disease [501]. In addition, analgesics may help relieve dyspnea associated with pain.

CONSTIPATION

Constipation can be defined as a reduced frequency of bowel movements and an increased stool consistency. In defining constipation in people with life-limiting disease, measurable symptoms, as well as the person's perception of constipation and the level of discomfort, are factors [297; 298]. The condition may be accompanied by cramps and abdominal bloating, as well as by discomfort caused by straining and rectal pressure. The patient who complains of "constipation" should be encouraged to elaborate so that the full nature and extent of the difficulty, including associated symptoms, can be defined for that individual [297].

Prevalence

The prevalence of constipation among adults with life-limiting disease ranges from 8% to 70%, and constipation occurs in almost all patients taking opioids [208; 223; 290]. The prevalence of constipation in palliative care settings is even higher, at 30% to 90% [502].

Etiology

Opioids are the primary factor in constipation in the palliative care setting, and many other prescribed drugs can contribute to constipation, including tricyclic antidepressants, antacids, antiepileptic drugs, anticholinergic agents, and antihypertensives [297]. Additional factors that may contribute to constipation are diverticuli, inflammatory bowel disease, metabolic conditions (hypercalcemia, hypokalemia, hypothyroidism, uremia), cerebral tumors, dehydration, and radiation fibrosis [183; 297]. For patients with cancer, constipation may be directly due to tumor involvement that causes intestinal obstruction. A diet low in fiber and decreased physical activity also increase the likelihood of constipation.

Prevention

Prevention of constipation is key, as prophylaxis is more effective than treatment after constipation has been identified. As such, all treatment guidelines strongly recommend that a prophylactic bowel regimen be initiated when treatment with opioids (or other constipation-causing drugs) begins [183; 297; 298; 502]. The recommended prophylaxis is an osmotic and/or a stimulant laxative [297; 298]. Many nonpharmacologic approaches are recommended, and patients should be encouraged to plan a diet with adequate fiber, to increase fluid intake, and to engage in physical activity, as appropriate [297; 298; 502]. Family members should be asked to help the patient comply with these measures. Ensuring that the patient has sufficient privacy and comfort with toileting is also recommended [297; 298; 502].

Assessment

Issues of personal privacy often lead to a reluctance of patients to discuss constipation, so clinicians and other healthcare professionals must initiate the discussion and talk honestly about what to expect and measures to prevent and manage the symptom. The assessment tools used most often are the Bristol Stool Form Scale and the Constipation Assessment Scale [297; 298]. Assessment should include a review of the list of medications, a history of bowel habits, and abdominal and rectal examination. In addition to checking the list of prescribed medications to determine if constipation is a side effect, the physician should ask the patient about over-the-counter drugs and herbal remedies, as constipation can be a consequence of aluminum-containing antacids, ibuprofen, iron supplements, antidiarrhea drugs, antihistamines, mulberry, and flax. A detailed history of bowel habits helps to establish what is considered normal for the individual patient. The patient should be asked about frequency of stool, the appearance and consistency of stools, use of bowel medications, and previous occurrence of constipation. In general, physical examination of the abdomen for tenderness, distention, and bowel sounds can rule out intestinal obstruction as the cause of constipation. A rectal examination can identify the presence of stool, fecal impaction, or tumor. Imaging of the abdomen (by plain x-ray or computerized tomography) may be appropriate to confirm the presence of obstruction. Consideration of the patient's prognosis and preferences for care should be factored into a decision to carry out diagnostic testing. As with assessment of all symptoms, constipation should be reassessed frequently; assessment at least every three days is recommended [298].

Management

The goal of treatment should be relief of symptoms related to constipation and re-establishment of bowel habits to the patient's comfort and satisfaction; some recommend a goal of one nonforced bowel movement every one to two days, or at least three times per week [183; 298; 502]. Systematic reviews have demonstrated that data are insufficient to support one laxative or combination of laxatives over others [297; 299; 300; 302].

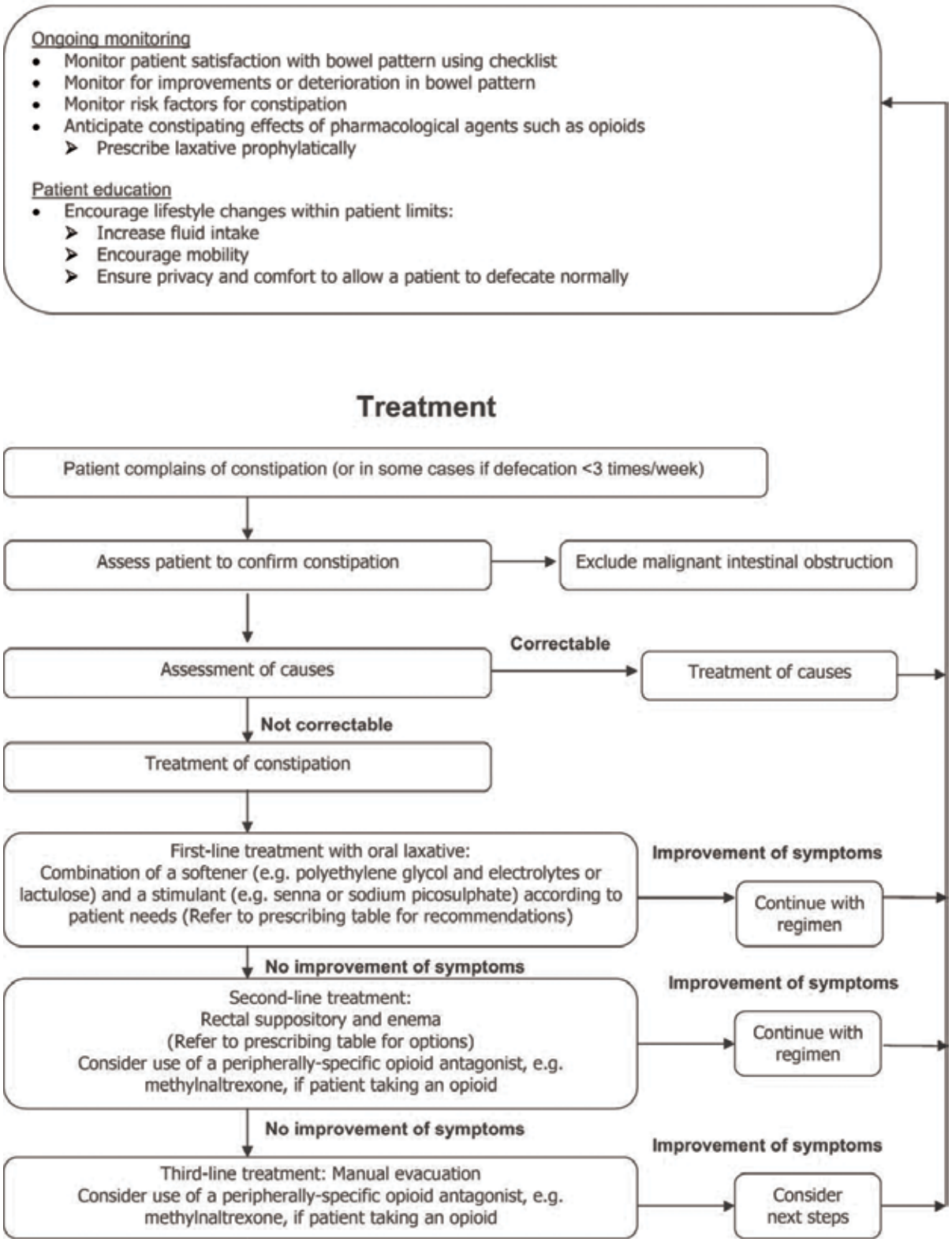
Many laxatives are FDA approved for occasional constipation, and much of the evidence on their efficacy has come from studies of chronic constipation, not patients with life-limiting disease. In its guidelines for the management of chronic constipation, the American College of Gastroenterology notes the following [300]:

- Polyethylene glycol (PEG) and lactulose (both osmotic) improve stool frequency and stool consistency.
- Data are insufficient to make a recommendation about the efficacy of stool softeners (docusate [Colace or Surfak]); stimulant laxatives (senna [Senokot, Ex-Lax] or bisacodyl [Dulcolax, Correctol]); milk of magnesia; herbal supplements (aloe); lubricants (mineral oil); or combination laxatives (psyllium plus senna).

The results of a systematic review of studies in the palliative care setting also demonstrated insufficient data for recommendations because of a lack of direct comparisons of laxatives [299]. Researchers have concluded that the choice of a laxative should be made on an individual basis, with considerations of patient preferences and the side-effect profile [183; 297; 299]. For all patients, oral formulations are recommended over rectal suppositories [297; 298]. The use of rectal suppositories and/or enemas are contraindicated in patients with neutropenia or thrombocytopenia [183].

 Copyright © 2019 NetCE

ALGORITHM FOR THE MANAGEMENT OF CONSTIPATION IN PATIENTS RECEIVING PALLIATIVE CARE



Source: [297] Reprinted, with permission from Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med. 2008;22(7):796-807. *Figure 11*

CAUSES OF NAUSEA AND VOMITING ACCORDING TO PATHWAY STIMULATED AND CLASS OF ANTIEMETICS		
Pathway Stimulated	**Causes**	**Class of Antiemetics**
Chemoreceptor trigger zone	Metabolic disorders (hypercalcemia, hyponatremia, hepatic/renal failure)	Dopamine antagonists
	Opioids	Prokinetic agent, dopamine antagonists
	Malignant bowel obstruction	Prokinetic agent, dopamine antagonists, corticosteroids
Cortex of brain	Increased intracranial pressure, anxiety, five senses	Corticosteroids, anxiolytics
Peripheral pathways (gastrointestinal tract)	Gastroparesis	Prokinetic agent
Vestibular system	Motion	Muscarinic acetylcholine receptor, antihistamine
Source: [202; 303]		*Table 14*

European and Canadian consensus groups and the NCCN have developed practice guidelines for constipation in the palliative care setting on the basis of the available data and expert opinion (***Figure 11***) [183; 297; 298]. First-line recommended treatment is a stimulant laxative plus a stool softener (PEG or lactulose) [183; 297; 299]. A small study of senna with and without docusate for hospitalized patients with cancer showed no significant benefit to the addition of docusate; docusate is specifically not recommended in the Canadian consensus recommendations [298; 301]. If constipation persists, other options are bisacodyl, magnesium hydroxide, or sorbitol [183]. Methylnaltrexone (Relistor) was approved by the FDA in 2008 for the treatment of opioid-induced constipation. A systematic review indicated that the subcutaneous drug is effective in the palliative care setting, and is especially useful for patients with constipation refractory to conventional laxatives [302]. In 2014, the FDA approved naloxegol, an oral agent for the management of opioid-associated constipation [488]. However, this drug's approval is limited to patients with chronic non-cancer pain. Practice recommendations note that methylnaltrexone or naloxegol should be considered for patients taking opioids after failure of other laxatives [183; 297; 298]. Withdrawal of opioids should never be a strategy to manage constipation.

Nonpharmacologic interventions are important adjuncts to laxatives, and the interventions used as prophylaxis are recommended for ongoing management [297; 298].

NAUSEA AND VOMITING

Nausea may occur alone or with vomiting, a neuromuscular reflex. Nausea and vomiting can exacerbate pain and contribute to insomnia, fatigue and weakness, and anorexia. It can also limit activities and cause distress for the patient and family. Nausea is the result of stimulation of one of several pathways: the chemoreceptor trigger zone (located in the medulla), the cortex of the brain, the vestibulocochlear nerve, or the gastrointestinal tract [66].

Prevalence

Nausea alone affects approximately 6% to 68% of adults with life-limiting disease, and vomiting affects 40% [208]. The rate of nausea and vomiting is highest among patients with cancer [208].

Etiology

The potential causes of nausea and vomiting near the end of life vary according to life-limiting disease [202; 211; 243; 303; 304]:

- Medications (chemotherapy agents, opioids, antidepressants, antibiotics)
- Radiation therapy (especially to the abdomen or lumbosacral spine)
- History of peptic ulcer disease or gastroesophageal reflux
- Delayed gastric emptying
- Primary or metastatic brain tumor
- Gastrointestinal tract obstruction
- Constipation
- Renal failure
- Hepatic failure
- Pancreatitis
- Hypercalcemia
- High serum levels of dioxin or anticonvulsants

 Copyright © 2019 NetCE

The causes also differ according to the pathway stimulated (***Table 14***) [303; 304]. Most often the cause is multifactorial, but sometimes no cause can be determined.

Prevention

The prevention of nausea and vomiting has focused on prophylactic treatment for patients receiving chemotherapy or radiation therapy for cancer. Although most patients at the end of life do not receive anticancer treatment, chemotherapy may be given as part of palliative care. ASCO classifies chemotherapy drugs according to their emetogenic potential: high (>90% incidence of emesis without an antiemetic), moderate (30% to 90% incidence), low (10% to 30% incidence), and minimal (<10% incidence) [305]. According to ASCO guidelines, a 5-hydroxytryptamine type 3 (5-HT3) antagonist, dexamethasone (Decadron), and a neurokinin 1 (NK1) receptor antagonist (such as aprepitant [Emend]) should be used as prophylaxis for a highly emetic chemotherapy agent or combination (such as an anthracycline and cyclophosphamide) [305]. Palonosetron (Aloxi), in combination with dexamethasone or netupitant, is recommended for chemotherapy agents with moderate emetic risk, and dexamethasone is recommended before the first dose of chemotherapy with a low emetic risk. For nausea and vomiting not related to chemotherapy, treatment with regular dosing of an antiemetic will help prevent subsequent episodes of the symptoms.

Assessment

A detailed history, physical examination, and review of the medication list are essential for planning effective management of nausea and vomiting. In talking with the patient, the clinician should ensure that the patient is actually experiencing nausea, as patients have used the term nausea to describe other feelings, such as pain, distention, abdominal discomfort, and early satiety [66]. The clinician should ask about the onset of the nausea, how frequently it occurs, if there are precipitating factors, and if there is a relationship to food intake. It may be helpful to ask the patient to rate the intensity of nausea on a scale similar to a pain scale (a 10-point numerical scale). Because the cause of nausea and vomiting is often multifactorial, a multidimensional assessment is beneficial, with particular attention paid to such other symptoms as pain, appetite, fatigue, depression, and anxiety. The physical examination should include evaluation for signs of cachexia or malnutrition, assessment of the abdomen for evidence of bowel obstruction, increased bowel sounds, and abdominal distention. In addition, a neurologic examination should be done to determine if there are signs of increased intracranial pressure, papilledema, or autonomic insufficiency [66]. Diagnostic testing may include laboratory studies to rule out metabolic disorders, renal impairment, or liver failure, or radiographs of the abdomen to determine if there is obstruction.

Nausea is often not reported; patients should be asked if they have experienced nausea even if they have not vomited [243].

Management

Evidence-based guidelines for the management of nausea and vomiting unrelated to chemotherapy and radiation are lacking [306]. In addition, most studies of these symptoms and recommendations are related to the cancer setting. In general, experts have recommended that antiemetics be selected on the basis of the emetic pathway and the etiology of the nausea and/or vomiting, but systematic reviews have found that the evidence for recommendations is weak to moderate at best [202; 303; 304; 306; 307; 308]. One systematic review found no evidence that the choice of antiemetic according to etiology or multiple antiemetics was better than a single antiemetic [306].

Several classes of pharmacologic agents can be used to manage nausea and vomiting; the main classes used in the end-of-life setting are prokinetic agents, dopamine receptor antagonists, antihistamines, anticholinergics, 5-HT3 receptors, and corticosteroids (***Table 15***) [303; 304; 308]. The prokinetic agent metoclopramide (Reglan) has been recommended as a first-line treatment because of its central and peripheral actions and its effectiveness for many chemical causes of nausea [202; 243; 303]. The drug should be used with caution in patients with heart failure, diabetes, and kidney or liver disease; the dose should be reduced by 50% for older patients and those with moderate-to-severe renal impairment [304]. Chronic use of prokinetic agents and dopamine receptor antagonists may be associated with the development of tardive dyskinesia, especially in frail, elderly patients [183]. Octreotide (Sandostatin), dexamethasone, and hyoscine hydrobromide (Scopolamine) are recommended for bowel obstruction [89; 303; 304; 306]. Ondansetron (Zofran) has been suggested for chronic nausea, but in September 2011, the FDA issued a safety announcement about the drug, noting that it may increase the risk of QT prolongation on electrocardiogram; more research is being done [240; 304]. Haloperidol (Haldol) is recommended for uremia-induced nausea in people with end-stage chronic kidney disease [211]. Dexamethasone is used for nausea and vomiting related to increased intracranial pressure and, although the evidence is limited, it is also used as second-line treatment for intractable nausea and vomiting and as an adjuvant antiemetic [243; 303; 304]. Olanzapine (Zyprexa), an atypical antipsychotic, has also been effective for nausea that has been resistant to other traditional antiemetics, as well as for opioid-induced nausea [309]. A benzodiazepine (such as lorazepam [Ativan]) may be of benefit if anxiety is thought to be contributing to nausea or vomiting [304].

PHARMACOLOGIC MANAGEMENT OF NAUSEA AND VOMITING		
Drug Class	**Drug**	**Typical Starting Dose and Frequency**
Prokinetic agents	Metoclopramide	10–20 mg PO/IV/SC, every 6 to 8 hours
Dopamine antagonists	Haloperidol	0.5–1.5 mg PO/IV/SC every 6 to 8 hours
	Prochlorperazine	5–10 mg PO every 6 hours
	Chlorpromazine	10–25 mg PO/IV every 4 to 6 hours
	Olanzapine	5–10 mg PO daily
	Levomepromazine	6.25–25 mg SC twice daily
Antihistamines	Promethazine	25 PO 4 to 6 hours
Anticholinergics	Hyoscine hydrobromide	0.1–0.4 mcg PO/IV/SC every 4 hours
5-hydroxytryptamine type 3 receptor antagonists	Ondansetron	4–8 mg PO/IV 1 or 2 times daily
	Granisetron	1 mg twice daily
	Dolasetron	200 mg daily
	Palonosetron	0.25 mg IV daily
	Mirtazapine	15–45 mg PO, every night
Corticosteroids	Dexamethasone	4–8 mg daily
PO = orally, IV = intravenously, SC = subcutaneously.		
Source: [183; 202; 304]		*Table 15*

In addition to pharmacologic management of nausea and vomiting, other supportive approaches include maintenance of oral hygiene, regular baths to reduce unpleasant odors, and small meals at regular intervals [202; 243]. Cold foods may be better tolerated than hot foods because of decreased smells.

ANOREXIA AND CACHEXIA

The symptoms of anorexia and cachexia often occur in tandem. While anorexia encompasses decreased appetite and food intake, cachexia involves loss of skeletal mass, with accompanying asthenia and autonomic failure. The two conditions are often linked by the term "anorexia-cachexia syndrome," but the exact relationship between the two conditions is unclear [310]. For example, decreased food intake may lead to weight loss, but the body wasting of cachexia is not solely the result of decreased intake [311]. "Wasting" is often used as a synonym for cachexia, but wasting indicates weight loss due to inadequate nutritional intake, whereas cachexia refers to a loss of lean body mass resulting metabolic derangement rather than nutritional deficiency [312].

Cachexia is associated with a poor prognosis in many life-limiting diseases. In fact, unintentional, progressive weight loss of more than 10% of body weight over the past six months, with an albumin level less than 2.5 mg/dL is a prognostic indicator for hospice referral [73]. Despite this relationship between cachexia and poor prognosis, the condition is underrecognized and underdiagnosed [313].

Cachexia has also been challenging to define. The lack of an operational definition led to a consensus conference at which a definition was crafted [311]. This definition joins others for disease-specific cachexia (***Table 16***). The diagnosis and management of anorexia/cachexia has been studied the most in the settings of cancer and HIV infection.

Prevalence

Anorexia occurs in 21% to 92% of adults with life-limiting disease, with the highest rates found among patients with cancer [204; 208; 290]. Cachexia has been reported in 16% to 57%, again with the highest rates found among people with cancer [313].

Etiology

Across life-limiting diseases, anorexia can occur as a result of several other symptoms, such as fatigue, constipation, xerostomia, dysphagia, mucositis, and nausea. Endocrine abnormalities may also be the cause, and psychologic, social, and spiritual distress can affect the desire to eat [183; 317]. Changes in taste sensations (leading to food aversions), altered sense of smell, and early satiety have been common among people with cancer and anorexia [317; 318].

 Copyright © 2019 NetCE

DEFINITIONS AND DIAGNOSTIC CRITERIA FOR CACHEXIA	
Condition	**Definition and/or Diagnostic Criteria**
All patients with chronic disease	Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. Chronic disease AND Loss of body weight of 5% or more within the past 3 to 12 months AND Presence of at least three of the following: Reduced muscle strength Fatigue Anorexia Low fat-free mass index Abnormal inflammatory marker levels, anemia, or low albumin level
Cancer cachexia	A multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.
Cardiac cachexia	6% non-edematous, nonvoluntary weight loss over 6 months
HIV-associated wasting	At least one of the following: 10% unintentional weight loss over 12 months 7.5% unintentional weight loss over 6 months 5% body cell mass (BCM) loss within 6 months Body mass index (BMI) <20 kg/m^2 BCM <35% body weight AND BMI <27 kg/m^2 (men) BCM <23% body weight AND BMI <27 kg/m^2 (women)
Source: [311; 312; 314; 315; 316]	*Table 16*

Studies have shown that multiple factors contribute to cachexia. Abnormal metabolism is thought to lead to a negative protein and energy balance, with subsequent loss of muscle mass [197; 311; 314; 315]. Inflammation, increased neurohormonal activity, insulin resistance, and increased muscle protein breakdown are often associated with cachexia [311; 315; 319]. The role these factors play in the development of cachexia may differ according to the underlying chronic condition.

Prevention

Preventive measures for anorexia include effective management of symptoms that are known to have a potential impact on the desire and/or ability to eat. No appropriate measures to prevent cachexia are available.

Assessment

Guidelines for assessing anorexia and cachexia have been developed for the cancer and HIV settings [183; 320]. According to NCCN guidelines, assessment of anorexia and cachexia in patients with cancer include the following [183]:

- Determination of the rate and severity of weight loss
- Examination of the oral cavity (the mucous membranes, teeth, gingiva, and lips)
- Review of the medications list for drugs that interfere with intake
- Evaluation of symptoms that have the potential to interfere with eating and drinking
- Evaluation for endocrine abnormalities that may be an underlying cause
- Assessment of social and economic factors

The guidelines for the assessment of HIV-related wasting recommend the following [320]:

- Thorough and complete history and physical examination, with specific questions related to the patient's nutritional status, caloric intake, appetite, and gastrointestinal and physiologic functioning
- Measurements of body composition (considering the following factors: age, height, weight, ideal body weight, body cell mass (by BIA), and body mass index

PHARMACOLOGIC MANAGEMENT OF ANOREXIA AND CACHEXIA			
Drug	**Dose Range**	**Findings**	**FDA Approval**
Megestrol acetate	400–800 mg/day	Increased appetite, food intake, and weight	For the treatment of anorexia, cachexia, or unexplained weight loss in patients with AIDS
Dronabinol	2.5–20 mg, twice daily (before lunch and dinner)	Stimulated appetite and improved body weight	For anorexia associated with weight loss in people with AIDS
Metoclopramide	10 mg, 3 times daily	Enhanced appetite in people with early satiety	For nausea and vomiting
Recombinant human growth hormone	0.1 mg/kg SC at bedtime (max: 6 mg)	Increased lean body mass and improved physical endurance and quality of life among people with HIV-related cachexia	For HIV-related wasting or cachexia (with concomitant antiretroviral therapy)
Oxandrolone (anabolic steroid)	5–20 mg/day	Increased body weight and lean body mass in cachexia related to HIV and COPD	Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infection, or severe trauma and for some patients without a definitive pathophysiologic cause of weight loss
Ghrelin	Not defined	Increased lean body mass in people with end-stage renal disease, COPD, and heart failure	Not approved
AIDS = acquired immune deficiency syndrome, COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, SC = subcutaneous.			
Source: [183; 240; 321; 323; 324; 325; 326; 327; 328]			*Table 17*

- Laboratory tests (plasma HIV RNA, CD4 cell count, free and total serum testosterone, and serum albumin and thyroid function (if clinically warranted)
- Psychosocial evaluation
- Dietary assessment

Management

Few evidence-based guidelines for the treatment of anorexia and cachexia are available, primarily because of the lack of studies on these under-recognized conditions and the still-emerging understanding of the causes of cachexia. The first step in managing anorexia is to treat symptoms that interfere with appetite and/or the ability to eat. In addition, nonpharmacologic interventions should be directed at improving enjoyment of food, increasing the sense of well-being, and enhancing a sense of normalcy in daily activities. The patient should be encouraged to try favorite foods, to eat small frequent meals, and to drink high-calorie nutritional supplements [183; 319; 321; 322]. Other interventions include an exercise program and consultation with a nutritionist [183]. For people with end-stage liver disease and an inadequate caloric intake, protein restriction (to prevent hepatic encephalopathy) should be avoided [197].

Two drugs are FDA approved as appetite stimulants for anorexia associated with life-limiting disease (***Table 17***). Megestrol acetate is FDA approved for the treatment of anorexia, cachexia, or unexplained weight loss in patients with AIDS [323]. It has become the most widely used drug for these indications for people with other life-limiting diseases, and a meta-analysis of data from studies (involving people with a variety of life-limiting illnesses) demonstrated that megestrol acetate was beneficial, especially with respect to improving appetite and weight gain in people with cancer [323]. The data were insufficient to recommend megestrol acetate for conditions other than cancer or to recommend an optimal dose [323]. Dronabinol (Marinol), an oral cannabinoid, is FDA approved for anorexia associated with weight loss in people with AIDS [240]. Because of its effects, dronabinol should be used with caution for people with cardiac disorders, depression, or a history of substance abuse; people taking concomitant sedatives or hypnotics; and older individuals [240].

 Copyright © 2019 NetCE

In addition to appetite stimulants, metoclopramide, a drug approved for treatment of nausea and vomiting, is recommended for anorexia related to early satiety in people with cancer [183; 321].

The treatment of cachexia is more challenging because its pathophysiology is poorly understood and because treatments may differ according to the life-limiting disease. According to the guidelines for cachexia related to cancer and HIV infection, management includes improving nutritional intake, treating disease-related causes of cachexia, treating anorexia, and addressing psychosocial or lifestyle issues [183; 320].

Currently, there is no one treatment or combination of treatments that is effective for all patients with cachexia [322]. Increasing oral intake alone is not sufficient, and reversal of wasting may not always be possible; the goal should be to prevent or delay further wasting and functional decline [183; 320; 322]. As noted, the use of megestrol acetate is effective in increasing weight, but increased nutrition and weight are not sufficient to effectively manage cachexia, and more research is needed to identify agents to increase body mass and to define a multimodal strategy to stop and/or reverse wasting. These strategies may differ according to the underlying chronic disease.

Studies have indicated that recombinant human growth hormone (rhGH) significantly increases lean body mass and improved physical endurance and quality of life in people with HIV [324; 325]. In addition, rhGH has shown benefit in cachexia related to pulmonary and cardiac disease [326]. Recombinant somatropin (Serostim) is approved for the treatment of people with HIV with wasting or cachexia; concomitant antiretroviral therapy is necessary [240]. The drug is contraindicated in active neoplasia [240].

The anabolic steroid oxandrolone (Oxandrin) is FDA approved as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infection, or severe trauma and for some patients without a definitive pathophysiologic cause of weight loss [240]. The drug has shown benefit in increasing body weight and lean body mass in cachexia related to HIV and COPD [327; 328]. The drug is safe and well tolerated, but more studies are needed to determine its risk-benefit ratio before it can be used more widely [329].

Ghrelin has been evaluated for the treatment of cachexia, and its anti-inflammatory properties may address the proposed role of inflammation in the development of cachexia [330]. The results of small studies have demonstrated that ghrelin increases lean body mass in people with end-stage renal disease, COPD, and heart failure [326]. Again, more research is needed before this agent can become part of clinical practice.

For people with a limited life expectancy (weeks to days), the clinician should assess the importance of anorexia and cachexia to the patient and the family before prescribing interventions [183]. The clinician should also talk to the patient and family about the risks of artificial nutrition and should consider consulting a spiritual counselor or bioethicist about discontinuing nutrition [183].

DIARRHEA

Diarrhea is characterized by the frequent passage of loose, watery stools, usually defined as more than three unformed stools within a 24-hour period [331]. Diarrhea is most often acute, lasting for a few days; diarrhea is chronic when it persists for more than three weeks [331]. Left unchecked, diarrhea can result in dehydration, electrolyte imbalance, and fatigue.

Prevalence

The prevalence of diarrhea among adults with life-limiting disease varies widely, ranging from 3% to 90%, with the highest rates reported among people with HIV infection or AIDS [208].

Etiology

The most frequent cause of diarrhea in patients receiving palliative care is overuse of laxatives and leakage around a fecal impaction [331]. Other causes are infectious disease or underlying disease in people with HIV/AIDS or metastatic colorectal cancer. Diarrhea is also a side effect of many drugs, including antihypertensives, antacids containing magnesium, some NSAIDs, potassium supplements, quinidine, thiazide diuretics, retroviral agents, prokinetic agents (metoclopramide), and antibiotics [331].

Prevention

No appropriate measures to prevent diarrhea are available.

Assessment

A detailed history is the cornerstone of assessing patients for diarrhea. The condition is distressful, yet embarrassing, and direct questions should be asked because the patient may not be forthcoming about the symptom. The clinician should ask the patient about the onset of diarrhea, dietary habits, food intolerances, timing of diarrhea in relation to eating, and medications [331; 332]. The patient should also describe bowel movements in terms of frequency, color, and consistency. If possible, a stool specimen should be evaluated.

If infectious diarrhea is suspected, a stool sample should be evaluated to identify the causative organism [332; 333].

Management

The American Gastroenterological Association developed guidelines for the treatment of chronic disease in the general clinical setting, but no specific guidelines are available for the management of diarrhea in palliative care [333].

Treatment of an underlying condition is the optimal approach to managing diarrhea. The clinician should review the medication list and discontinue or reduce the dose of any medication that may be the cause [331; 332].

Nonpharmacologic approaches to managing diarrhea include avoiding gas-forming and bulky foods, hot spices, fats, alcohol, and milk until diarrhea is controlled. The patient should be encouraged to drink plenty of fluids to avoid dehydration; beverages with added electrolytes, such as sports drinks, can help maintain proper electrolyte balance.

Pharmacologic management includes the use of bulk-forming agents, adsorbents, and opioids [332]. Kaolin and pectin (Kaopectate), available over the counter, is a combination of adsorbent and bulk-forming agents. However, it provides modest relief and it may take up to 48 hours to be effective [332]. Loperamide (Imodium) is the drug of choice for diarrhea because its side effect profile is better than that for codeine or diphenoxylate (Lomotil) [332]. The initial dose of loperamide is 4 mg, with an additional 2 mg after each loose stool [332]. The package insert for loperamide notes that the maximum daily dose in a 24-hour period is 16 mg, but doses of up to 54 mg a day have been used as part of palliative care with few adverse events [332]. Octreotide has been effective for profuse secretory diarrhea associated with HIV infection and can be used to treat refractory diarrhea [332]. The use of octreotide for diarrhea in the palliative setting is usually off-label, as the drug is FDA approved for the treatment of diarrhea and flushing associated with metastatic carcinoid tumors [240]. Octreotide is administered as a continuous subcutaneous infusion at a rate of 10–80 mcg/hr until improvement of symptoms [332]. Infectious diarrhea should be treated with an appropriate antibiotic. A systematic review found probiotic agents to be of benefit in the management of acute infectious diarrhea [334].

INSOMNIA

As defined, insomnia refers to a variety of sleep disturbances, including difficulty falling asleep and difficulty staying asleep (insufficient amount of sleep or frequent awakenings), that results in impaired function during the day [335]. The most frequent type of insomnia among people at the end of life is difficulty staying asleep, primarily because of pain [336]. A lack of sufficient sleep affects the quality of life by contributing to daytime fatigue and weakness, exacerbating pain, and increasing the potential for depression. Family members also become distressed when the patient is unable to sleep, which, in turn, may increase the burden on caregivers.

Prevalence

Insomnia is common among the general population, and rates reported for adults with life-limiting disease are even higher, ranging from 9% to 83% [197; 204; 208; 337]. The highest rates have been found among patients with end-stage renal disease [208].

Etiology

What is the most common contributor to sleep disturbances in patients at the end of life?

The primary difference between insomnia in the general population and in people with life-limiting diseases is that insomnia in the latter group is usually secondary to the life-limiting disease or its symptoms [336]. Overall, uncontrolled pain is the most common contributor to the inability to sleep well [336; 337]. Other common physical symptoms such as dyspnea, nocturnal hypoxia, nausea and vomiting, pruritus, and hot flashes are also causes of insomnia. Restless legs syndrome may be a substantial contributor to the disruption of sleep in persons with end-stage renal disease [207; 338; 339].

In addition, many psychologic conditions associated with a life-limiting disease can cause insomnia; depression, anxiety, delirium, spiritual distress, and grief can make it difficult to fall or remain asleep [336]. Insomnia is a side effect of many drugs, most notably corticosteroids, antidepressants, decongestants, opioids, and some antiemetics [335; 340]. Patients also may have difficulty sleeping because of disruptions in the normal sleep-wake cycle that result from inactivity and napping during the day. Lastly, stimulants, such as caffeine, and alcohol may keep patients from falling asleep easily.

Prevention

Adequate relief of pain and other symptoms is the mainstay of preventing insomnia. The most effective preventive measure is limiting the amount of time in bed during the day and restricting the amount of daytime sleep [336]. Encouraging patients to increase activity during the day, as tolerated; to adhere to a regular schedule with limited naps; and to avoid caffeine and alcohol in the afternoon and evening can help lead to more healthy sleep patterns.

Assessment

Few patients with life-limiting diseases report insomnia, and few clinicians pursue sleep symptoms in their patients [336]. Clinicians should obtain a sleep history from all patients, following guidelines developed by the American Academy of Sleep (***Table 18***) [335]. The Epworth Sleepiness Scale has been recommended as an assessment tool [183; 341].

Clinicians should evaluate patients physically as well as psychologically for signs and symptoms that have been identified as contributors to sleep disturbances.

 Copyright © 2019 NetCE

QUESTIONS TO OBTAIN A SLEEP HISTORY
What is your primary problem with sleep: difficulty falling asleep, waking up frequently during the night, and/or poor quality of sleep?
When did your sleep problems begin?
How often do you have trouble sleeping (every night, most nights)?
Have you ever taken any medication for sleep problems in the past? If so, what did and did not help?
What do you do before you go to bed?
What is your bedroom environment like?
How do you feel (physically and emotionally) in the evening?
What is your average sleep-wake schedule?
How long does it typically take you to fall asleep?
What factors make it longer for you to fall asleep?
What factors shorten your sleep?
How often do you awaken during the night?
When you awaken during the night, how long are you awake?
Do you have symptoms that cause you to awaken during the night?
What do you do to try to fall back asleep after awakening during the night?
How many hours do you sleep each night (on average)?
Do you nap during the day? If so, how often and for how long?
Do you feel sleepy during the day?
How do your sleep problems affect you during the day? Do you have mood disturbances? Feel confused? Feel like your symptoms are worse?
Source: [335] *Table 18*

Management

The American Academy of Sleep has developed an evidence-based guideline for the evaluation and management of chronic insomnia in adults and a practice parameter for the psychologic and behavioral treatment of insomnia, but neither offers specific guidelines for managing insomnia at the end of life [335; 342]. Nonpharmacologic interventions should be implemented first, with pharmacologic therapy added to the treatment plan if these interventions are not effective [336]. Optimizing sleep habits can be useful, especially if they are begun early in the course of the disease.

The nonpharmacologic approaches used to prevent insomnia are also the primary management strategies. Among the recommended behavioral strategies are the following [335; 342]:

- Stimulus control therapy: Training the patient to reassociate the bed and bedroom with sleep and to re-establish a consistent sleep-wake cycle
- Relaxation training: Progressive muscle relaxation and reducing thoughts that interfere with sleep
- Sleep restriction: Limiting the time spent in bed to time spent sleeping

Cognitive behavioral therapy has also been reported to be effective when used in combination with behavioral interventions [335; 342]. No nonpharmacologic strategy has been found to be superior to another [342]. These interventions are effective and recommended for older individuals and can also be effective for people with life-limiting disease when strategies are individualized according to the patient [336; 342].

Several drugs have been approved by the FDA for the treatment of insomnia; the classes of these drugs are sedative-hypnotics and benzodiazepines (***Table 19***). In addition, antidepressants and antihistamines are often used for insomnia, but this use is off-label.

Among sedative-hypnotics, zolpidem (Ambien) is a short- to intermediate-acting drug used primarily for sleep-onset insomnia [335; 343]. Zolpidem is recommended by the NCCN for insomnia as part of palliative care for people with cancer [183]. Another sedative-hypnotic, eszopiclone (Lunesta), is intermediate-acting and is one of only three insomnia medications approved by the FDA for long-term use [343].

PHARMACOLOGIC MANAGEMENT OF INSOMNIA		
Drug	**Typical Dose (mg)[a]**	**Comments**
Sedative-Hypnotics (FDA approved for insomnia)		
Zolpidem	5–20 mg	Useful for sleep-onset insomnia; lower dose should be used for older or debilitated individuals or those with impaired hepatic function
Zaleplon	5–20 mg	Useful for sleep-onset insomnia; lower dose should be used for older or debilitated individuals, patients with impaired hepatic function, and patients taking cimetidine
Eszopiclone	1–3 mg	Has favorable side-effect profile in older individuals, though a lower dose should be used for debilitated individuals; FDA approved for long-term use
Benzodiazepines (FDA approved for insomnia)		
Flurazepam	15–30 mg	Lower dose should be used for female, older, or debilitated individuals; long-acting effect increases risk of daytime drowsiness
Estazolam	0.5–2 mg	Lower dose should be used for older or debilitated individuals
Temazepam	7.5–30 mg	Lower dose should be used for older or debilitated individuals
Triazolam	0.125–0.25 mg	Lower dose should be used for older or debilitated individuals
Quazepam	7.5–15 mg	—
Melatonin Receptor Agonists (FDA approved for insomnia)		
Ramelteon	8 mg	Useful for sleep-onset insomnia; FDA approved for long-term use
Orexin Receptor Agonists (FDA approved for insomnia)		
Suvorexant	10–20 mg	Adjust dose with concomitant use of CYP3A inhibitors
Antidepressants (Not FDA approved for insomnia)		
Trazodone	50–150 mg	—
Amitriptyline	10–100 mg	—
Antidepressants (FDA approved for insomnia)		
Doxepin	3–6 mg	Useful for difficulty with sleep maintenance
Nonprescription (FDA approved for occasional insomnia)		
Diphenhydramine	25–50 mg	For occasional use only
[a]Doses are given as guidelines; actual doses should be determined on an individual basis.		
Source: [183; 335; 343; 494]		*Table 19*

There is a limited number of studies regarding the use of benzodiazepines in palliative care [344]. However drugs in this class are the most commonly used drugs for the treatment of short-term insomnia in people with life-limiting disease [336]. Benzodiazepines are effective in decreasing the time needed to fall asleep as well as the likelihood of waking up during the night [336; 343]. Their use should be short term, as their long-term efficacy has not been clearly defined, although this issue is not as important for patients with a limited life expectancy [336]. Lorazepam (Ativan) is a recommended drug for insomnia in people with cancer [183]. The long-acting effect of flurazepam (Dalmane) may be of benefit for some patients [336].

The antidepressant trazodone (Desyrel) is the preferred antidepressant for insomnia (although it is not FDA approved for this indication) [336]. It is the drug of choice among tricyclic antidepressants because of its shorter half-life and its milder anticholinergic side effects [336]. Antidepressants are especially useful for people who have anxiety or depression.

The most recently FDA-approved drug for insomnia is suvorexant (Belsomra), an orexin receptor antagonist [503]. The first approved drug of this class, this agent supports sleep through inhibition of orexin A and B, which are neuropeptides that promote wakefulness [504]. Another newer drug is ramelteon (Rozerem), a melatonin receptor agonist.

 Copyright © 2019 NetCE

This drug is short acting and used primarily for sleep-onset insomnia [343]. Ramelteon is FDA approved for long-term use [335].

For insomnia related to restless legs, a systematic review showed that dopamine agonists are effective, with cabergoline (Dostinex) and pramipexole (Mirapex) often having a greater efficacy than levodopa (L-Dopa) [345].

Barbiturates are not recommended for insomnia because of the rapid development of tolerance [336]. Two supplements promoted for sleep enhancement—melatonin and valerian—have not been shown to be effective for managing insomnia [336; 346].

Several factors must be considered when treating older patients with insomnia. For example, it has been recommended that benzodiazepines be avoided in older individuals because of side effects such as increased risk for falls, confusion, and "hangover" [343]. However, these side effects must be considered in light of an individual's particular situation and weighed against the benefits [343; 336]. Eszopiclone and ramelteon have been studied in older individuals and have a favorable side-effect profile for that population [343]. Lower doses are often recommended for older individuals [335].

DELIRIUM

Delirium is a disturbance of attention and awareness with reduced ability to direct, focus, sustain, or shift attention, as well as changes in cognition (e.g., disorientation, memory deficit, language impairment) [347]. Patients may seem confused or be restless, agitated, or combative. Delirium is often difficult to recognize because it shares diagnostic features with other symptoms, especially dementia and depression. As a result, delirium is often unrecognized or misdiagnosed and consequently inappropriately treated or not treated [348]. Delirium is classified into three clinical subtypes: hypoactive, hyperactive, and mixed [349]. Hypoactive delirium is characterized by lethargy, reduced awareness of surroundings, sedation, and psychomotor retardation, whereas hyperactive delirium is characterized by agitation, restlessness, hallucinations, hypervigilance, and delusions [349]. In the palliative care setting, about half of patients with delirium will have the hypoactive subtype [349; 350].

Delirium can be extremely distressful for the patient and even more so for family members. The healthcare team can help alleviate family members' distress by educating them about the nature and cause of the syndrome and the potential for reversal. Encouraging them to participate in nonpharmacologic interventions may also help to provide a positive experience.

Prevalence

The prevalence of delirium among adults in hospice or receiving palliative care ranges from 28% to 80%, occurring most frequently among patients with cancer [355; 505]. Terminal delirium is a distinct entity that occurs within the last days or hours of life, and it is estimated to occur in 80% of dying patients [351].

Etiology

Many factors may cause delirium, and although the cause is usually multifactorial, often no cause is found [352]. In one comprehensive review, the primary contributor to delirium was unrelieved pain [353]. Delirium is also often caused by medications, including several that are used in the end-of-life setting, such as opioids, corticosteroids, benzodiazepines, and NSAIDs, or the sudden withdrawal from alcohol or drugs (particularly benzodiazepines) upon admittance to a hospital or hospice [351; 505]. In addition, age, cognitive deficits, impaired vision/hearing, emotional stress, depression, and comorbidities are predisposing factors of delirium [350; 351].

Prevention

Because of the substantial influence of unrelieved pain, adequate pain management can help prevent delirium. Prevention strategies are directed at minimizing precipitating factors, which include a high number of medications (more than six), dehydration, decreased sensory input, psychotropic medications, and a change in environment.

Assessment

The diagnosis of delirium relies on identifying its two features: cognitive impairment and deficits in attention; these features can be assessed with the Mini-Mental State Examination [351]. The Confusion Assessment Method (CAM) is considered to be the gold standard for distinguishing between delirium from other causes of altered mental status, and other tools to evaluate delirium include the Delirium Rating Scale, the Delirium Symptom Interview, and the Memorial Delirium Assessment Scale [351]. Communication with the healthcare team and family is vital in assessing the patient to help determine the onset and course of delirium as well as signs indicative of the syndrome. Some specific ways to help determine if a patient has delirium include [349]:

- Ask the patient "Do you feel 100% awake?" If they do not, ask "How awake do you feel?"
- Evaluate whether the patient is easily distracted.
- Test registration and immediate recall.
- Assess psychomotor disturbances by noting whether the patient is restless and agitated or slow and hypoactive.
- Ask the patient if he or she is seeing or hearing strange things.

NONPHARMACOLOGIC TREATMENT OPTIONS FOR DELIRIUM
Review all medications; discontinue any unnecessary ones and replace those with a high likelihood of delirium as a side effect.
Rotate opioids or lower the opioid dose.
Provide orienting cues (e.g., calendar, clock, familiar objects) in the patient's room.
Encourage family to sit with the patient.
Encourage activities that are cognitively stimulating (e.g., word puzzles).
Ensure good sleep hygiene.
Minimize noise and interventions at bedtime.
Encourage patient to get out of bed as much as possible.
Provide visual and hearing aids, if appropriate.
Monitor for dehydration.
Minimize use of devices/equipment that are immobilizing (e.g., catheter, intravenous lines).
Source: [183; 349; 351; 355] *Table 20*

- Ask the patient to state the days of the week or months backward, or to give a span of numbers frontward and backward.
- Ask the patient open-ended questions, and listen for incoherent speech or tangential thought processes.

Clinical assessment and physical examination should also be directed at ruling out underlying causes, such as infection or metabolic abnormalities, and the medication list should be reviewed carefully [183; 351].

Management

The treatment of an underlying cause, if identified, is a key step in managing delirium. Whether delirium can be reversed depends on the cause. Delirium caused by psychotropic medications, dehydration, or hypercalcemia is more likely to be reversible than delirium caused by hypoxia, metabolic abnormalities, or nonrespiratory infections [349; 354].

Several nonpharmacologic interventions have been successful in preventing and managing delirium (***Table 20***) [183; 349; 351; 355]. If delirium is refractory to nonpharmacologic measures, medications may be prescribed. Level 1 evidence supports the use of haloperidol and chlorpromazine (Thorazine) (typical antipsychotics), and these drugs have the advantage of being available in formulations that allow for multiple routes of administration and of being the most cost-effective [349]. Several systematic reviews have been done to determine the efficacy of antipsychotics for delirium, and although each review has identified only a few well-designed trials, the results have supported the continued use of these drugs (***Table 21***) [183; 349; 351; 356; 357; 358]. One of these reviews focused on patients with terminal illness; the review identified only one small study (30 subjects) eligible for analysis; haloperidol and chlorpromazine were equally effective, but the risk for cognitive impairment was slightly greater with chlorpromazine [356]. In the other reviews, the efficacy of haloperidol was found to be similar to that of olanzapine, risperidone (Risperdal), and quetiapine (Seroquel) (atypical antipsychotics) [357; 358]. In two small nonrandomized studies—one involving hospitalized patients with cancer—aripiprazole (Abilify) was safe and effective for the treatment of delirium, especially the hypoactive subtype [359; 360]. Mild-to-moderate delirium can be managed with low oral doses of antipsychotics, titrating the dose to optimum relief; higher doses can be used for severe delirium [183; 351]. For older patients and those with multiple comorbidities, treatment should begin with lower doses and titration should be slow [349]. Factors to consider when selecting a drug include the side-effect profile, the patient's age and baseline mental status, the time to response, and the subtype of delirium [349]. There is no recommendation regarding the use of other drug classes for delirium in palliative care (e.g., α-2 receptors agonists, cholinesterase inhibitors, melatonergic drugs, psychostimulants) [355].

According to the Institute for Clinical Systems Improvement, if symptoms of delirium and confusion are present and are attributable to opioids, a switch to a different opioid may be advisable.

(https://www.icsi.org/_asset/k056ab/PalliativeCare.pdf. Last accessed October 24, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

 Copyright © 2019 NetCE

PHARMACOLOGIC OPTIONS FOR DELIRIUM IN PALLIATIVE CARE			
Drug	**Dose Range**	**Routes of Administration**	**Comments**
Haloperidol	0.5–2 mg every 2 to 12 hours	PO, IV, IM, SC	Considered to be first-line treatment.
Chlorpromazine	12.5–50 mg every 4 to 6 hours	PO, IV, IM, SC, PR	Has more sedative effect than haloperidol, thus is preferred for patients with agitation.
Olanzapine	2.5–5 mg every 12 to 24 hours	PO	Sedation has been a dose-limiting effect; poorer response has been associated with older age, pre-existing dementia, and hypoactive subtype.
Risperidone	0.25–1 mg every 12 to 24 hours	PO	Response may be better with hypoactive subtype; orthostatic hypotension is possible adverse effect.
Quetiapine	12.5–100 mg every 12 to 24 hours	PO	Sedation and orthostatic hypotension are possible adverse effects.
Aripiprazole	5–30 mg every 24 hours	PO	Response may be better with hypoactive subtype.
Lorazepam	0.5–2 mg every 2 to 4 hours	IV, SC	May be added to treatment with haloperidol if agitation is refractory to high doses.
PO = orally, IV = intravenously, IM = intramuscularly, SC = subcutaneously, PR = rectally.			
Source: [183; 349; 351; 355; 356; 357; 358]			*Table 21*

The goal of treatment is to reach patients' baseline mental state, not to sedate them, and patients should be reassessed frequently until this goal is met [351]. If agitation is refractory to high doses of haloperidol, the antipsychotic lorazepam may be helpful [183; 351]. The management of delirium also includes providing support to family, to help them cope with the condition [183; 351]. The management of terminal delirium will be discussed later in this course.

PSYCHOSOCIAL CARE

What factors have been shown to be bothersome to the greatest proportion of individuals receiving palliative care?

The natural initial reaction to illness that threatens life expectancy is emotional, and patients and their families experience a wide range of emotions, including disbelief, anger, fear, and sadness. Over time, these emotions broaden; patients may feel isolated and lonely, anxious about the burden on their family, or hopeless. Patients expect, or hope, that the healthcare professional in attendance will pay attention, listen carefully, and provide comfort. Beyond personal issues raised for the patient, family members may have guilt about their own well-being, anxiety about the future, and grief about the loss of their loved one. Practical issues such as the cost of care and loss of income from the patient and/or caregiver can add substantially to the feelings of stress.

The prevalence of psychologic suffering is high during the last year of life, and addressing this aspect of care is integral to the patient's overall comfort and quality of life. Anxiety and depression are the most common psychologic symptoms at the end of life, yet they are among the most underdiagnosed and untreated symptoms [66; 361]. Psychologic suffering exacerbates pain and other symptoms, limits the patient's capacity for pleasurable activities, and causes distress for both the patient and the family [202; 362].

The term "distress" has become standard to describe the psychologic suffering experienced by patients with life-limiting disease. The NCCN notes that the word "distress" is more acceptable and is associated with less stigma than words such as "psychosocial" or "emotional" [183]. In its guidelines on distress management, the NCCN defines distress as existing "along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis" [183]. According to a study of patients in a palliative care program, the answers to the question "What bothers you most?" included [212]:

- Emotional, spiritual, existential, or nonspecific distress (16%)
- Relationships (15%)
- Concerns about the dying process and death (15%)
- Loss of function and normalcy (12%)

Patients at increased risk of distress include individuals with a history of psychiatric disorder, substance abuse, or depression/suicide attempt; with cognitive impairment or communication barriers; with severe comorbid conditions; and with spiritual/religious concerns. Other factors that predispose a patient to distress include rapidly progressing disease, unrelieved pain, and uncontrolled symptoms [202]. Women, younger individuals, and individuals with young children are also at increased risk [183]. Gender and sexual minority patients with life-limiting diseases often have distinct sources of suffering [66]. These patients may be disenfranchised from their families or have been subjected to social stigma, leading to fears of abandonment and isolation. In some instances, spiritual crises may be the result of guilt and shame from past behaviors. Many patients with HIV/AIDS have suffered through the loss of loved ones to the same disease, some of whom may have been part of the individual's defined family and network of social support.

As with physical symptoms, assessment of distress and the psychosocial and spiritual well-being of the patient must be ongoing, as changes occur over time [5; 66]. In addition, worsening symptoms and disease progression can affect patients' coping mechanisms [223]. One study found significant correlations between the will to live and existential, psychologic, and social sources of distress. In that study, hopelessness, burden to others, and dignity were the variables with the most influence [363]. Other studies have consistently shown that psychosocial suffering has a stronger association than pain with a desire to hasten death [364; 365; 366; 367; 368; 369].

How a patient responds to his or her disease and care is strongly influenced by attitudes and values learned through family interactions, and social workers should evaluate the patient and family to assess psychosocial as well as practical problems and recommend and/or carry out interventions [5; 183]. For many patients, the primary concern about their illness is its impact on the family. The need for palliative care raises issues regarding power, structure, and roles among the patient and his or her family [66]. The impact of a life-limiting disease and the ensuing care threatens the structure and integrity of the family, as family roles are reassigned, the rules of daily living are altered, and methods of problem-solving are revised. Families vary in their ability to adapt to such restructuring, and dysfunction can result from either limited or excessive adaptation. At one end of this spectrum, family members have difficulty breaking away from coping mechanisms, even though they are ineffective. At the other end of the spectrum, family members continually try new coping strategies to meet each crisis, resulting in chaos [66]. Both types of dysfunction can lead to increased demands on the healthcare team and can interfere with the delivery of appropriate care.

ANXIETY

Anxiety is a feeling of fear, apprehension, and dread. The patient feels uneasy, insecure, and uncertain about the future. Often, the patient is not able to identify the source of anxiety, but it can be related to any number of physical, psychologic, social, spiritual, or practical issues common during the end of life.

Prevalence

Severe anxiety varies widely among adults with life-limiting disease, ranging from 8% to 79%, with the highest rate among patients with cancer [208].

Etiology

One of the primary causes of anxiety is inadequate pain relief. Anxiety may also be the result of a patient's overwhelming concern about his or her illness, the burden of the illness on the family, and the prospect of death. In addition, anxiety is a potential side effect of many medications, including corticosteroids, metoclopramide, theophylline, albuterol, antihypertensives, neuroleptics, psychostimulants, antiparkinsonian medications, and anticholinergics. Lastly, withdrawal from opiates, alcohol, caffeine, cannabis, and sedatives can result in anxiety, particularly in the first few days of admission [506].

Prevention

Effective pain management is the best way to prevent anxiety. Also, educating the patient and the family about what to expect over the course of the illness and providing adequate psychologic and spiritual support can help comfort the patient, thereby preventing anxiety.

Assessment

Family members and friends may be able to provide information about the level of anxiety experienced by the patient currently and in past situations. All members of the healthcare team should evaluate the patient and the clinical record for reversible causes of anxiety, such as those caused by medications or withdrawal syndromes, and should try to distinguish anxiety from delirium, depression, or bipolar disorder [370; 371].

Anxiety manifests itself through physical as well as psychologic and cognitive signs and symptoms. These signs and symptoms include dyspnea, paresthesias, tachycardia, chest pain, urinary frequency, pallor, restlessness, agitation, hyperventilation, insomnia, tremors, excessive worrying, and difficulty concentrating.

Management

Nonpharmacologic approaches are essential for managing anxiety, and the addition of pharmacologic treatment depends on the severity of the anxiety [66; 372]. Effective management of pain and other distressing symptoms, such as constipation, dyspnea, and nausea, will also help to relieve

 Copyright © 2019 NetCE

PHARMACOLOGIC MANAGEMENT OF ANXIETY AND DEPRESSION					
Condition	**Drug Class, Drugs**	**Typical Starting Oral Dose[a]**	**Titration Recommended**	**Maximum Daily Dose**	**Comments**
Anxiety	**Benzodiazepines**				
	Lorazepam	0.5–2 mg, every 1 to 6 hours	May titrate upward	—	First choice
	Diazepam	2.5–10 mg, every 3 to 6 hours	May titrate upward	—	
	Midazolam	2–10 mg/day (SC)	May titrate upward	—	
	Clonazepam	0.5–1.0 mg, 3 times per day	May titrate upward 4 mg	—	
	Neuroleptics				
	Haloperidol	0.5–4.0 mg, every 4 to 6 hours	May titrate upward	—	—
	Thioridazine	10 mg, 3 times per day	May titrate upward	—	—
	Tricyclic Antidepressant				
	Imipramine	10–25 mg, 3 times per day	May titrate upward	—	—
Depression	**Selective Serotonin Reuptake Inhibitors**				
	Fluoxetine	20 mg/day	Increase by 10 mg every 1 to 2 weeks	20–60 mg	First choice when immediate onset not needed (onset at 4 to 6 weeks)
	Paroxetine	10 mg/day	Increase by 10 mg every 1 week	10–50 mg	
	Sertraline	50 mg/day	Increase by 25 mg every 1 week	50–150 mg	
	Escitalopram	10 mg/day	—	20 mg	
	Venlafaxine	18.75 mg/day	Increase by 75 mg every 1 week	75–225 mg	
	Tricyclic Antidepressants				
	Amitriptyline	25 mg/day	Increase by 25 mg every 1 to 2 days	50–150 mg	Less useful because of side effects; slow onset of action (3 to 6 weeks)
	Nortriptyline	25 mg/day		50–150 mg	
	Desipramine	25 mg/day		50–150 mg	
	Doxepin	25 mg/day		50–200 mg	
[a]Doses are given as guidelines; actual doses should be determined on an individual basis.					
Source: [66; 202; 223; 374]					*Table 22*

anxiety. If the anxiety is thought to be caused by medications, they should be replaced by alternate drugs. Other strategies include psychologic support that allows the patient to explore fears and concerns and to discuss practical issues with appropriate healthcare team members. Relaxation and guided imagery may also be of benefit [373]. A consult for psychologic therapy may be needed for patients with severe anxiety.

When pharmacologic management is deemed necessary, benzodiazepines are generally preferred, and administration on an as-needed basis is usually sufficient [66]. Neuroleptics and tricyclic antidepressants may also be effective (***Table 22***). For all medications, the initial dose should be low and subsequently titrated to produce the desired effect within the level of tolerance. Benzodiazepines should be given with caution in older patients, as these drugs may harm memory or cause confusion and agitation in patients who have cognitive impairment [375].

DEPRESSION

Depression is linked to many other symptoms, especially pain, and is a primary source of suffering. Depression in patients with life-limiting disease is a challenge to identify, as feelings of sadness, helplessness, and hopelessness are a typical reaction to the situation [202; 373]. Depression is more likely when sadness and/or hopelessness is overwhelming or pervasive and is accompanied by a sense of despair [373; 376]. Early diagnosis is essential for effective treatment and relief of other symptoms.

Prevalence

The prevalence of depression varies widely among adults with life-limiting diseases, ranging from 3% to 82%, with the highest rate among patients with HIV/AIDS and end-stage liver disease [197; 208].

Etiology

What are psychosocial causes of depression at the end of life?

Unrelieved pain is one of the primary risk factors for depression. Other causes within the physical domain include metabolic disorders (hyponatremia or hypercalcemia), lesions in the brain, insomnia, or side effects of medications (corticosteroids or opioids). Many patients with heart failure have comorbidities and polypharmacy, both of which can increase the risk of depression [377; 378]. Psychosocial causes include despair about progressive physical impairment and loss of independence, financial stress, family concerns, lack of social support, and spiritual distress.

Prevention

Adequate management of pain, attention to psychosocial and spiritual well-being, and early referral for mental health or pastoral counseling are the best strategies to prevent depression.

Assessment

The diagnosis of depression is complicated, as the usual somatic signs of depression—anorexia, sleep disturbances, weight loss, and fatigue—are often symptoms related to the underlying disease or part of the constellation of symptoms experienced by patients with life-limiting disease [223]. Because of this, assessment should focus on psychologic and cognitive symptoms, such as:

- Persistent dysphoria
- Loss of pleasure in activities
- Frequent crying
- Loss of self-esteem
- Sense of worthlessness
- Excessive guilt
- Pervasive despair
- Thoughts of suicide

A diagnosis of depression requires the presence of at least five depression-related symptoms within the same two-week period, and the symptoms must represent a change from a previous level of functioning [347]. A simple screening tool that has been found to be effective is to ask the patient, "Are you depressed?" or, "Do you feel depressed most of the time?" [223; 379; 380]. The physician should also discuss the patient's mood and behavior with other members of the healthcare team and family to help determine a diagnosis. Patients who have thoughts of suicide must be assessed carefully. The physician should differentiate between depression and a desire to hasten death because of uncontrolled symptoms [66]. Psychologic counseling should be sought, as well as measures to enhance the management of symptoms.

It is important to differentiate grief from depression. Grieving can be an appropriate response to loss, but if the symptoms persist, the Institute for Clinical Systems Improvement recommends that depression be considered.

(https://www.icsi.org/_asset/k056ab/PalliativeCare.pdf. Last accessed October 24, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Management

The effective management of depression requires a multimodal approach, incorporating supportive psychotherapy, cognitive strategies, behavioral techniques, and antidepressant medications [46]. Patients with depression should be referred to mental health services for evaluation, and resultant approaches may include formal therapy sessions with psychiatrists or psychologists or counseling from social workers or pastoral advisors. In addition, physicians can help by having discussions with the patient to enhance his or her understanding of the disease, treatments, and outcomes, and to explore expectations, fears, and goals. Behavioral interventions, such as relaxation techniques, distraction therapy, and pleasant imagery have been effective for patients with mild-to-moderate depression [46].

Strong evidence supports the use of tricyclic antidepressants or SSRIs, along with psychosocial interventions, for the management of depression in patients with cancer [46; 209]. Evidence to support the use of specific pharmacologic agents to treat depression in patients with noncancer diagnoses is not as strong, but psychostimulants may also be helpful [46; 66; 223; 381]. The choice of medication depends on the time

 Copyright © 2019 NetCE

SPIRITUAL AND EXISTENTIAL CONCERNS OF PATIENTS AT THE END OF LIFE	
Relation of Concern	**Concerns**
Past	Value and meaning of the person's life Worth of relationships Value of previous achievements Painful memories or shame Guilt about failures, unfulfilled aspirations
Present	Disruption of personal integrity Physical, psychologic, and social changes Increased dependency Meaning of the person's life Meaning of suffering
Future	Impending separation Hopelessness Meaninglessness Death
Religion	Strength of faith A life lived without disgrace to the faith Existence of afterlife
Source: [202]	*Table 23*

available for treatment. The most immediate effect (within days) is achieved with a rapid-acting psychostimulant (e.g., dextroamphetamine, methylphenidate); longer times to therapeutic effect are associated with SSRIs (two to four weeks) and tricyclic antidepressants (three to six weeks).

SPIRITUAL NEEDS

Spirituality is unique to each person. It is founded in cultural, religious, and family traditions and is modified by life experiences. Spirituality is considered to be separate from religious faith, and many surveys have shown that spirituality or religion is an integral component of people's lives [66; 382]. Spirituality also plays a significant role in health and illness. Studies have shown spirituality to be the greatest factor in protecting against end-of-life distress and to have a positive effect on a patient's sense of meaning [376; 383]. Thus, a spiritual assessment and spiritual care to address individual needs are essential components of the multidimensional evaluation of the patient and family [202; 384].

A life-limiting disease will lead patients to ask questions that may give way to spiritual conflicts, such as "Why would God let me suffer this way?" Patients may also carry out life review in search of meaning for their illness; some may view their illness as punishment for past "sins." Left unanswered, spiritual questions and concerns lead to spiritual distress and suffering, which can cause or exacerbate pain and other physical and psychosocial symptoms. It then becomes critical for the healthcare team to facilitate pastoral services to address patients' spiritual concerns [5]. In general, the spiritual and existential concerns of patients at the end of life relate to four areas: the past, the present, the future, and religion (***Table 23***) [202].

The need for spirituality at the end of life is heightened, and patients will search for meaning as a way to cope with emotional and existential suffering [385]. Spirituality helps patients cope with dying through hope. At the time of diagnosis, patients hope for cure, but over time, the object of hope changes and the patient may hope for enough time to achieve important goals, personal growth, reconciliation with loved ones, and a peaceful death [13; 66].

In a landmark nursing care study conducted through a structured interview, researchers explored the meaning of hope and identified strategies used to foster hope among 30 adults facing terminal illness [507]. Hope was defined as an inner power directed toward enrichment of "being." Seven defining characteristics or strategies for fostering/maintaining hope were identified [507]:

- Interpersonal connectedness: The presence of a meaningful shared relationship(s) with another person(s)
- Lightheartedness: Verbal and nonverbal communication characterized by delight, joy, or playfulness
- Personal attributes: Determination, courage, serenity
- Attainable aims: Directing efforts at some purposeful and attainable goal, such as writing notes/letters to distant family members or friends (from the past)

- Spiritual base: The presence of active spiritual beliefs and practices
- Uplifting memories: Recalling positive moments and uplifting times in the past
- Affirmation of worth: Having one's individuality accepted, honored, and acknowledged

Spirituality can also help a patient gain a sense of control, acceptance, and strength. As a result, greater spiritual well-being has been associated with decreased rates of anxiety and depression among people with advanced disease [204; 386]. There has been a growing emphasis on the need for physicians to discuss spirituality with their patients [384; 387]. A spiritual history should be obtained to elicit answers to such questions as:

- Do you consider yourself spiritual or religious?
- Do you have spiritual beliefs that help you cope with stress?
- What importance does your faith or belief have in your life?
- Are you part of a spiritual or religious community?

One recommended mnemonic for the components of a spiritual history is SPIRIT: spiritual belief system; personal spirituality; integration with a spiritual community; ritualized practices and restrictions; implications for medical care; and terminal events planning [388].

Although spiritual care is an essential component of palliative care, what patients and families perceive to be spiritual care and how it should be delivered have not been well-defined [382]. Patients and families have found spiritual comfort with friends and family, clergy and other pastoral care providers, and healthcare professionals [382]. Among healthcare professionals, barriers to providing spiritual care are time; social, religious, or cultural discordance; and lack of privacy and care continuity [382].

FAMILY-CENTERED PSYCHOSOCIAL NEEDS

Adequate psychosocial support is also needed for the patient's family. The structure of families varies widely, and it is important to note that what constitutes a family is defined by the patient. It is essential for the healthcare team to talk to patients during the initial assessment about who provides support, with whom they wish to share information, and who should be involved in planning care and decision making [5; 66]. For some patients, friends provide the support network when families are not near or the patient is disenfranchised from his or her family. Social workers have a prominent role in helping these patients overcome such barriers as discrimination and legal and financial issues, as well as ensuring appropriate support for grieving partners who may be disenfranchised [389].

Family caregivers can become overwhelmed with added responsibilities. Often, the caregiver is a spouse who is older and may also have illnesses. In addition, children and teenagers are frequently forgotten, but addressing their concerns and needs is essential for their psychologic well-being and appropriate grieving [66]. Young children will realize that the family structure has been disrupted. They should be encouraged to ask questions, and they usually need time to interpret answers. Adolescence is a challenging time in itself, and dealing with the illness and loss of a parent or close family member may result in aggressive behavior, isolation, or sexuality. Frequent evaluation of family members' coping strategies, moods, and behaviors can help to determine if early referral for individual counseling or family therapy is necessary. Support should be provided to ensure that the patient and family has access to resources to help with finances, that the home environment is safe, that caregivers are available, and that adequate transportation is available [183].

Family roles are also important to understand, and these roles are strongly influenced by culture. Many cultures highly value family, with strong family ties across many generations. Patients from such cultures will often have many visitors at one time. The palliative care team should accommodate such visits when possible. In addition, family hierarchy may dictate behavior of family caregivers. For example, in traditional Vietnamese families, a female member of the family is expected to stay at the bedside of the patient for comfort and support [390]. In Asian families, elders are revered and a young person cannot tell an older person what to do [391]. This may make it difficult for a healthcare professional who is younger than the patient. Patients and families who adhere to Native American cultures have unique traditions and rituals that should be respected [392].

All members of the healthcare team should become familiar with the cultural context of their patients and provide resources from within the cultural community if possible. A bilingual healthcare worker can provide an important link to a community [393].

IMMINENT DEATH AND LOSS

In the last days, the goals of the healthcare team are to ensure a peaceful death for the patient and to support the family during the dying process and throughout grief and mourning. The focus for the patient is management of symptoms and emotional and spiritual ease, and the focus for the family is education to prepare them for the dying process.

 Copyright © 2019 NetCE

INTERVENTIONS FOR PATIENTS WHO ARE IMMINENTLY DYING
Intensify ongoing care.
Try to ensure privacy (if not at home, arrange for private room if possible).
Discontinue diagnostic tests.
Reposition for comfort as appropriate.
Avoid unnecessary needle sticks.
Provide mouth care (e.g., hydrogen peroxide/water solution).
Treat for urinary retention and fecal impaction.
Ensure access to medication even when oral route is not available.
Prepare to meet request for organ donation and autopsy.
Allow patient and family uninterrupted time together.
Ensure the patient and family understand the signs and symptoms of imminent death and are supported through the dying process.
Offer anticipatory bereavement support.
Provide support to children and grandchildren.
Encourage visits by children if consistent with family values.
Support culturally meaningful rituals.
Facilitate around-the-clock family presence.
Ensure that caregivers understand and will honor advance directives.
Provide respectful space for families.
Facilitate closure.
Source: [183] *Table 24*

THE PATIENT'S NEEDS

Which measures are appropriate for managing the so-called "death rattle?"

During the last days, all care should be directed at comfort, and the NCCN has listed several interventions for imminently dying patients (***Table 24***) [183]. The physician should minimize the number of medications by reassessing the need for each one. The symptoms that occur most commonly during the last days are pain, noisy breathing, dyspnea, and delirium, and medications to manage these symptoms should be maintained or initiated [66]. In addition, medication may be required to reduce the risk of seizures. Medications should be prescribed for the least invasive route of administration (oral or buccal mucosa), but patients may lose the ability to swallow, making a subcutaneous, transdermal, or intravenous route necessary.

Treatment of pain should continue, and knowledge of opioid pharmacology becomes critical during the last hours of life [66; 394]. The metabolites of morphine and some other opioids remain active until they are cleared through the kidneys. If urine output stops, alternative opioids, such as fentanyl or methadone, should be considered, as they have inactive metabolites [211; 395].

Anticholinergic medications can eliminate the so-called "death rattle" brought on by the build-up of secretions when the gag reflex is lost or swallowing is difficult. Specific drugs recommended include scopolamine, glycopyrrolate, hyoscyamine, and atropine (***Table 25***) [66; 183; 394; 396]. For patients with advanced kidney disease, the dose of glycopyrrolate should be reduced 50% (because evidence indicates that the drug accumulates in renal impairment) and hyoscine butylbromide should not be used (because of a risk of excessive drowsiness or paradoxical agitation) [211]. Some evidence suggests that treatment is more effective when given earlier; however, if the patient is alert, the dryness of the mouth and throat caused by these medications can be distressful. Repositioning the patient to one side or the other or in the semiprone position may reduce the sound. Oropharyngeal suctioning is not only often ineffective but also may disturb the patient or cause further distress for the family. Therefore, it is not recommended.

TREATMENT OF EXCESSIVE RESPIRATORY SECRETIONS CAUSING "DEATH RATTLE"	
Drug	**Dose**
Scopolamine (transdermal patch)	One (1.5-mg) patch applied behind the ear and changed every 72 hours Onset of action may be delayed several hours, so other anticholinergic treatment should be provided until effective.
Glycopyrrolate	0.2–0.4 mg SC, repeat at 30 minutes, then every 4 to 6 hours, as needed; or 0.6–1.2 mg/day CSCI
Hyoscyamine	0.4 mg SC, repeat at 30 minutes, then every 2 to 4 hours, as needed; or 0.6–1.2 mg/day CSCI
Atropine	0.4–0.8 mg SC, repeat every 2 to 4 hours
CSCI = continuous subcutaneous infusion, SC = subcutaneously.	
Source: [202]	*Table 25*

Terminal delirium should be treated aggressively at its first signs (restlessness, moaning, increasing confusion, and drowsiness). Haloperidol is frequently the first choice for its relatively quick action [202; 394]. Other drugs may include olanzapine, chlorpromazine, levomepromazine, and benzodiazepines [202; 394]. For terminal delirium associated with agitation, benzodiazepines, including clonazepam, midazolam, diazepam, and lorazepam may be helpful [202; 223; 394]. Depending on which drug is used, administration may intravenous, subcutaneous, or rectal, and the dose can be titrated until effective.

Seizures at the end of life may be managed with high doses of benzodiazepines. Other antiepileptics such as phenytoin (administered intravenously), fosphenytoin (administered subcutaneously), or phenobarbital (60–120 mg rectally, intravenously, or intramuscularly every 10 to 20 minutes as needed) may become necessary until control is established.

A calm and peaceful environment should be maintained for the patient. Family and spiritual leaders should be allowed to carry out traditional rites and rituals associated with death.

Palliative Sedation

Palliative sedation may be considered when an imminently dying patient is experiencing suffering (physical, psychologic, and/or spiritual) that is refractory to the best palliative care efforts. Terminal restlessness and dyspnea have been the most common indications for palliative sedation, and thiopental and midazolam are the typical sedatives used [183; 397; 398]. For patients who have advanced kidney disease, midazolam is recommended, but the dose should be reduced because more unbound drug becomes available [211]. Before beginning palliative sedation, the clinician should consult with a psychiatrist and pastoral services (if appropriate) and talk to the patient, family members, and other members of the healthcare team about the medical, emotional, and ethical issues surrounding the decision [66; 183; 223; 399; 400]. Formal informed consent should be obtained from the patient or from the healthcare proxy.

Physician-Assisted Suicide

Physician-assisted suicide, or hastened death, is defined as active euthanasia (direct administration of a lethal agent with a merciful intent) or assisted suicide (aiding a patient in ending his or her life at the request of the patient) [66]. The following are not considered to be physician-assisted suicide: carrying out a patient's wishes to refuse treatment, withdrawal of treatment, and the use of high-dose opioids with the intent to relieve pain. The American Medical Association Code of Ethics explicitly states, "Physician-assisted suicide is fundamentally incompatible with the physician's role as healer, would be difficult or impossible to control, and would pose serious societal risks" [401]. Position statements against the use of physician-assisted suicide have been issued by many other professional organizations, including the NHPCO and the NCCN [183; 402; 403]. The AAHPM states that their position is one of "studied neutrality." The basis for these declarations is that appropriate hospice care is an effective choice for providing comfort to dying patients.

In 2010, in a first-of-its-kind comprehensive consensus statement, the Heart Rhythm Society in collaboration with the major cardiology, geriatrics, and palliative care societies, emphasized that deactivation of implantable cardioverter-defibrillators is neither euthanasia nor physician-assisted suicide [404]. The organizations urged clinicians to respect the right of patients to request deactivation.

 Copyright © 2019 NetCE

The NCCN guidelines recommend that physicians explore requests for assisted suicide and explain to the patient the distinctions among assisted suicide, treatment withdrawal, and aggressive symptom management [183]. Some states have enacted assisted suicide statutes. State laws vary, and knowledge of your local statutes is necessary.

THE FAMILY'S NEEDS

Ongoing communication with family members is essential to ensure their well-being as their loved one dies. The healthcare team should discuss what will happen over the course of dying so the family can be better prepared for symptoms such as altered breathing patterns and sounds, terminal delirium, and unconsciousness [5; 183; 394]. The family should be reassured that what they may think the patient is experiencing is not the patient's actual reality.

The altered breathing patterns that are present as death is imminent are distressful for family members, as they believe that the patient is experiencing a sense of suffocation. Also distressful to family is the sound of the death rattle. The healthcare team should assure family that these signs do not indicate that the patient is suffering and explain that additional therapy will not be of benefit.

Families often misinterpret the early signs of terminal delirium as signs of uncontrollable pain. However, if pain has been adequately managed throughout the delivery of palliative care, such pain will not begin during the last hours. As the patient slips in and out of consciousness, family members may become increasingly distressed about not being able to communicate anymore with their loved one. Although it is unknown what a dying patient can hear, other experiences in medicine suggest that awareness may be greater than the ability to respond. Family members should be encouraged to continue talking with their loved one to help them attain a sense of closure.

Despite the best efforts to prepare the family, reactions are unpredictable when death occurs. The clinician should take time to answer questions from family members, including children, and perhaps provide information on the physiologic events associated with death [66]. For family members who were not present during the death, the clinician should describe the event, while reassuring them that the patient died peacefully.

Many experts believe that people can handle grief better if they spend time with a loved one immediately after death. Family members should be allowed to touch, hold, and kiss their loved one as they feel comfortable. The healthcare team should respect the needs of the family to conduct personal, cultural, or religious traditions, rites, and rituals.

GRIEF, MOURNING, AND BEREAVEMENT

Palliative care extends beyond the patient's death, with the focus shifting to support of the family during bereavement and mourning. Although the terms "grief," "mourning," and "bereavement" are often used interchangeably, their definitions are different. Grief is a normal reaction to a loss; mourning is the process by which individuals adjust to the loss; and bereavement is the period of time during which grief and mourning occur [66; 405]. Psychosocial support of the family is essential throughout the duration of palliative care and can help to decrease the risks of morbidity, substance abuse, and mortality that have been found among spouses and other loved ones of patients who have died [5].

Grief

When should grief counseling be initiated?

Grief comprises a range of feelings, thoughts, and behaviors that fall in the realm of the physical, emotional, and social domains [66]. Individuals may have trouble sleeping, changes in appetite, or other physical symptoms or illness. Emotions can include sadness, anxiety, guilt, and anger. Return to work, activities with friends, and taking care of family can be beneficial.

Grief counseling for the family and patient should begin when the patient is alive, with a focus on life meaning and the contributions from the patient's family. An understanding of the mediators of the grief response can help physicians and other members of the healthcare team recognize the family members who may be at increased risk for adapting poorly to the loss [406]. These mediators are:

- Nature of attachment (how close and/or dependent the individual was with regard to the patient)
- Mode of death (the suddenness of the death)
- Historical antecedents (how the individual has handled loss in the past)
- Personality variables (factors related to age, gender, ability to express feelings)
- Social factors (availability of social support, involvement in ethnic and religious groups)
- Changes and concurrent stressors (number of other stressors in the individual's life, coping styles)

Clinical assessment should be carried out for individuals at risk of complicated grief. Distinguishing between grief and depression can be challenging, as many signs and symptoms are similar. However, the hallmarks of depression are constant and unremitting feelings of worthlessness, hopelessness, helplessness, anhedonia, and suicidal ideation [202].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The British Columbia Medical Services Commission asserts that the relationship between the physician and the patient is one of the most potent therapeutic tools for assisting patients who are dealing with grief. Reassurance about the normal pattern of grief and a commitment to supporting the patient in an ongoing way is the mainstay of care. It may involve scheduled follow-up visits as necessary.

(https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/palliative3.pdf. Last accessed October 24, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Mourning

Satisfactory adaptation to loss depends on "tasks" of mourning [406]. Previous research referred to "stages" of mourning, but the term "task" is now used because the stages were not clear-cut and were not always followed in the same order. The tasks include:

- Accepting the reality of the loss
- Experiencing the pain of the loss
- Adjusting to the environment in which the deceased is missing (external, internal, and spiritual adjustments)
- Finding a way to remember the deceased while moving forward with life

After the patient's death, members of the palliative care team should encourage the family to talk about the patient, as this promotes acceptance of the death. Explaining that a wide range of emotions is normal during the mourning process can help family members understand that experiencing these emotions is a necessary aspect of grieving. Frequent contact with family members after the loved one's death can ensure that the family is adjusting to the loss. Referrals for psychosocial and spiritual interventions should be made as early as possible to optimize their efficacy.

Bereavement

Bereavement support should begin immediately with a handwritten condolence note from the clinician. Such notes have been found to provide comfort to the family [407; 408]. The physician should emphasize the personal strengths of the family that will help them cope with the loss and should offer help with specific issues. Attendance at the patient's funeral, if possible, is also appropriate.

How bereavement services are provided through a hospice/palliative care program vary. Programs usually involve contacting the family at regular intervals to provide resources on grieving, coping strategies, professional services, and support groups [183; 223]. When notes are sent, family members should be invited to contact the physician or other members of the healthcare team with questions. Notes are especially beneficial at the time of the first holidays without the patient, significant days for the family (patient's birthday, spouse's birthday), and the anniversary of the patient's death. Bereavement services should extend for at least one year after the patient's death, but a longer period may be necessary [5; 223].

PALLIATIVE CARE FOR SPECIFIC POPULATIONS

The needs of some patient populations present unique challenges to the delivery of high-quality palliative care. Among these populations are older patients, including those with dementia and/or debility; children and adolescents; and patients in the critical care setting.

OLDER PATIENTS AND NURSING FACILITY RESIDENTS

The issue of perhaps greatest importance regarding palliative care for older individuals is improving care for which patients?

At present, the number of residents of nursing facilities in the United States is approaching 2 million, and that number is expected to double by 2030 [1]. Older persons comprise the largest percentage of patients who receive palliative care through hospice. In 2017, patients 75 years and older represented 77% of the individuals who received such care [1]. The majority of older individuals receive hospice care at home, but up to 25% are residents at a nursing home or residential facility at the time of death [1; 410]. A study of Medicare beneficiaries dying in nursing homes showed that between 1999 and 2006, the number of hospices providing care increased from 1,850 to 2,768, and rates of nursing home hospice use more than doubled (from 14% to 33%) [508].

The care of the frail elderly in the home is burdensome, as the long disease trajectory often requires an extended need for family caregivers. In addition, the primary caregiver may be a spouse who is older than 75 years of age and may have multiple health issues. For patients in nursing facilities, care may be fragmented and staff often lack an appropriate understanding of pharmacology, drug addiction and dependence, management of side effects, and effective nonpharmacologic therapies [411; 412; 413]. Also, family members often have grief symptoms before the death of the patient; the most frequent grief symptom is yearning (separation distress) [414]. Thus, early psychosocial support and bereavement services for family are important.

 Copyright © 2019 NetCE

Older patients, especially those with end-stage organ disease, often have substantial comorbidities and take multiple medications, both of which add to the complexity of care [101; 377; 415]. One study of patients with heart failure found that approximately 33% had COPD, 40% had diabetes, and more than 50% had coronary heart disease or hypertension [416]. With respect to multiple medications, a study found that older patients took an average of 6.5 medications and that 29% of the patients were taking a medication that was considered to be "never appropriate" [417]. Polypharmacy increases the likelihood of drug interactions, and clinicians should review the medication list and eliminate those drugs that are not providing clear benefit [415]. Knowledge of pharmacokinetics, pharmacodynamics, and pathophysiology are needed in making decisions to stop or adjust drugs [418]. Consulting with a pharmacist can be valuable.

As with the overall population of patients at the end of life, pain management is also inadequate for older patients, with pain experienced by more than 50% of patients at home and as many as 80% of patients in nursing facilities [419; 420; 421]. Studies have confirmed that older patients receive less pain medication at the end of life than younger patients and that pain management is inadequate for residents of nursing facilities [422; 423; 424; 425]. The American Geriatrics Society has issued guidelines for the management of chronic pain for older patients, and physicians and nursing facility staff should become familiar with this resource and other guidelines for pain [421]. Improvement is also needed in the treatment of patients who have psychosocial symptoms, such as depression, agitation, anxiety, and loneliness [426].

Perhaps the greatest issue is the need for better palliative care for patients with dementia [100; 411; 427]. The prevalence of dementia has been reported to be 40% to 50% among persons older than 80 years of age, and the majority of persons with dementia spend the last weeks to months of life in a nursing home [409]. Underlying dementia makes it difficult to identify symptoms, especially pain and psychosocial disorders. As a result, suffering is prevalent among patients with dementia. In fact, one study showed that 93% of patients with dementia died with an intermediate or high level of suffering [428]. The assessment of pain can be particularly challenging when the patient is unable to communicate. This situation calls for a multipronged approach consisting of observation, discussion with family and caregivers, and evaluation of the response to pain medication or nonpharmacologic measures. Recommendations for assessing pain in nonverbal patients have been developed by the American Society for Pain Management Nursing [429].

As dementia progresses, behavioral disturbances become more frequent, and symptoms include hallucinations, sleep disorders, agitation, paranoia, delusions, anxiety, and combativeness. Care should be taken to differentiate these symptoms from those associated with the underlying disease or as an adverse effect of drugs. In addition, dementia can affect the prognosis of other chronic diseases, and health events or complications such as hip fracture, pneumonia, febrile episodes, or eating problems can substantially reduce the life span for patients with advanced dementia [170; 422].

The understanding of advanced dementia is limited, and as noted, the uncertainty of the disease course makes it difficult for advance care planning and referral to hospice care [170; 411; 430; 431; 432]. The progressive nature of dementia adds importance to the need for advance directives, and involvement of the family in decision making is crucial [170; 433]. Educational resources about palliative care and hospice can help family and patients better understand the language needed in advance directives and the benefit of hospice services [410; 433].

In an effort to enhance the quality of care at the end of life for older patients, the CAPC published the report Improving Palliative Care in Nursing Homes [21]. Based on their research, the authors of this report identified four different models for integrating preferred practices for palliative and hospice care for patients in nursing homes [21; 434]:

- Palliative Care Consult Service: Palliative care services are provided by healthcare professionals as requested by the nursing home Medical Director or Director of Nursing or the patient's attending physician.
- Hospice-Based Palliative Care Consult Service: Palliative care services are provided by healthcare professionals employed at a local hospice as requested by the nursing home Medical Director or Director of Nursing or the patient's attending physician.
- Nursing Home Services Integrated Palliative Care: Palliative care services are provided by staff employed directly by a nursing home that incorporates one or more of the NQF's domains of care.
- Hospice Care: Specialized end-of-life palliative care services are provided by contracted hospice providers to hospice-eligible residents.

CHILDREN/ADOLESCENTS

Although the majority of physicians involved in the care of children/adolescents with life-limiting diseases are likely to make referrals for palliative or hospice care, the rate of hospice use among eligible children/adolescents is lower than that among adults, estimated at less than 10% in the United States [435; 436; 437]. The cause of most deaths among children is cancer, and it has been proposed that referral to hospice at the time of disease relapse would enhance the quality of care for children and their families; yet, only 2.5% of referrals are made at that time [438; 439]. Instead, most hospice referrals are made at the time of disease progression (44%), at the end of therapeutic options (26%), or at the time of imminent death (20%) [438]. Similarly, most palliative care referrals are made late, with 30% to 44% of pediatricians preferring a palliative care consultation when curative therapy is no longer the goal [439].

BARRIERS TO EFFECTIVE PALLIATIVE CARE FOR CHILDREN
Rarity of death among children
Uncertain prognosis
Unrealistic expectations or denial of parents
Association of palliative care with "giving up" or hopelessness
Immeasurable parental distress at loss of child
Lack of pediatricians' knowledge about distinction between palliative care and hospice
Provider sense of failure when a child dies
Lack of symptom assessment tools
Lack of knowledge regarding pediatric dosing of symptom-relief medications
Fragmentation of medical and psychosocial/spiritual services for children
Lack of adequately trained pediatric hospice professionals
Inadequate education for providers and families about palliative care
Lack of adequate reimbursement
Source: [14; 87; 438; 439] — *Table 26*

One factor contributing to inadequate palliative/hospice care referral may be availability of appropriate services. A survey of institutions participating in Children's Oncology Group clinical trials found that a palliative care team was available in 58% of institutions and hospice care in 60% [440]. Furthermore, even when available, most services were not well used by patients [440]. In addition, many healthcare professionals are inexperienced with pediatric palliative care, and the availability of sufficiently trained pediatric hospice professionals is limited [87; 435; 438].

Research has identified several additional barriers to palliative care at the end of life for children/adolescents, many of which differ from those in the adult setting (***Table 26***) [14; 87; 438; 439]. The sense of failure or of "giving up" may be heightened among both pediatric healthcare professionals and family members because the potential death of a child goes against the natural order. Compared with pediatric oncology professionals, parents are more likely to favor the use of aggressive treatment near the end of the child's life and consider hope a more important factor in treatment decision making [441]. As with adults, integrating palliative care early in the disease continuum can help overcome conflicts in treatment goals related to uncertainty of the prognosis [87]. Although aggressive treatment should be discontinued when it is of no benefit, the Patient Protection and Affordable Care Act of 2010 now allows for disease-directed treatment to be given concurrently with hospice [442]. (A life expectancy of six months is still a criterion for eligibility.) Clinicians usually recognize the lack of a realistic chance for cure before parents do and should talk openly with parents about discontinuing aggressive treatment and directing attention to enhancing the quality of life that remains for the child [443]. Members of the palliative care team should discuss treatment goals with the family, outline choices for interventions as the end of life draws near, and establish limits of care as the health status changes [435; 444; 445].

The American Association of Neuroscience Nurses recommends that nurses evaluate parents' overall concerns related to their child's end-of-life trajectory and address those concerns when planning care. Parents should be educated about symptoms that may be observed during their child's end of life, especially signs of possible impending death.

(https://bibliosjd.files.wordpress.com/2015/02/aann13_pbt_e.pdf. Last accessed October 24, 2018.)

Level of Evidence: Level 3 (Recommendations are supported by qualitative study, case study or series, expert committee reports, and/or expert opinion)

The involvement of the young patient in discussions about diagnosis, prognosis, and treatment goals is another important issue in the pediatric population. Members of the healthcare team should collaborate with parents to determine how much information should be shared with the child and how involved the child should be with decision making; these determinations should be based on the child's intellectual and emotional maturity [14; 446]. Many parents wish to protect their child by withholding information, but studies have shown that children often recognize the seriousness of their illness and prefer open communication about their disease and prognosis [447; 448]. Such open exchange of information can help to avoid the fear of the unknown and

 Copyright © 2019 NetCE

PREVALENCE OF SYMPTOMS AMONG CHILDREN IN THE LAST MONTH OF LIFE	
Symptom	**Range in Prevalence**
Pain	73% to 92%
Fatigue/weakness	86% to 91%
Anorexia	68% to 81%
Reduced mobility	61% to 76%
Nausea/vomiting	57% to 63%
Constipation	55% to 59%
Anxiety/depression	45% to 48%
Dyspnea	41% to 81%
Source: [443; 452; 453]	*Table 27*

preserve the child's trust in his or her parents and/or family and caregivers [448]. Thus, as much as possible and appropriate, the child should be allowed to participate in discussions about the direction of care [446].

When parents and clinicians involve the child in discussions, the language used should be developmentally appropriate for the child and the clinician should check often to make sure the child understands. Having the child repeat the information in his or her own words is one way to assess comprehension. When the child demonstrates an understanding of the illness and the prognosis, the emphasis should be on his or her preferences for care, and the child's preferences should be given equal weight in the decision making [434; 449; 450]. The physician should be an advocate for the child's preferences and decision [451].

Symptom management is a key issue in the pediatric setting. One study indicated that 89% of dying children suffered "a lot" or "a great deal" from at least one symptom in their last month of life, and other end-of-life symptoms have often been intractable [443; 452]. These problems are compounded by the fact that many clinicians who provide components of pediatric palliative care do not have confidence in their ability to manage end-of-life symptoms [437]. Inadequate training and the paucity of data on symptoms in children/adolescents contribute to this lack of confidence. Few studies have been done to determine the prevalence of symptoms in children/adolescents with life-limiting diseases, the studies that do exist are in the cancer setting, and evidence-based recommendations for interventions are not available.

According to reports of parents, the most common symptoms during the last month of life are similar to those among adults; fatigue (weakness) and pain have been the most frequently reported (***Table 27***) [443; 452; 453]. When evaluating fatigue in children, age is a consideration in how fatigue is discussed. Children think about fatigue as a physical sensation, and adolescents think about fatigue as either physical and/or mental tiredness [454]. Parents or other caregivers tend to report fatigue in terms of how it interferes with the child's activities [454].

As with adults, the patient's self-report of pain is the most reliable indicator [66; 455], which makes assessment particularly challenging in young children. Pain assessment must be appropriate for each child's age, developmental level, and cultural context, and assessment tools have been developed for four age groups, from infants to 18 years of age, and for nonverbal or cognitively impaired children [456; 457; 458]. These tools include lists of behaviors for the parents or caregivers to rate, as well as areas for parents to provide their own rating of the child's pain and to note what has previously helped to alleviate pain (***Table 28***). The tools for children who are 5 years of age and older include age-appropriate items such as drawings of a child's body on which the child is asked to mark with a crayon or pencil the area that hurts and different sized circles to indicate pain intensity. The tools are available on the Promoting Excellence in End-of-Life Care website (http://www.promotingexcellence.org/tools/index.html). The Wong-Baker FACES scale is recommended for children who are at least 3 years of age [235]. This scale has been found to be valid and reliable for Japanese, Thai, Chinese, and black children and has been modified for use with Alaska native children [460; 461; 462].

For children who are too young to verbally express pain, clinicians and parents must rely on behavioral cues, such as frowning, a furrowed brow, a quivering chin, crying, sucking, flexing of fingers and toes, and breath-holding in infants. Behavioral indicators in older children include decreased energy level, eating, and interest in usual activities; holding or protecting part of the body; seeking comfort or closeness; and whining or groaning [456; 457; 458].

Pain management according to the WHO ladder has been found to be effective for children/adolescents, and the NCCN has developed guidelines for pediatric pain management [183; 463; 464]. Acetaminophen or NSAIDs, codeine, or oxycodone is recommended for pain rated as 0–3 on a scale of 0 to 10; an acetaminophen/opioid combination, NSAIDs, oxycodone, or morphine is recommended for pain rated as 4–6; and morphine or oxycodone is recommended for pain rated as 7–10 [183]. It is important to note that codeine may not be metabolized in 35% of children, and analgesia will be ineffective in those children [183]. Pharmacokinetic data for pediatric medications are lacking, and physicians should consult pediatric specialists for appropriate dosing of medications for symptom relief. Pain medication should be complemented by age-appropriate nonpharmacologic interventions; touch, massage, stroking, and rocking are effective for infants, toddlers, and young children, and guided imagery, music and art therapy, play therapy, controlled breathing, and relaxation techniques are beneficial for older children [455; 465; 466].

BEHAVIORS TO EVALUATE IN ASSESSING PAIN IN CHILDREN AND ADOLESCENTS	
Age of Child	**Behaviors**
Infants (<1 year)	Sleep during the previous hour Facial expressions (frown, furrowed brow, quivering chin) Consolability Crying Sucking Flexing of fingers and toes Motor activity Breath-holding
Children (1 year and older)	Energy level Eating behavior Interest in usual activities Whining, crying, groaning, complaining Holding or protecting part of body Seeking comfort, closeness
Source: [413; 456; 457; 459; 460]	*Table 28*

Attention to psychosocial support for the patient, parents, and other family members is crucial in the pediatric setting. Although most parents think that psychosocial issues should be discussed with the child's physician and would find that discussion to be valuable, fewer than half of parents raise such topics [467]. Furthermore, parents report that only 15% to 20% of physicians assess the family's psychosocial issues [467]. Among the psychosocial issues common in children/adolescents and their families are ineffective family coping strategies, the patient's relationships with peers, psychologic adjustment of healthy siblings, and long-term psychologic adjustment for parents [446; 465; 468; 469; 470; 471; 472]. The palliative care team must carefully evaluate the patient and family and provide resources and appropriate referrals.

CRITICAL CARE SETTING

Nearly 50% of patients who die in the hospital are in the ICU for some period of time during the last three days of life [473; 474]. In addition, 13% of patients admitted to the ICU with traumatic injury will die [473]. The abruptness of a traumatic injury is vastly different from the illness trajectories of life-limiting diseases, and palliative care seems incongruous in the ICU, a high-technology environment of the most aggressive life-prolonging treatments. The effective delivery of palliative care is challenged by many factors inherent in the ICU setting, including inadequate training of healthcare professionals, unrealistic expectations of patients and families, misunderstanding of lifesaving measures, and a greater need for surrogate decision making [473; 475; 476]. As these factors gain greater recognition, there is a growing emphasis on integrating palliative care elements into the care of patients with traumatic injury and/or patients in an ICU [119; 473; 475; 476; 477; 478].

The focus on complex, lifesaving care in the ICU creates a gap in providing relief of patients' symptoms. As in all settings, symptom assessment and management should be a priority for ICU patients. It has been suggested that an interdisciplinary palliative care assessment be carried out early in an ICU stay, preferably within 24 hours after admission, with documentation of a comprehensive care plan within 72 hours after admission [476; 479].

ICU patients are often young, and families expect lifesaving procedures to be effective [476]. Misunderstanding of lifesaving measures has been reported to be an obstacle to high-quality palliative care [480]. Clinicians and other members of the team should maintain open, ongoing communication about the patient's prognosis, the feasibility of recovery, and the burden of treatment. The sudden, often catastrophic events that bring patients to the ICU compound stress and grief in family members, whose psychosocial needs peak earlier than in other palliative care settings [476]. As a result, psychosocial and bereavement support for families must begin early in the course of the patient's stay in ICU, preferable within 24 hours after the patient's admission to the ICU [476].

The abruptness of traumatic injury or catastrophic illness is also associated with the lack of preparation of advance directives for many patients. There is often no time for planning during the short end-of-life process, and approximately 95% of patients are unable to participate in their care [476]. As a consequence, surrogates must make decisions, and such decisions have been shown to correlate poorly with the preferences of patients [481; 482].

 Copyright © 2019 NetCE

The most critical decision in the ICU setting is the withdrawal of life-support technologies. Withdrawal of mechanical ventilator support should be discussed with the family or surrogate when they (or the patient) raise the issue or when the clinician believes that the ventilator is no longer meeting the patient's goals or is more burdensome than beneficial [119]. To ease the discussion for families, the clinician should review the patient's status and care goals before discussing withdrawal of support [119]. Once the decision has been made to withdraw life support, the physician should review the process with family members, clarify the decision, ensure that the patient's spiritual and cultural context are considered, and reassure the family that comfort measures will be carried out [119; 476]. Withdrawal of life support should then be immediate, not carried out over hours or days, and established protocols for withdrawal of mechanical ventilation should be followed [476; 483].

Recognizing the importance of palliative care in critical care settings, the Society of Critical Care Medicine developed recommendations calling for, among other improvements, [473]:

- Increased competency in all aspects of palliative care, including the use of sedatives, analgesics, and nonpharmacologic approaches to manage symptoms
- Improved communication with family
- Better understanding of the practical and ethical aspects of withdrawing life-sustaining treatment
- Development of comprehensive bereavement programs to support both families and the needs of the clinical staff

To specifically address the needs of patients' families, the American College of Critical Care Medicine developed guidelines with 43 recommendations that included endorsement of a shared decision-making model, early and repeated care conferencing to reduce family stress and improve consistency in communication, honoring culturally appropriate requests for truth-telling and informed refusal, spiritual support, family presence at rounds and resuscitation, open flexible visitation, and family support before, during, and after a death [484].

Many other initiatives have focused on improving palliative care in the ICU, primarily by having a palliative care team screen patients for potential consultation and increasing communication between the team and attending physicians. This approach increased the use palliative care consultation 113% in one study and from 5% to 21% in another study [24; 485]. Another model that integrates palliative care into the ICU improved the quality of care and led to a higher rate of formalization of advance directives, better utilization of hospice, and a decreased use of nonbeneficial life-prolonging treatments [474].

CONCLUSION

As a result of ongoing advances in medicine, the trajectory of illness for many diseases has shifted, yielding an increasing number of patients needing palliative care throughout the continuum of care and, especially, at the end of life. High-quality palliative care focuses on the physical, psychosocial, and spiritual well-being of the patient as well as the family. Care is provided by a palliative healthcare team comprised of members who have expertise in communication, pharmacologic principles of pain management, and identification of associated psychosocial and spiritual needs. Palliative care eases the burden of suffering experienced by patients approaching life's end and provides for grief counseling and bereavement services for a family adjusting to loss. Physicians and other healthcare professionals should strive to enhance their knowledge of key strategies to achieve high-quality palliative care, as detailed in this course.

Customer Information/Evaluation insert located between pages 96–97.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 96–97.
We encourage you to **GO GREEN**. Access your courses **online** or download as an **eBook** to save paper and **receive a discount** or sign up for **One Year of Unlimited Online CE for only $69!** Additional titles are also available.

www.NetCE.com

Like us at NetCE4Nurses

MULTIPLE MYELOMA

#30712 • 10 ANCC / 4 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: Multiple myeloma is the second most prevalent hematologic cancer after non-Hodgkin lymphoma. While great strides have been made to improve survival rates with this disease, and positive outcomes have been attained over the last ten years, multiple myeloma remains an incurable disease. The purpose of this course is to provide healthcare professionals in contact with multiple myeloma patients the information necessary to provide optimum care, treatment, and patient education.

Faculty: Jacqueline Houtman, RN, MA, CDP

Audience: This course is designed for nurses and allied healthcare professionals involved in the care, treatment, and education of patients with the diagnosis of multiple myeloma.

Additional Approval: AACN Synergy CERP Category A

RENAL DISEASE AND FAILURE

#34232 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to provide primary care clinicians with the information necessary to appropriately identify and treat renal disease, with the objective of minimizing the long-term effects and complications of the disease.

Faculty: Carol Whelan, APRN

Audience: This course is designed for nurses involved in the care of patients with kidney disease or failure.

Additional Approval: AACN Synergy CERP Category A, CCMC

DIABETES PHARMACOLOGY

#35322 • 10 ANCC / 10 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to meet the needs of nursing professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.

Faculty: Diane Thompson, RN, MSN, CDE, CLNC

Audience: This course is designed for nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.

Additional Approval: AACN Synergy CERP Category A, CCMC

PATHOPHYSIOLOGY: THE CENTRAL NERVOUS SYSTEM

NEW!

#38920 • 15 ANCC / 2 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: 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 management of their central nervous system disorder.

Faculty: Jane C. Norman, RN, MSN, CNE, PhD

Audience: This course is designed for nurses working in both critical care and general and specialty medical-surgical units in which patients with multiple system problems are found.

Additional Approval: AACN Synergy CERP Category A, CCMC

CARING FOR THE GERIATRIC PATIENT

NEW!

#39100 • 3 ANCC Hours

By Mail – $21 • Online/eBook – $15

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.

Faculty: Alice Yick Flanagan, PhD, MSW; Allan G. Hedberg, PhD

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

Additional Approval: AACN Synergy CERP Category A

DIAGNOSING AND MANAGING HEADACHES

#90212 • 10 ANCC / 8 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: Given the common and difficult diagnoses associated with headaches, the purpose of this course is to educate the healthcare professional about the epidemiology and treatment of the various types of headaches so they may make early and accurate diagnoses, begin effective treatment, and/or refer patients to a specialist when necessary.

Faculty: John J. Whyte, MD, MPH

Audience: This course is designed for physicians and will be of interest to nurses and other medical personnel who may encounter patients who complain of headaches.

Additional Approval: AACN Synergy CERP Category A, CCMC

Are you licensed in other states?
Our Unlimited Online Special Offer includes all state mandates!
www.NetCE.com/NurseUnlimited

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

 Copyright © 2019 NetCE

Course Availability List *(Cont'd)*

ISCHEMIC STROKE
#90282 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to provide needed information about the roles of diagnosis and screening, evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.
Additional Approval: AACN Synergy CERP Category A, CCMC

CLINICAL MANAGEMENT OF VENTRICULAR ARRHYTHMIAS
#90372 • 15 ANCC / 4 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals with up-to-date knowledge of risk factors for development of ventricular arrhythmias, recommended therapies for the immediate and long-term management of arrhythmias, and indications of complications or side effects of therapy necessary to facilitate effective patient management, early identification of problems, and appropriate patient and family education.
Faculty: Karen Majorowicz, RN, ARNP
Audience: This course is designed for physicians, physician assistants, nurse practitioners, and nurses seeking to enhance their knowledge of foodborne illness. The course is of particular importance for clinicians in the primary care and emergency settings.
Additional Approval: AACN Synergy CERP Category A, CCMC

HYPERLIPIDEMIAS AND CARDIOVASCULAR DISEASE
#90842 • 10 ANCC / 7 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to increase awareness of the crucial role of hyperlipidemias in the development of cardiovascular disease, evaluate the therapeutic benefits of pharmacological and nonpharmacological approaches to lipid control, and contribute to a more positive interaction between the healthcare professional and the patient, through fostering patient awareness, implementation of lifestyle changes, and compliance to therapy.
Faculty: A. José Lança, MD, PhD
Audience: This course is designed for physicians, physician assistants, nurses, and nurse practitioners who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.
Additional Approval: AACN Synergy CERP Category A

CARE OF THE PEDIATRIC TRAUMA PATIENT
#92072 • 15 ANCC Hours

By Mail – $66 • Online/eBook – $60

Purpose: As injury remains a leading cause of mortality and morbidity among children, the purpose of this course is to allow healthcare professionals to provide timely care to pediatric trauma patients and to assist parents and caregivers in recognizing measures that prevent this type of injury.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all healthcare professionals involved in the care of pediatric patients, especially those in trauma care centers.
Additional Approval: AACN Synergy CERP Category A

SEPSIS: DIAGNOSIS AND MANAGEMENT
#94342 • 4 ANCC / 3 Pharm Hours

By Mail – $22 • Online/eBook – $16

UPDATE

Purpose: The purpose of this course is to provide healthcare professionals with a current review and updated, evidence-based guidance for the diagnosis and management of sepsis and septic shock. The objective is to address knowledge gaps, enhance clinical skill, and enable effective strategies of collaborative care to improve patient outcomes.
Faculty: Patricia Lea, RN, DNP, MSEd, CCRN; John M. Leonard, MD
Audience: This course is designed for all healthcare professionals who work with patients who present with sepsis, including nurses and physicians.
Additional Approval: AACN Synergy CERP Category A, CCMC

AUTOIMMUNE DISEASES
#94452 • 15 ANCC / 10 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat the most common autoimmune disorders according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with autoimmune diseases.
Additional Approval: AACN Synergy CERP Category A, CCMC

HIV/AIDS: EPIDEMIC UPDATE FOR WASHINGTON
#94732 • 7 ANCC / 2 Pharm Hours

By Mail – $34 • Online/eBook – $28

WA Mandate

Purpose: The purpose of this course is to discuss the epidemiology, organism characteristics, pathophysiology, transmission, clinical manifestations, complications, treatment advancements, prevention, ethical and legal aspects of care, and workplace concerns.
Faculty: Jane C. Norman, RN, MSN, CNE, PhD; John M. Leonard, MD
Audience: This course is designed for all nurses and allied healthcare professionals in Washington involved in the care of patients with HIV/AIDS.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course is designed to fulfill the Washington requirement for HIV/AIDS education. Participants will receive 7 hours of continuing education for completing this course.

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

Course Availability List *(Cont'd)*

GASTROESOPHAGEAL REFLUX DISEASE IN ADULTS

NEW!

#94900 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriately diagnose, treat, and care for patients with GERD.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for physicians, nurses, and members of the interprofessional healthcare team involved in the diagnosis, treatment, and care of patients with gastroesophageal reflux disease (GERD).

Additional Approval: AACN Synergy CERP Category A, CCMC

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

Opioid/ Controlled Substances

#95150 • 3 ANCC / 3 Pharm Hours

By Mail – $21 • Online/eBook – $15

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for all physicians, osteopaths, physician assistants, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approval: AACN Synergy CERP Category A, CCMC

Special Approvals: This course is designed to meet the requirement for opioid/controlled substance education.

ANXIETY DISORDERS

#96180 • 15 ANCC / 10 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

Additional Approval: AACN Synergy CERP Category A, CCMC

SUICIDE ASSESSMENT AND PREVENTION

#96440 • 6 ANCC Hours

WA Mandate

By Mail – $30 • Online/eBook – $24

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for nurses and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

Additional Approval: AACN Synergy CERP Category A, CCMC

Special Approval: This course is approved by the State of Washington Department of Health to fulfill the requirement for Suicide Prevention training for healthcare professionals. Approval number TRNG.TG.60715375-SUIC.

CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT

NY Mandate

#97532 • 2 ANCC Hours

By Mail – $21 • Online/eBook – $15

Purpose: The purpose of this course is to enable healthcare professionals in all practice settings to define child abuse and identify the children who are affected by violence. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of New York for child abuse victims.

Faculty: Alice Yick Flanagan, PhD, MSW

Audience: This course is designed for all New York physicians, physician assistants, nurses, and other professionals required to complete child abuse education.

Additional Approval: AACN Synergy CERP Category B

Special Approval: This course is approved by the New York State Education Department to fulfill the requirement for 2 hours of training in the Identification and Reporting of Child Abuse and Maltreatment. Provider #80673.

INFECTION CONTROL: THE NEW YORK REQUIREMENT

NY Mandate

#98642 • 5 ANCC / 1 Pharm Hour

By Mail – $26 • Online/eBook – $20

Purpose: The purpose of this course is to provide a review of current infection control practices and accepted standards, with an emphasis on the application of infection control standards and practices in outpatient and ambulatory settings.

Faculty: Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals in New York required to complete education to enhance their knowledge of infection control.

Additional Approval: AACN Synergy CERP Category A

Special Approval: This course is approved by the New York State Department of Health to fulfill the requirement for 3 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #TP02078.

PARKINSON DISEASE

#98771 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to provide needed information about the assessment and treatment of Parkinson disease so healthcare professionals may implement the necessary interventions appropriately.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.

Additional Approval: AACN Synergy CERP Category A

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

Copyright © 2019 NetCE

NetCE
Continuing Education

Customer Information

(Incomplete information may delay processing.)

For office use only:
GIA19

Please print your Customer ID # located on the back of this catalog. *(Optional)*

Order/complete by mail
P.O. Box 997571
Sacramento, CA 95899-7571

Order/complete by fax
(916) 783-6067

Contact us
(800) 232-4238

Email us
help@NetCE.com

Order/complete online
www.NetCE.com/GIA19

Last Name First Name MI

State License # Exp.

State Additional License # Exp.

License Type (circle one): RN / LPN / APRN / APN / CNP / CNS / FNP / RN, C / Other:

Address

City State Zip

Phone ( )

Fax ( )

Email

☐ Sign me up for NetCE Alerts, Promotions, License Reminders, and More!

Receive certificate(s) by:
- ☐ Online Access - FREE! Email required
- ☐ Email - FREE!
- ☐ Fax - FREE!
- ☐ Mail - Add $6 for shipping and handling

ONLY
$39
(Regularly $120)
$49 after January 31, 2020*

❑ ENCLOSED SPECIAL OFFER: 30 HOURS

You may complete all three courses or any combination of these three courses for a maximum payment of $39 (or pay the individual course price, whichever is less).

✓	Course #	Course Title / Contact Hours	Price
☐	95171	Medical Marijuana and Other Cannabinoids / 5 Contact Hours	$20
☐	98400	Dizziness and Vertigo / 10 Contact Hours	$40
☐	97382	Palliative Care and Pain Management at the End of Life / 15 Contact Hours	$60

Additional Courses Available by Mail (Access Online for a Discount!)
Payment must accompany this form. To order by phone, please have your credit card ready.

✓	Course #	Course Title / Contact Hours	Price
☐	30712	Multiple Myeloma / 10	$46
☐	34232	Renal Disease and Failure / 10	$46
☐	35322	Diabetes Pharmacology / 10	$46
☐	38920	Pathophysiology: The Central Nervous System / 15	$66
☐	39100	Caring for the Geriatric Patient / 3	$21
☐	90212	Diagnosing and Managing Headaches / 10	$46
☐	90282	Ischemic Stroke / 10	$46
☐	90372	Clinical Management of Ventricular Arrhythmias / 15	$66
☐	90842	Hyperlipidemias and Cardiovascular Disease / 10	$46
☐	92072	Care of the Pediatric Trauma Patient / 15	$66
☐	94342	Sepsis: Diagnosis and Management / 4	$22
☐	94452	Autoimmune Diseases / 15	$66
☐	94732	HIV/AIDS: Epidemic Update for Washington / 7	$34
☐	94900	Gastroesophageal Reflux Disease in Adults / 10	$46
☐	95150	Responsible and Effective Opioid Prescribing / 3	$21
☐	96180	Anxiety Disorders / 15	$66
☐	96440	Suicide Assessment and Prevention / 6	$30
☐	97532	NY Child Abuse Identification and Reporting / 2	$21
☐	98642	Infection Control: The NY Requirement / 5	$26
☐	98771	Parkinson Disease / 10	$46

☐ Check or Money Order (*payable to NetCE*)
☐ VISA / MasterCard / AmEx / Discover

Please print name (as shown on credit card)

Credit card #

/
Expiration date Security code

Security code is last three numbers from back of credit card, in the signature area. Four numbers on front of card, above the account number on AmEx cards.

Signature

Special Offer **$39**
($49 after January 31, 2020)*
I would like my certificates mailed for an additional $6
Additional Courses
Subtotal
Expedited Delivery
Applicable state sales tax included in price **$ 0**
Grand Total

Expedited mail delivery (within 2 to 3 days) is available in most areas at an additional charge of $35.
Call for information on international delivery.

***$49 special offer price expires February 29, 2020.**
Prices are subject to change. Visit www.NetCE.com for a list of current prices.

NetCE
Continuing Education

Evaluation

(Completion of this form is mandatory)

GIA19

Last Name _____ First Name _____ MI _____

State _____ License # _____ Expiration Date _____

To receive continuing education credit, completion of this Evaluation is mandatory.
Please answer all of the following questions and provide your signature at the bottom of this page.
Your postmark or facsimile date will be used as your completion date.

Please read the following questions and choose the most appropriate answer for each course completed.

1. Was the course content new or review?
2. How much time did you spend on this activity?
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. Did the activity strengthen your interest in and commitment to interprofessional team learning and collaborative practice?
14. Do you plan to make changes in your nursing practice as a result of this course content?

#95171
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
14. ☐ Yes ☐ No

#98400
Dizziness and Vertigo
10 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
14. ☐ Yes ☐ No

#97382
Palliative Care and Pain Management at the End of Life
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
14. ☐ Yes ☐ No

#95171 Medical Marijuana and Other Cannabinoids — If you answered yes to question #14, what change(s) do you plan to make in your practice?

_____

#98400 Dizziness and Vertigo — If you answered yes to question #14, what change(s) do you plan to make in your practice? _____

_____

#97382 Palliative Care & Pain Management at the EOL — If you answered yes to question #14, what change(s) do you plan to make in your practice?

_____

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

I have read the course(s) and completed the Evaluation(s) in full.
I understand my postmark or facsimile date will be used as my completion date.

Signature _____

Signature required to receive continuing education credit.

NOW AVAILABLE
UNLIMITED ONLINE CE
$69 FOR ONE YEAR

Purchase our Unlimited Special Offer and receive access to more than 1000 hours of CE, including special offers and state-required courses.

Suicide Assessment
Medical Marijuana
Prediabetes
Herbal Medications
Diabetes Pharmacology
Parkinson Disease
Depression and Suicide
Thyroid Dysfunction
Alzheimer Disease
Influenza

...and many more!

To access this Special Offer, please visit:

NetCE.com/NurseUnlimited

CALL FOR AUTHORS

NetCE, a nationally accredited provider of continuing education, is seeking coursework in all areas of health care.

Author Qualifications:

Currently licensed health professional, knowledgeable and skillful in the subject area of choice.

Contact us for our detailed *Faculty Guide to Activity Development*.

Tel: 800-232-4238 • Email: development@NetCE.com

Want More CE Choices?

NetCE
Continuing Education

Get One Year of Unlimited Online CE for ONLY $69!
Includes access to our entire course library of more than 1000 hours, including special offers and state-required courses!

The following Online Specials are included with your Unlimited Subscription, or may be purchased individually.

ADVANCED PRACTICE SPECIAL OFFER
Sepsis: Diagnosis and Management • Antibiotics Review • Herbal Medications • Chronic Pain Syndromes
34 Hours (includes 23 Pharm Hours) $59

PHARMACOLOGY SPECIAL OFFER
Epidural Analgesia Update • Diabetes Pharmacology • Moderate Sedation/Analgesia
30 Hours (includes 28 Pharm Hours) $59

GERIATRIC SPECIAL OFFER
Aging and Long-Term Care • Osteoporosis • Alzheimer Disease
23 Hours $49

PEDIATRIC SPECIAL OFFER
Type 2 Diabetes in Youth • Newborn Assessment • Childhood Leukemias and Lymphomas
30 Hours $59

WOUND MANAGEMENT SPECIAL OFFER
Pressure Ulcers and Skin Care • Hyperglycemia and Wound Management • Treating Pressure Ulcers and Chronic Wounds
15 Hours $39

TRAUMA SPECIAL OFFER
Postoperative Complications • Transport Methods for the Critically Ill Patient
30 Hours $59

NetCE.com/NurseUnlimited for more details.

NOW AVAILABLE

Download NetCE courses to your eReader!

For more details visit **NetCE.com**

BUSINESS HOURS: Monday through Friday, 8am-5pm Pacific Time. We are closed on weekends and holidays. If you call after hours, please leave us a message. We'll return your call the next business day.

CUSTOMER SERVICE: 800-232-4238 or help@netce.com. Call or email us for customer assistance, course catalogs, additional certificates, or transcripts. If you require special assistance, please contact the Director of Academic Affairs to inform her of your needs by calling 800-232-4238.

RETURN POLICY: Satisfaction guaranteed or your money back within 30 days of purchase, unless certificates have been issued. Please return the materials and include a brief note of explanation. For more information, please contact help@NetCE.com.

TURNAROUND TIME: Your order is processed the day it is received. Course material and/or certificates of successful completion are returned to you via first class mail, fax, or email.

MAILING PREFERENCES: To modify your mailing preferences or to view our privacy policy, please go to www.NetCE.com.

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

RETURNED CHECKS: If, for any reason, your check is returned, you will be contacted requesting a cashier's check or money order for the full amount of the order plus a $35 reinstatement fee. In addition, we are unable to accept temporary checks.

If you have questions about your license or certification renewal or state requirements, please contact your board. A list of approvals and accreditations is available on our website at www.NetCE.com.

NetCE
Continuing Education

NetCE | P.O. Box 997571 | Sacramento, CA 95899 | 800-232-4238 | Fax: 916-783-6067

Copyright © 2019 NetCE, Sacramento, CA

NetCE
Continuing Education

P.O. Box 997571
Sacramento, CA 95899

PRESORTED
STANDARD
U.S. POSTAGE PAID
PERMIT NO. 182
SACRAMENTO, CA

Vol. 144
No. 14
APRN19

Complete online at NetCE.com/GIA19

Quick Code#

Customer ID#

NO TESTS REQUIRED!

Like us at NetCE4Nurses

We Recycle

Scan this QR code to get started.
If you do not have a smartphone or
QR code reader, please visit
NetCE.com/GIA19.