NetCE

A TRC Healthcare Company

2023
CONTINUING EDUCATION FOR MICHIGAN NURSES

25 Hours
15 Pharmacology Hours
$41

INSIDE THIS EDITION:

Diabetes and Stroke

Anxiety Disorders in Older Adults

Multimodal Pharmacotherapy for Pain Management
(Meets the Michigan Pain Management Requirement)

Pathophysiology: Muscles, Joints, and Connective Tissues

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/MI23

We offer Human Trafficking and Opioid CE
(see Course Availability List, pg. 87).

NetCE
A TRC Healthcare Company

SPECIAL OFFER $41

25 Hours
Regular Price $130

#34943 Diabetes and Stroke: Making the Connection (2 contact hours)..... 1
#96690 Anxiety Disorders in Older Adults (3 contact hours) 10
#35270 Multimodal Pharmacotherapy for Pain Management (5 contact hours) 22
Customer Information/Evaluation .....Located between pages 44–45
#38950 Pathophysiology: Muscles, Joints, and Connective Tissues (15 contact hours) 45
Course Availability List 86–88

Special Offer price of $41 valid through December 31, 2023
After December 31, 2023, price increases to $62

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/MI23**.
Enter your Quick Code and Customer ID (found on the back of your booklet), or complete the enclosed forms located between pages 44–45.

DONE.

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

Advanced Practice Nurses,

Need more Pharmacology hours?

Our Advanced Practice special offers are designed just for you. You can also create your own **Special Offer** with **Design a Deal**. Choose from our entire library of courses to create your own Special Offer. Your price is based on the number of hours you select.

Starting at only $52!

(See inside back cover for details.)

Nurses,

Need more hours?

Get One Year of Unlimited Online CE Starting at Only $79.

NetCE.com/NurseUnlimited

(See inside back cover for details.)

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

CONTINUING EDUCATION FOR MICHIGAN NURSES 2023

Published by NetCE,
a TRC Healthcare Company
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

NETCE
Director of Development and Academic Affairs, Sarah Campbell
Director of NetCE, Julie Goodwin
Chief Information Officer, Kevin Bluck
Director of Graphic Services, Kathryn Harris
Director of Operations, Alma Parra

Division Planners
Alice Yick Flanagan, PhD, MSW
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
Mark J. Szarejko, DDS, FAGD
James Trent, PhD

Featured Contributing Faculty
Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN, LTC US Army Nurse Corps (Retired)
Beyon Miloyan, PhD
Jane C. Norman, RN, MSN, CNE, PhD
Diane Thompson, RN, MSN, CDE, CLNC

Diabetes and Stroke: Making the Connection

Includes 1 Pharmacotherapeutic/Pharmacology Hour

Audience
This course is designed for nurses in all practice settings who care for patients with diabetes.

Course Objective
Due to the widespread and potentially life-threatening nature of this issue, having a firm understanding of the implications of diabetes and how they relate to stroke is paramount. The purpose of this course is to provide nurses with the information necessary to identify patients with diabetes who are at risk for stroke and intervene early.

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

1. Outline the prevalence and diagnosis of diabetes.
2. Evaluate the etiology and presentation of stroke in patients with diabetes.
3. Identify treatment options for acute stroke.
4. Describe primary stroke prevention strategies for patients with diabetes.

Faculty
Diane Thompson, RN, MSN, CDE, CLNC, has an extensive history in nursing and nursing education. She possesses a strong background in diabetes and cardiac care, starting her professional career at the cardiac care area of the Cleveland Clinic in Cleveland, Ohio. Ms. Thompson took the knowledge and experience she learned from the Cleveland Clinic and transferred it into the home health arena in rural Ohio, after which she moved to Florida and obtained further knowledge while working as a PRN nurse in all areas, including medical/surgical, intensive care, emergency, critical care, and cardiology. With a desire to have a specific area to concentrate her profession, Ms. Thompson accepted a position as a pneumonia case manager, which led into a diabetes case manager career.

Ms. Thompson has been employed in diabetes care since 2001, when she was hired as a diabetes case manager. After the completion of 1,000 hours of education to diabetes patients, Ms. Thompson earned her certification as a diabetes educator in 2003. From 2006 to 2018, Ms. Thompson was the Director of Diabetes Healthways at Munroe Regional Medical Center in Ocala, Florida. As the director of the diabetes center, Ms. Thompson was responsible for the hospital diabetes clinicians, hospital wound care clinicians, and out-patient education program. Today, she is the nurse manager of a heart, vascular, and pulmonary ambulatory clinic at Metro Health System in Cleveland, Ohio. Ms. Thompson has also lectured at the local, state, and national level regarding diabetes and the hospital management of hyperglycemia. Ms. Thompson is a member of the ADA, AADE, Florida Nurses Association, and the National Alliance of Certified Legal Nurse Consultants.

Ms. Thompson acknowledges her family as her greatest accomplishment. She is a wife of more than 30 years and a mother of a daughter and son, of which she is very proud. Ms. Thompson credits her husband for the support needed to set a goal and achieve it. He has been by her side through nursing school and completion of her Bachelor's degree and Master's degree, which she was awarded in 2015 from Jacksonville University in Florida.

Faculty Disclosure
Contributing faculty, Diane Thompson, RN, MSN, CDE, CLNC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure
The division planner and director have 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 2 ANCC contact hours.

NetCE designates this continuing education activity for 1 pharmacotherapeutic/pharmacology contact hour.

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 07/29/2025); 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 12/31/2023); 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/MI23**.
- 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

Both diabetes and stroke are major public health issues in the United States. An estimated 34.2 million American children and adults, or 10.5% of the total population, have diabetes [1]. Cerebrovascular disease is one of the most common complications of diabetes and is an area of serious concern as the population ages and the trend for diabetes to be diagnosed at an earlier age continues.

The risk of stroke is two to four times greater for individuals with diabetes compared to those without. As of 2016, 313,000 (18.9 per 1,000) patients discharged with documented stroke also had diabetes [1]. Due to the widespread and potentially life-threatening nature of this issue, having a firm understanding of the implications of diabetes and how they relate to stroke is paramount.

AN OVERVIEW OF DIABETES

EPIDEMIOLOGY

Which racial/ethnic group has the highest prevalence of diabetes in the United States?

Diabetes is a progressive disease process influencing fuel metabolism [2]. Carbohydrate, protein, and fat metabolism are altered when insulin, the mediator of fuel, is not available. This insulin deficiency can result from defects in insulin secretion and/or diminished tissue response to insulin, resulting in hyperglycemia [3]. The chronic metabolic dysregulation associated with diabetes can result in long-standing damage to various organs, including the eyes, kidneys, nerves, heart, and blood vessels [2].

According to the American Diabetes Association (ADA), the prevalence of diabetes increased 382% between 1988 and 2014. However, the incidence of diabetes appears to have peaked in 2008 with an incidence of 8.4 per 1,000 adults in 2008; it has since decreased to an incidence of 6.7 per 1,000 adults in 2018 [1; 4]. As stated, 10.5% of the U.S. population, or 34.2 million Americans, have a diagnosis of diabetes. In addition, an estimated 7.3 million adults have diabetes but remain undiagnosed [1]. By 2045, it is predicted that 36 million American adults will have diagnosed or undiagnosed diabetes or impaired glucose tolerance, an increase of 1.8 million adults from current rates [5].

The scope of the diabetes problem is vast and diverse, particularly among geographical regions. In 2018, the prevalence of diabetes in the United States varied from 6.6% in Colorado to 13.4% in West Virginia [6]. Genetics, race, age, and lifestyle significantly influence the onset and progression of the disease process [1]. Although all races and ethnicities can develop diabetes, the prevalence is greatest (14.7%) among Native Americans/Alaska Natives. This group also has a risk for development of type 2 diabetes that is nearly two times greater than that of White Americans [1]. The prevalence of diabetes is 12.5% in Hispanic Americans, 11.7% in non-Hispanic Black Americans, 9.2% in Asian Americans/Pacific Islanders, and 7.5% in non-Hispanic White Americans [1]. Compared to non-Hispanic White Americans, African Americans and Hispanics are 40% to 50% more likely to have diabetes [4]. The highest prevalence of diabetes in the United States is observed in Native Americans in certain areas of the Southwest, where more than 30% of the population has the disease [1].

Diabetes is considered to be one of the most important risk factors for ischemic stroke, especially in individuals younger than 65 years of age. Individuals with diabetes who experience an ischemic stroke are typically younger than those without diabetes and often also have signs of hypertension, myocardial infarction (MI), and hyperlipidemia [7]. In 2016, after adjusting for age, the percentage of adults with diabetes who reported stroke was lowest among Hispanics (7.3%) compared with White (7.6%) or Black (9.4%) adults [8].

DIAGNOSIS OF DIABETES

The most common types of diabetes are type 1 and type 2. However, gestational diabetes is also relatively common and is a source of significant morbidity and mortality. Gestational diabetes is first recognized in pregnancy, usually after 27 weeks' gestation, and typically resolves after the birth of the child [9]. Other less common types of diabetes include [5; 10]:

- Maturity-onset diabetes of the young: A genetic, autosomal-dominant defect of the pancreatic beta cells resulting in insulin deficiency and decreased insulin release without the presence of insulin resistance and obesity. This form of diabetes typically develops in patients younger than 25 years of age. It is a different clinical entity than type 2 diabetes of the adolescent, which presents with insulin resistance.
- Diabetes related to diseases of the exocrine pancreas, such as cystic fibrosis, and various endocrine diseases, such as Cushing syndrome, acromegaly, and chromocytoma
- Drug-induced diabetes resulting from the use of certain medications, particularly high-dose corticosteroids

DIAGNOSTIC CRITERIA FOR TYPE 2 DIABETES			
Stage	**Fasting Plasma Glucose Level**	**Two-Hour Postprandial Plasma Glucose Level**	**Glycated Hemoglobin (HbA1c)**
Euglycemia	≤100 mg/dL	<140 mg/dL	<5.7%
Prediabetes	>100 mg/dL but <126 mg/dL	≥140 mg/dL but <200 mg/dL	5.7% to 6.4%
Diabetes[a]	≥126 mg/dL	≥200 mg/dL	≥6.5%
[a]A random blood glucose level ≥200 mg/dL with symptoms of hyperglycemia is also indicative of diabetes.			
Source: [9; 10; 11]			*Table 1*

According to 2022 recommendations from the American Diabetes Association, all adults older than 35 years of age should be screened for type 2 diabetes every three years, or sooner with symptoms or in the presence of risk factors [9]. In addition, individuals of any age who are at risk for or are suspected of having diabetes should be screened. Established risk factors for type 2 diabetes include [9]:

- Age older than 35 years
- Body mass index (BMI) greater thanor equal to 25, or greater than or equal to 23 in Asian Americans
- Family history of type 2 diabetes
- Habitual physical inactivity
- Race/ethnicity (e.g., African American, Hispanic American, Native American, Alaska Native, or Pacific Islander)
- Impaired glucose tolerance or elevated fasting glucose
- Previous history of gestational diabetes or giving birth to a child weighing more than 9 pounds
- Hypertension (i.e., blood pressure greater than 140/90 mm Hg in adults)
- Abnormal lipid levels (i.e., high-density lipoprotein [HDL] level <35 mg/dL and/or triglyceride level >250 mg/dL)
- Polycystic ovary syndrome
- History of vascular disease
- Acanthosis nigricans (most common among individuals of African descent)

The diagnostic criteria for type 2 diabetes are fairly straightforward and are based on fasting plasma glucose and postprandial plasma glucose levels (***Table 1***). After a diagnosis of type 2 diabetes has been definitively made, education on self-care management is necessary in order to obtain euglycemia and prevent complications related to the detrimental effects of hyperglycemia [9]. It is estimated that as many as 90% of patients with type 2 diabetes will require oral medications to achieve adequate glucose control within five years of diagnosis [9]. When glucose levels cannot be adequately controlled with oral medications, the use of injectable medications is necessary. If elevated blood glucose levels are untreated and continue to rise, the result can be hyperosmolar hyperglycemic nonketotic syndrome and ultimately death [11].

CEREBROVASCULAR DISEASE AND DIABETES

What is the earliest vascular abnormality seen in patients with diabetes?

The main cause of cerebrovascular disease in patients with diabetes is atherosclerosis, or thickening of artery walls. It is generally believed that patients with diabetes are at an increased risk for atherosclerosis due to endothelial dysfunction. The endothelium is the biologically active lining of the blood vessel that functions to [12]:

- Provide a mechanical lining
- Maintain vascular patency
- Prevent platelet aggregation and thrombosis
- Promote fibrinolysis

Endothelial dysfunction is the earliest vascular abnormality seen in patients with diabetes and is associated with blood vessel constriction, aggregation of platelets, and a proinflammatory state, with the accumulation of leukocytes and coagulation products on the endothelium [12]. This inflammatory response is mainly caused by the chronic effects of hyperglycemia and specifically the formation of biologically active glycated proteins and lipids that promote inflammation [13]. Visceral obesity, hypertension, and hyperlipidemia also contribute to oxidative stress, which can damage the endothelium [14].

The normal metabolic response to a glucose load is an increase in free fatty acids and insulin. These changes result in a transient decrease in endothelium-derived nitric oxide production and in endothelium-mediated vasoconstriction. In persons without diabetes, endothelial nitric oxide production and vasodilation returns to normal within two hours. In the presence of diabetes, endothelial-mediated vasoconstriction extends for hours [15].

In addition to vasoconstriction, aggregation of platelets and an increase in leukocytes and coagulation products on the endothelium also occur. Fibrinolysis is decreased, and thrombosis is increased. As the secretion of prostacyclin and nitric oxide induce vasoconstriction, plasma cytokine and prothrombin levels increase, making the plasma markedly procoagulant and antifibrolytic and promoting atherosclerosis [12]. These changes at the microvascular and macrovascular levels lead to reduced vascular reactivity and impaired blood flow to end organs [15].

Defects in endothelial function may be further compounded by the hypercoagulable state of the patient with diabetes. Plasminogen activator inhibitor-1, antithrombin III (which inhibits fibrinolysis), and tissue plasminogen activator antigen (a marker of impaired fibrinolysis) are consistently elevated in individuals with diabetes or insulin resistance [16]. Over time, these changes may lead atheromatous plaques to form at branching and curves in the cerebral circulation. The smooth stenotic area can degenerate, resulting in an ulcerated area of the vessel wall. Platelets and fibrin adhere to the damaged wall and a clot forms, gradually occluding the artery and eventually causing a stroke [17].

The American Diabetes Association asserts that cardiovascular disease risk factors should be identified and treated in all patients with prediabetes or type 2 diabetes.

(https://diabetesjournals.org/care/issue/45/Supplement_1. Last accessed May 20, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

TYPES OF CEREBROVASCULAR ACCIDENTS

The two primary types of stroke are ischemic and hemorrhagic. In the United States, approximately 87% of all strokes are ischemic and 13% are hemorrhagic [18]. An ischemic stroke occurs when any artery that supplies the brain with oxygen becomes stenosed or occluded, resulting in infarction [19]. In the case of hemorrhagic stroke, bleeding occurs below the arachnoid, the location of the brain's blood supply, allowing blood to directly contact and damage brain tissue. Research has linked diabetes (particularly poorly controlled type 2 diabetes) with ischemic stroke, a result of the disease's impact on vascular health and predisposition for atherosclerosis, as discussed [20]. The link between diabetes and hemorrhagic stroke is not well established. Therefore, the focus of this course will be on ischemic stroke.

Ischemic stroke can be further classified as either thrombolic or embolic depending on its origin. A thrombotic stroke occurs when a thrombus impairs cerebral blood flow by further narrowing or blocking an artery, typically around an atherosclerotic plaque. The stenosed or occluded artery may be a large vessel (e.g., carotid artery systems, vertebral arteries, the circle of Willis) or a small vessel (e.g., branches of the circle of Willis, the posterior circulation). Approximately 21% to 27% of ischemic strokes arise from atherosclerotic disease of the large vessels [21; 22]. In these cases, the cerebral artery branch points, especially those of the internal carotid artery, are the most vulnerable [23]. Small-vessel disease is associated with 21% to 25% of ischemic strokes [21; 22]. Thrombotic strokes caused by small-vessel disease are traditionally associated with lacunar infarcts, small, deep, subcortical lesions 15 mm or less in diameter resulting from occlusion of a single penetrating artery [24; 25]. As many as 20% of older individuals who are otherwise healthy have asymptomatic lacunar infarcts unrelated to an ictal event [26]. These silent infarctions were previously believed to be benign with a good long-term prognosis. However, they now have been linked to increased risks of stroke and death and can lead to debilitating cognitive impairments such as vascular dementia [26; 27]. Independent risk factors for lacunar infarcts include hypertension, gender, age, diabetes, smoking, and a history of transient ischemic attack (TIA) [26; 28].

GENERAL REGIONS OF ISCHEMIC STROKE AND CORRESPONDING NEUROLOGIC DEFICITS	
Affected Region	**Common Signs and Potential Sequelae**
Left anterior hemisphere	Aphasia (especially difficulty reading, writing, and calculating) Right limb weakness and sensory loss Right field visual defect
Right anterior hemisphere	Limb motor weakness or loss Left field visual neglect Unable to determine two-point stimuli on left side
Left posterior cerebral artery	Aphasia (esp. difficulty reading and naming objects) Right visual field defect Occasionally, right-sided numbness
Right posterior cerebral artery	Left limb sensory loss Left-sided neglect Left field visual defect
Vertebrobasilar territory (posterior circulation)	Bilateral vision disturbances and nystagmus Dysarthria and dysphagia Ataxia Dizziness, vomiting, headache No cortical deficits (e.g., aphasia and cognitive impairments)
Caudate nucleus, thalamus, frontal lobe (anterior circulation)	Sudden abnormal behavior
Thalamus (posterior circulation)	Numbness, decreased sensation in the face, arm, leg on same side
Source: [33; 34]	*Table 2*

An embolic stroke occurs when an embolus (i.e., any circulating clot or particle originating from a distal point) blocks an artery that supplies oxygen to the brain. Stroke registries indicate that 26% to 29% of ischemic strokes are embolic [21; 22]. Emboli include blood clots, fatty deposits, atherosclerotic plaque fragments, and cancerous cells or infectious materials emanating from conditions such as atrial myxoma and endocarditis, respectively. Clinical symptoms of the resulting infarct correspond to the location of the embolus, not its type. The region of the middle cerebral artery is most frequently blocked by emboli [29].

RISK FACTORS

As discussed, diabetes is a well-established risk factor for stroke, particularly ischemic stroke, and cerebrovascular disease. In addition to diabetes, other risk factors include [17; 30; 31]:

- Advanced age (older than 65 years)
- Positive family history
- Arterial hypertension (elevated systolic and/or diastolic blood pressure)
- Carotid artery disease
- Cigarette or cigar use
- Physical inactivity
- Hyperlipidemia
- Obesity
- Atrial fibrillation
- Cardiac conditions other than atrial fibrillation
- History of myocardial infarction or TIA
- Asymptomatic carotid stenosis
- Atherosclerosis of the aortic arch
- Postmenopausal hormone replacement therapy
- Polycythemia and thrombocythemia
- Alcohol or drug abuse
- Sleep-disordered breathing

SIGNS AND SYMPTOMS

The National Institute of Neurological Disorders and Stroke has identified the following signs and symptoms of stroke [17; 30; 32]:

- Sudden unilateral weakness or numbness of the face, arm, or leg
- Sudden loss of vision or dimming of vision
- Sudden aphasia or confusion
- Sudden severe headache

- Sudden falling, gait disturbance, or dizziness
- Hemiparesis or paralysis
- Homonymous hemianopia

The physical signs, symptoms, and sequelae of ischemic stroke are usually unilateral because of the circulatory anatomy of the brain (***Table 2***).

Because neurons surrounding the ischemic or infarcted tissues undergo changes that disrupt the plasma membranes, cellular edema ensues, resulting in further compression of capillaries. Cerebral edema reaches its maximum in about 72 hours and takes about two weeks to subside. Most individuals survive an initial hemispheric ischemic stroke cerebral vascular accident unless there is massive cerebral edema, which is typically fatal [17].

TREATMENT OF STROKE

Occlusions treated within what time frame following the onset of symptoms show the most improvement?

Individuals who present with symptoms of cerebrovascular accident should have a full neurologic assessment by a physician [30]. After etiology is determined, treatment related to the causative source may be initiated. In thrombotic strokes, treatment is directed at prevention of ischemic injury [15]. Occlusions treated within 90 minutes of the onset of symptoms show the most improvement. Tissue plasminogen activator (t-PA) is recommended for select patients who may be treated within three hours after the onset of symptoms [24; 31]. In 2009, the American Heart Association/American Stroke Association (AHA/ASA) revised guidelines for administration of rt-PA after acute stroke, expanding the window of treatment from 3 hours to 4.5 hours. Eligibility criteria for treatment during this later period are similar to those for treatment within three hours, but also include the following exclusion criteria [24; 36; 37; 38]:

- Age older than 80 years
- Use of oral anticoagulants, regardless of the international normalized ratio (INR)
- Baseline score on the National Institutes of Health Stroke Scale (NIHSS) >25
- History of stroke and diabetes

As time goes on, there is a diminishing effect of treatment, and there may be almost no benefit when treatment is initiated more than six hours after onset [24; 39].

Between 31% and 50% of patients treated with rt-PA have a 4-point or greater NIHSS score improvement by three months after the stroke [24]. These clinical improvements do not recede for at least one year after the stroke. In general, the best response to rt-PA has been found for patients who are younger than 75 years of age and have a baseline NIHSS score greater than 20 [24].

The most common serious medical complication of rt-PA is secondary brain hemorrhage, which occurs in 6% of patients [24; 40]. Yet, the risk does not outweigh the benefits of rt-PA [41; 42]. In most cases, the mortality rate for patients receiving treatment or placebo is comparable at three months (17% compared with 20%) and one year (24% compared with 28%) [43; 44]. Other dangerous complications of rt-PA, although rare, are angioedema, anaphylaxis, systemic hemorrhage, and if rt-PA is administered soon after an acute MI, myocardial rupture [45].

MECHANICAL EMBOLECTOMY

Mechanical embolectomy may be an option for patients with acute stroke who are ineligible for intravenous rt-PA or who fail to respond to intravenous rt-PA [32; 46]. This procedure consists of a device that is threaded through the artery to remove the thrombus and restore blood flow. Mechanical embolectomy can remove a clot in a matter of minutes, compared with pharmaceuticals, which may take as long as two hours to dissolve a thrombus [47]. The procedure is effective for up to eight hours after the onset of symptoms [46]. Several different devices are available, and more are under review [32].

In 2004, the Merci Retriever became the first mechanical stroke device to be approved by the U.S. Food and Drug Administration (FDA) [47]. Although the Merci is still in use, in 2015, and again in 2019, the AHA/ASA issued updated guidelines for treatment of acute stroke, recommending the use of stent retrievers due to higher recanalization rates and better outcomes than those seen with the Merci [24; 47; 48; 49]. Newer stent retrievers include [47; 50; 51]:

- The Penumbra System
- The Stryker Trevo stent retriever
- The Solitaire stent retriever system

ANTICOAGULANTS

The AHA Task Force reviewed and discussed several studies addressing the use of heparin or low-molecular-weight heparin and danaparoid as an adjunct to a thrombolytic agent in the treatment of stroke [24]. In general, the Task Force concluded that early administration of heparin or low-molecular-weight heparin and danaparoid is inadvisable partly due to the increased risk of bleeding complications, especially the hemorrhagic transformation of ischemic strokes. Additionally, early administration has not been shown to prevent recurrent stroke, lessen the risk of neurologic worsening, or improve patient outcomes [24].

ANTIPLATELETS

Data combined from two large clinical trials suggest that administration of aspirin (160–300 mg) within 48 hours after the onset of stroke slightly reduces mortality and morbidity by preventing early recurrent stroke in some patients [52; 53]. A 2014 Cochrane review found that the daily administration of aspirin (160–300 mg) within 48 hours of onset of stroke reduced the risk of early recurrent stroke without a major risk of early hemorrhagic complications. Long-term outcomes were also improved [54]. Although no new data have emerged since the publication of these results, the 2018 AHA guideline recommendations for antiplatelet therapy have changed to include the administration of aspirin in patients with acute ischemic stroke within 24 to 48 hours after onset. For patients treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in select patients [24]. Other oral antiplatelet therapies (e.g., ticlopidine, clopidogrel, dipyridamole) have not been tested sufficiently in the setting of acute ischemic stroke. The efficacy of intravenous glycoprotein IIb/IIIa receptor blockers in combination with other interventions or alone is under investigation. These agents may accelerate spontaneous recanalization and improve microvascular patency [55]. If administered alone, these agents have been shown to have an adequate safety profile [56].

PREVENTION

Why is glycemic control essential in the prevention of stroke?

Primary stroke prevention relies primarily on lifestyle changes to reduce the impact of modifiable risk factors, and this should be a part of the treatment plan for all patients with diabetes. Elimination of tobacco use via cigarettes or cigars should be stressed. In addition to smoking cessation, stress management techniques should be investigated to attempt to control hypertension. If these techniques do not succeed, medications may be necessary [12]. The combination of hyperglycemia and hypertension is thought to increase the risk of stroke [57]. The AHA recommends that the target blood pressure for individuals with diabetes be less than 130/80 mm Hg [57]. Pharmacologic therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been shown to be safe and effective in this population [57]. A low-cholesterol diet should be encouraged in order to address dyslipidemia [46]. In addition, lipid-lowering statins reduce the risk of first-time strokes in patients with diabetes, irrespective of the baseline lipid levels, pre-existing vascular conditions, or glycemic control [57]. Niacin, bile acid sequestrants, ezetimibe, or fibric acid derivatives may also be considered for individuals with known coronary heart disease and low levels of HDL cholesterol, such as people in whom target cholesterol levels cannot be achieved with statins or tolerate statin therapy; however, their effectiveness in decreasing stroke risk has not been established [57].

Obesity and excess weight place pressure on the entire circulatory system and are associated with hyperlipidemia, hypertension, and diabetes—all of which create an increased risk for cerebrovascular accidents. Adopting healthy eating habits and increasing physical activity can help reduce stroke risk in these patients [46].

Glycemic control is also essential in the prevention of stroke or extension of the injury. Intracellular acidosis resulting from hyperglycemia increases lactate, leading to glial and neuronal membrane damage due to reactive oxygen species generation and impaired vasodilatation. Potentially viable neurons in the ischemic penumbra are more likely to infarct under conditions of hyperglycemia, and research has demonstrated a disruption of the blood brain barrier associated with greater degrees of hemorrhage and cerebral edema. Hyperglycemia with or without a diagnosis of diabetes is associated with transformation from ischemic to hemorrhagic stroke [59]. Therefore, patients with diabetes should be encouraged to monitor their blood glucose levels regularly and remain compliant with prescribed medications.

KNOWLEDGE OF STROKE WARNING SIGNS

Although public knowledge regarding the warning signs and risks of stroke has improved, the majority of the general public is still unaware that early treatment can prevent severe disability and death [60; 61]. According to one estimate, five out of six people are unable to name the signs that signify a stroke [62]. Estimates vary widely, however. The International Stroke Trial found that only 4% of patients suffering an acute ischemic stroke arrive at the emergency department (ED) within three hours after the onset of symptoms, and a separate study found that 21% to 25% of individuals with acute ischemic stroke arrive at an ED within the same timeframe [63; 64]. Of these individuals, 2% to 4% receive thrombolytic treatment [65; 66]. It has been estimated that if all individuals called for emergency help at the onset of symptoms, as many as 29% could realistically receive treatment within three hours [65]. If all patients arrived at the ED within one hour after known symptom onset and received optimal treatment, the projected rate of thrombolysis would be 57%.

To improve the rate of early arrival in the ED, public education campaigns designed to help individuals recognize a stroke and seek early treatment often use the "five sudden warning signs" devised by the Brain Attack Coalition or "FAST," a mnemonic device created by study investigators on the basis of the Cincinnati Prehospital Stroke Scale [67; 68]. FAST was designed to focus on fewer common signs of stroke onset (face numbness, arm numbness, and slurred speech) and to include an action component (time) for lay persons who may have trouble recalling the warning signs and the appropriate action. A retrospective study exploring the capacity of the FAST campaign to facilitate the recognition of stroke suggests that it leads to the identification of approximately 89% of individuals who have a stroke or TIA [68]. The most common stroke symptoms were related to the face, arm, and speech/language. The same study found that a modified version of FAST (with removal of the word "numbness") decreased the number of TIAs identified and targeted ischemic stroke more readily than hemorrhagic stroke. Ultimately, it is unknown whether the general public is more likely to remember FAST or the five sudden warning signs.

Another education program—Hip-Hop Stroke (HHS)—is a school-based, child-mediated, stroke communication intervention designed to improve stroke literacy among school-aged children and their parents in low-income urban communities [35]. Researchers recruited 3,070 fourth- through sixth-grade schoolchildren and 1,144 parents from 22 schools, randomized to the HHS intervention or attentional control (i.e., nutritional classes) [58]. Among the children, an estimated 1% of controls and 2% of the intervention group demonstrated optimal stroke preparedness (i.e., perfect scores on the knowledge/preparedness test) at baseline. This increased to 57% immediately following the program in the intervention group compared with 1% among controls. At three-month follow-up, 24% of the intervention group retained optimal preparedness, compared with 2% of controls. Only 3% of parents in the intervention group could identify all four letters of the stroke FAST acronym at baseline, which increased to 20% immediately post-test and to 17% at three months post-test. There were no significant changes among controls. Among children in the intervention group, four called 911 for real-life stroke symptoms, in one instance over-ruling a parent's wait-and-see approach [58].

CONCLUSION

Every year, thousands of individuals will die as a result of their diabetes complications, and stroke is one of the leading causes of death in this population. Good control of diabetes and of other causes of cerebrovascular disease can reduce the associated morbidity and mortality and improve patients' quality of life. Healthcare professionals play a crucial role in identifying patients with diabetes who are at risk for stroke and intervening to address modifiable factors. This course is intended to raise nurses' awareness of the connection between diabetes and stroke in order to improve patient care.

Customer Information/Evaluation insert located between pages 44–45.

Anxiety Disorders in Older Adults

Includes 1 Pharmacotherapeutic/Pharmacology Hour

Audience
This course is designed for the benefit of a broad range of allied health professionals, including but not limited to, physicians, nurses, medical assistants, and nursing home administrators.

Course Objective
Older adults are the fastest growing demographic in the world, and anxiety disorders are the most common mental disorder in this age group. The purpose of this course is to provide clinicians with the knowledge and skills necessary in order to improve the assessment and treatment of anxiety disorders in older adults.

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

1. Describe the history and neuroanatomy of anxiety and anxiety disorder.
2. Discuss the assessment and classification of anxiety disorders in older adults.
3. Analyze the epidemiology of anxiety disorders in elderly patients.
4. Describe the clinical implications of late-life anxiety disorders and their treatment.

Faculty
Beyon Miloyan, PhD, received his PhD in Psychology from the University of Queensland in 2015 for his thesis on late-life anxiety disorders. He completed his postdoctoral training in the Epidemiology and Biostatistics of Aging program at the Johns Hopkins University before taking a tenure-track position in the School of Psychology and Health Sciences at Federation University, Australia. Dr. Miloyan has published 30 peer-reviewed journal articles and book chapters and has been teaching since 2012. He has supervised 10 student theses at doctoral, Master's, and undergraduate levels and served as an ad hoc peer reviewer for various journals in the fields of psychology, psychiatry, and public health.

Faculty Disclosure
Contributing faculty, Beyon Miloyan, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure
The division planner and director have 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 3 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 3 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 1 pharmacotherapeutic/pharmacology contact hour.

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 07/29/2025); 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 12/31/2023); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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

Mention of commercial products does not indicate endorsement.

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/MI23**.
- 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

The first known clinical case description of an anxiety disorder appeared in the medical corpus of the Ancient Greek physician Hippocrates. The description tells of Nicanor, a man who developed an extreme fear of a "flute girl" whom he encountered one night at a drinking party and who haunted him every night for many years. Five hundred years after this case description, the Ancient Roman Stoic philosophers Seneca the Younger and Cicero addressed the topic of anxiety at length, recognizing both its benefits and harms, depending on the severity and circumstances of the anxiety [1]. These texts reveal a sophisticated understanding of fear and anxiety among these ancient authors, even by modern medical standards. It was not until the 19th century that Charles Darwin noted essential similarities in the expression of fear and anxiety in mammals, reinforcing Seneca's notion that fear and anxiety are ultimately adaptive traits [2]. In its normal state, anxiety facilitates the management of potential future hazards [3; 4; 5]. In its extreme state, the individual regards it as excessive or distressing or it can cause impairment in the individual's daily life, thus constituting a disorder [6; 7].

The analogy of a smoke detector demonstrates the adaptive and maladaptive aspects of anxiety [8; 9]. Just as the function of a smoke detector is to signal potential fires so that one can take action to prevent harm, the function of anxiety is to signal any potential hazards so that preventive actions can be taken. In this analogy, an anxiety disorder is an extreme that renders the individual more sensitive to threat signals [10]. Although those with higher anxiety experience more false alarms (signals for a threat that does not occur), this is advantageous to the extent that it reduces the risk of a fatal miss. In other words, the costs associated with false alarms and misses are not equal: over-reacting to non-threats is generally less costly than failing to detect one danger. Nonetheless, living in a chronic state of high anxiety can take a long-term toll on an individual's health and quality of life, and in these cases, intervention is warranted.

Age-related changes in anxiety can occur over the course of one's life, and understanding these changes is key to facilitating clinical detection and treatment, particularly among older adults, who are the largest and fastest-growing age demographic in the United States. This course begins by addressing the neuroanatomy of anxiety, followed by its classification and a review of commonly used methods of assessment. The course goes on to cover the epidemiology of anxiety disorders in older adults, including its prevalence, incidence, course, risk factors, and consequences. Finally, treatment considerations are addressed.

NEUROANATOMY

Which two neural structures are necessary for anxiety responses?

In 1949, the Nobel Prize in Medicine was awarded to António Egas Moniz for his discovery of "a simple operation, always safe, [and] which may prove to be an effective surgical treatment in certain cases of mental disorder" [11]. Specifically, Moniz discovered the prefrontal leukotomy as a treatment for mental disorders, including anxiety disorders [12]. Since then, studies have found that damage to the ventromedial prefrontal cortex produces resistance against anxiety and depression [13; 14; 15; 16]. Despite the effective reduction of anxiety in these patients, it took many decades until research began to address the harms imposed by damage to the prefrontal cortex. For example, in addition to reducing anxiety, damage to the ventromedial prefrontal cortex also impairs self-regulation and decision-making and can induce sociopathic behaviors [17; 18; 19; 20; 21]. Similar patterns of anxiety reduction were also observed in one patient with focal bilateral lesions to the amygdalae who showed a similar pattern of impairment in her daily life as those with damage to the prefrontal cortex [22]. Although the prefrontal cortex and amygdala are critical structures in a neural network that is necessary for anxiety, these findings highlight the fact that damage to these structures comes with unintended consequences. These findings also highlight the more general point that, in treating anxiety disorders, it is also important to not abolish otherwise useful traits as it is to reduce the anxiety to a manageable level.

CLASSIFICATION

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) sub-classifies anxiety disorders into panic disorder, agoraphobia, specific phobia, social anxiety disorder, and generalized anxiety disorder (GAD) [6]. In the following sections, each of these subtypes are described, including the relevant criteria for diagnosis and a description of age-related differences in symptom patterns. The most frequently reported symptom(s) for each disorder in older adults are based on data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC).

PANIC DISORDER AND AGORAPHOBIA

Panic disorder is characterized by the occurrence of panic attacks. Panic attacks are defined as sudden, unexpected, and brief onsets of terror, accompanied by at least four of the following symptoms: sweating, trembling, chest pain, dizziness, nausea, chills or hot flashes, numbness or tingling, shortness of breath or choking, a feeling of loss of control, desensitization, or a fear of death. In order to be classified as panic disorder, the DSM requires such panic attacks to be accompanied by a period of at least one month in which the individual also fears the possibility of a future panic attack [6].

Two main subtypes of panic disorder have been observed, diverging between individuals with respiratory and non-respiratory symptoms [23; 24; 25]. Determining the subtype may be informative for treatment purposes. Older adults with panic disorder experience fewer symptoms of panic compared with younger adults, and their panic attacks are also reported to be less intense and shorter in duration [26; 27; 28; 29].

Agoraphobia is characterized by a fear or avoidance of situations from which escape is difficult. The diagnosis requires a fear or avoidance of two or more of the following specific situations: public transportation, open spaces, closed spaces, crowds, or being alone in public. Although the presence of these fears is also associated with panic disorder and specific phobia, a distinguishing factor of agoraphobia is defined by the frequency of the aforementioned fears. Individuals with greater and more frequent occurrences of these fears tend to be classified as having agoraphobia [30].

Table 1 displays the most commonly reported panic symptoms among older adults (55 years of age and older) with a diagnosis of panic disorder (with or without agoraphobia). The total percentage of each symptom is displayed. The prevalence of panic disorder in this sample was 1.2% (95% confidence interval [CI]: 1.0–1.5).

SPECIFIC PHOBIA

The central feature of specific phobia is the fear or avoidance of specific objects or situations. These include, but are not limited to, animals (e.g., snakes or insects), the natural environment (e.g., storms, water, or heights), situations (e.g., typically closed or open spaces), and blood, injections, or injury. A diagnosis of specific phobia requires the individual to recognize that the fear or avoidance is unreasonable and to regard it as distressing or interfering with their everyday life. The most common fears reported by adults involve animals, heights, and flying [32; 33; 34]. However, older adults frequently report situational fears [35]. Individuals who report having at least one specific fear are likely to report having other fears [33; 36].

Table 2 displays the most commonly reported specific fears among older adults (55 years of age and older) with a diagnosis of specific phobia. The prevalence of specific phobia in this sample was 5.5% (95% CI: 5.0–6.0).

SOCIAL ANXIETY DISORDER

The core feature of social anxiety disorder is the fear or avoidance of social situations. The fear or avoidance concerns the possibility of negative judgment by others (e.g., resulting in embarrassment or humiliation). Social anxiety may pertain to particular types of social settings or situations, such as small or large group settings, or the anxiety may generalize to a variety of social situations. Older adults endorse fewer social anxiety

PREVALENCE OF PANIC SYMPTOMS AMONG OLDER ADULTS WITH PANIC DISORDER			
Symptom	**Age Groups**		
	55 to 64 Years	**65 Years and Older**	**55 Years and Older**
Shortness of breath	82%	85%	83%
Heart racing/pounding	91%	82%	88%
Trembling/shaking	73%	69%	72%
Perspiring/sweating	75%	65%	72%
Felt as if choking	45%	57%	50%
Dizzy/lightheaded	74%	74%	74%
Things seemed unreal	61%	56%	59%
Tingling/numbness	57%	50%	54%
Flushes/hot flashes/chills	71%	53%	64%
Nauseous/upset stomach	50%	56%	53%
Pain/pressure in chest	63%	56%	60%
Going crazy/losing control	63%	61%	62%
Felt might die	58%	64%	60%
Source: [31]			*Table 1*

PREVALENCE OF SPECIFIC FEARS AMONG OLDER ADULTS WITH SPECIFIC PHOBIA				
Object of Fear/ Avoidance	**Age Groups**			
	55 to 64 Years	**65 to 74 Years**	**75 Years and Older**	**55 Years and Older**
Animals	57%	56%	62%	58%
Heights	53%	60%	49%	55%
Storms	26%	30%	45%	31%
Being in/on water	31%	41%	45%	37%
Flying	35%	36%	33%	35%
Crowds/lines	13%	12%	23%	15%
Closed spaces	40%	38%	41%	40%
Blood/injections	16%	11%	17%	15%
Public transportation	9%	6%	7%	7%
Going to the dentist	31%	32%	27%	30%
Hospitals	15%	12%	17%	15%
Source: [31]				*Table 2*

symptoms relative to younger adults [37]. The most common social fears among older adults include public speaking or being confronted or criticized by others, while discomfort with and avoidance of social situations and experiencing anxiety when thinking about social situations appears equally common to both younger and older adults [37; 38].

Table 3 displays the most commonly reported social fears among older adults (55 years of age and older) with a diagnosis of social anxiety disorder. The prevalence of social anxiety disorder in this sample was 2.0% (95% CI: 1.7–2.3).

GENERALIZED ANXIETY DISORDER

The central feature of GAD is intrusive worry, defined as repetitive thinking about potentially harmful future events. Worries generally pertain to everyday concerns and involve attempts to minimize the likelihood or consequences of disadvantageous outcomes. Although some degree of worry is recognized as helpful, when the individual reports experiences of excessive and uncontrollable worry for a period of six months or more, this constitutes a diagnosis of GAD if, and only if, the worry is also regarded by the individual as causing distress or impair-

PREVALENCE OF SOCIAL ANXIETY SYMPTOMS AMONG OLDER ADULTS WITH SOCIAL ANXIETY DISORDER

Symptom	Age Groups		
	55 to 64 Years	65 Years and Older	55 Years and Older
Social situations made you nervous	81%	85%	83%
Social situations made you upset/anxious	93%	93%	93%
Endured social situations that frightened you	88%	85%	87%
Avoided social situations out of strong fear	82%	72%	77%
More frightened in social situations than most people	80%	76%	78%
Thought fear of social situations stronger than it should be	92%	89%	90%
Had a panic attack in social situations	22%	8%	15%
Frightened of social situations out of fear of panic attack	16%	8%	12%
Remained in social situation despite fear of panic attack	20%	11%	15%

Source: [31] *Table 3*

PREVALENCE OF GENERALIZED ANXIETY DISORDER SYMPTOMS AMONG OLDER ADULTS WITH GENERALIZED ANXIETY DISORDER

Symptom	Age Groups		
	55 to 64 Years	65 Years and Older	55 Years and Older
Worry a lot about things you usually didn't worry about?	83%	72%	78%
Ever think your worrying was excessive?	56%	47%	52%
Often got tired easily	83%	81%	82%
Often had tense, sore, aching muscles	76%	67%	71%
Became so restless you paced, fidgeted, or could not sit still	62%	55%	58%
Often felt keyed up or on edge	82%	78%	80%
Often had trouble concentrating	83%	83%	83%
Often felt irritable	80%	62%	71%
Often had trouble falling/staying asleep	77%	72%	74%
Often forgot what you were talking about/mind went blank	75%	66%	70%
Often felt heart racing, skipping, or pounding in chest	59%	45%	52%
Often perspired/sweated	50%	35%	43%
Often had cold and clammy hands	44%	27%	36%
Often had dry mouth	58%	49%	54%
Often felt dizzy/lightheaded/like might faint	48%	53%	50%
Often felt nauseous	54%	34%	45%
Often urinated frequently	54%	47%	51%
Often had trouble swallowing/felt like lump in throat	37%	34%	35%
Often had pain/pressure in chest	40%	31%	36%
Often trembled/shook	34%	39%	36%
Often had trouble catching breath/felt like smothering	43%	33%	39%

Source: [31] *Table 4*

ment [39]. Age-related reductions in worry frequency have been observed in older adult samples from the United States, United Kingdom, Canada, and Australia [40; 41; 42; 43; 44; 45; 46]. There are also age-related differences in the subjects of individuals' worries. For example, for younger adults, common worries concern work, finances, and personal relationships. For older adults, these concerns give way to worries about personal health and the health and welfare of loved ones [41; 44; 46]. These "world issue" worries typically focus outwardly on problems that could be faced by future generations, which may be of particular relevance during this developmental life stage [43]. In fact, late-life developmental transitions have been associated with other context-specific worries, such as concerns of becoming a burden after transitioning out of a primary caregiver role and into retirement [47; 48]. Caregiving, too, can be a significant source of worry, anxiety, and distress in later life [49; 50; 51]. Older adults who report financial worries tend to be concerned about receiving care and about their own capacity to make decisions [52]. However, despite the observation that older adults with GAD tend to endorse a greater variety of worries than matched non-GAD controls, there are fewer differences in the experience of worry between older adults with and without GAD than there are between younger adults with and without GAD [53; 54]. In essence, the expression of worry may vary significantly as a function of the developmental stage of the individual, with older adults endorsing worries commensurate with their changing life circumstances [55].

Table 4 displays the most commonly reported generalized anxiety disorder symptoms among older adults (55 years of age and older) with a diagnosis of GAD. The prevalence of GAD in this sample was 2.0% (95% CI: 1.7–2.3).

ASSESSMENT

STRUCTURED AND SEMI-STRUCTURED INTERVIEWS

What is the standard for anxiety disorder assessment?

The standard procedure for anxiety disorder assessment is the structured diagnostic interview, which is administered by a trained professional. The structured interview consists of pre-determined questions that assess for relevant symptoms based on diagnostic criteria. For example, an interview for GAD would start by asking the individual questions about the presence of worry symptoms over the past six months. If the interviewee answers this question affirmatively, the interviewer would then ask the individual about the presence of secondary symptoms associated with the worry (e.g., sleep, irritability). If the individual responds affirmatively to the minimum number of secondary symptoms required for a diagnosis of GAD, the individual would then be queried about the presence of distress or impairment due to the worry. The key advantage of the structured interview is its standardized administration, procedure, and scoring, which minimize bias and error in assessment. Two commonly used structured interviews for the assessment of mental disorders are the Diagnostic Interview Schedule (DIS) and the Composite International Diagnostic Interview (CIDI) [56; 57]. In addition, the Anxiety Disorders Interview Schedule (ADIS) is a structured diagnostic interview that was developed specifically for anxiety disorder assessment [58]. These interviews are regularly updated along with diagnostic criteria, as for example with new editions of the DSM. Structured interviews rely essentially on self-report; in addition to being administered by clinicians, they may also be conducted by trained lay persons and/or computer-assisted technology (as in epidemiologic surveys).

The examination modality of assessment contrasts with the interview technique in that the person conducting the assessment, typically a trained clinician, decides about the presence or absence of a symptom instead of relying on the report of the individual. The Structured Clinical Interview for the DSM (SCID) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) are examples of semi-structured interviews/examinations that allow the clinician to take a more flexible approach to the interview while retaining some degree of structure [59; 60]. Structured interviews and semi-structured examinations are not always practical to use because they are time-consuming to administer. Nonetheless, they are essential for validating briefer, easier to administer, and more widely used questionnaires and screening tools for use in particular contexts.

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 diagnosing anxiety disorders is reliant on good communication, it is each practitioner's responsibility to ensure that interviews and assessments are conducted in such a way that allows for patient 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.

Mental health professionals should consider undertaking a language needs analysis for the service population and consider how to best meet identified needs. If possible, 10 to 15 minutes should be reserved in advance of sessions to brief the interpreter about the purpose of the meeting and to enable them to explain any cultural issues that may have bearing on the session.

RATING SCALES

Generalized Anxiety Disorder

The Generalized Anxiety Disorder 7-item (GAD-7) scale is a brief, self-administered screening instrument for use in medical settings. The scale assesses for symptoms occurring over the previous two weeks of the respondent's life [61; 62]. Each item is rated on a four-point scale (0 to 3) yielding a maximum score of 21. A score of 10 or greater indicates a probable diagnosis of

GAD based on validation against the psychiatrist-administered SCID [62]. There is also a shorter, two-item version called the GAD-2. The GAD-7 (along with scoring instructions) can be accessed online at https://adaa.org/sites/default/files/GAD-7_Anxiety-updated_0.pdf. The GAD-2 consists of only the first two items of the GAD-7, with scores of 3 or greater indicating clinically significant anxiety symptoms [63].

Panic Disorder

The Panic Disorder Severity Scale (PDSS) is a brief, self-administered screening instrument [64]. There are seven items, each rated on a five-point scale (0 to 4) yielding a maximum score of 28. A score of eight or greater indicates a probable diagnosis of panic disorder based on validation against the ADIS or the psychiatrist-administered SCID [65]. The PDSS and scoring instructions can be accessed online at http://www.goodmedicine.org.uk/files/panic,%20assessment%20pdss.pdf.

Social Anxiety Disorder

The Social Phobia Inventory (SPIN) is a self-administered screening instrument [66]. There are 17 items, each rated on a five-point scale (0 to 4), yielding a total score of 68. A score of 19 or greater indicates a probable diagnosis of social anxiety disorder. There also a shorter, three-item version called the Mini-SPIN [67; 68]. The SPIN and its scoring instructions can be accessed online at http://www.goodmedicine.org.uk/files/social%20anxiety,%20assessment%20spin.full_.tahoma_0.pdf.

Specific Phobia/Agoraphobia

There are currently no validated rating scales for the assessment of specific phobia or agoraphobia. However, screening for specific phobia is simpler than for other anxiety subtypes. The clinician starts by assessing whether the individual has a fear or avoidance of any specific stimulus or situation. If the individual answers affirmatively, then the clinician assesses whether the fear/avoidance is regarded as excessive or unreasonable and whether it interferes with the individual's life. Both criteria must be met for a patient to screen positive.

General (Transdiagnostic) Anxiety Screening

The Overall Anxiety Severity and Impairment Scale (OASIS) is a brief, transdiagnostic screening tool designed to assess for the severity of anxiety in the past week of the individual's life [69]. There are five items, each rated on a five-point scale (0 to 4), yielding a total possible score of 20. A raw score of 8 or greater indicates the presence of anxiety disorder based on validation against anxiety disorder diagnosis using the psychiatrist-administered SCID [70]. Raw scores of 10 and 12 indicate the presence of marked and severe anxiety, respectively, based on validation against the clinician-rated Clinical Global Impression-Severity (CGI-S) scale in a sample of individuals with any anxiety disorder ascertained using the Mini International Neuropsychiatric Interview (MINI) [71].

Scales for Older Adult/Geriatric Use

The Geriatric Anxiety Inventory (GAI) is a 20-item questionnaire designed specifically for older adults (65 years of age and older) [72; 73]. It is a self-report or clinician-administered measure, with each item rated on a binary response scale (agree/disagree), for a total score of 20. Scores of 10 or greater indicate a probable diagnosis of anxiety disorder. The GAI has been translated to more than 20 languages. The GAI has also been validated in clinical and non-clinical samples and in those with cognitive impairment and Parkinson disease [74; 75; 76]. There is also a five-item version called the Geriatric Anxiety Inventory-Short Form (GAI-SF) [77]. Both versions can be accessed online at http://gai.net.au.

The Geriatric Anxiety Scale (GAS) is a self-report questionnaire designed for use among adults 65 years of age and older [78]. The GAS contains 30 items, of which only 25 are used to derive a total score. The remaining five questions are used to help the clinician identify areas of concern for the respondent. Each item is rated on a four-point scale (from 0 to 3), yielding a total score of 100. The GAS consists of three sub-scales assessing somatic (9 items, total possible score: 36), cognitive (8 items, total possible score: 32), and affective (8 items, total possible score: 32) symptoms. There is also a shorter, 10-item version called the GAS-10 [79]. The standard GAS can be accessed at https://gerocentral.org/wp-content/uploads/2013/03/Geriatric-Anxiety-Scale-v2.0_FINAL.pdf, and the GAS-10 can be accessed at https://gerocentral.org/wp-content/uploads/2013/03/GAS-10-item-version-2015-1-15.pdf.

Assessment Implications

Compared with younger adults, older adults report fewer and less concrete anxiety symptoms across anxiety subtypes [40; 41; 42; 43; 45]. In addition to this, age-related neurocognitive impairment makes self-reporting a more difficult method of assessment [55]. For example, those with memory impairment can experience stressors that evoke negative effects without leaving memory traces [22; 80]. Although informant report can be a way of effectively gathering information about observable (e.g., physical) symptoms, it is ineffective for identifying unobservable (i.e., subjective) symptoms [81].

EPIDEMIOLOGY

This section addresses the epidemiology of anxiety disorders in older adults, which focuses on the occurrence, determinants, and course and consequences of anxiety disorders in the population. The focus is on the U.S. population, using data from nationally representative surveys. The section begins by addressing the occurrence of anxiety disorders by describing their prevalence and incidence. It then addresses the course and consequences of anxiety disorder, which includes their chronicity, persistence, and comorbidity. Finally, the determinants of anxiety disorders are explored by focusing on risk factors.

ONE-YEAR PREVALENCE OF ANXIETY DISORDER AMONG ADULTS 55 YEARS OF AGE AND OLDER IN TWO NATIONAL SAMPLES

Population	Specific Phobia		Social Anxiety Disorder		Generalized Anxiety Disorder		Panic Disorder		Any Anxiety Disorder	
	NESARC	CPES[a]	NESARC	CPES	NESARC	CPES	NESARC	CPES	NESARC	CPES[b]
Total	5%	6%	2%	3%	1%	3%	1%	2%	9%	6%
Age (years)										
55–64	6%	8%	3%	5%	2%	4%	2%	2%	11%	9%
65–74	5%	5%	2%	3%	1%	2%	1%	1%	8%	4%
75+	3%	4%	1%	1%	1%	15%	1%	2%	6%	4%
Sex										
Male	4%	4%	2%	2%	1%	2%	1%	1%	6%	5%
Female	7%	7%	2%	4%	2%	3%	2%	2%	11%	7%
Education										
Less than high school	6%	10%	3%	4%	2%	3%	2%	2%	9%	7%
Completed high school	6%	5%	2%	3%	1%	2%	1%	1%	9%	5%
Some college	6%	6%	2%	3%	2%	4%	1%	2%	9%	9%
Bachelor's degree	4%	4%	1%	2%	1%	2%	1%	1%	7%	5%
Marital status										
Married or cohabiting	5%	5%	2%	2%	1%	2%	1%	1%	8%	4%
Widowed, divorced or separated	6%	8%	2%	5%	2%	4%	2%	2%	10%	9%
Never married	5%	7%	2%	6%	2%	2%	1%	2%	9%	7%

[a]Specific phobia was assessed in a sub-sample of 9,282 respondents from the NCS-R.
[b]Specific phobia was not included in the overall anxiety disorder estimate for the CPES.

Source: [31; 84] *Table 5*

PREVALENCE

What is the most prevalent anxiety disorder subtype in older adults?

Prevalence is an estimate of the percent of individuals in the population who meet diagnostic criteria for anxiety disorder, either overall or by subtype. While lifetime prevalence estimates are concerned with the presence of anxiety disorders within the lifetime of individuals, these estimates are typically unreliable because they require respondents to recall prior episodes of anxiety and associated symptoms [82]. Estimating lifetime prevalence in older adults is particularly unreliable, due to general age-related memory deficits [83]. In contrast to lifetime prevalence, period prevalence estimates focus on the presence of anxiety disorder within a given timeframe, typically 12 months. The data in this section are one-year prevalence estimates of anxiety disorder (i.e., whether anxiety disorders were present or absent in the past year of respondents' lives) in nationally representative samples of the U.S. population.

Anxiety disorders are the most prevalent mental disorders in older adults [54; 84]. The most prevalent subtypes are, in descending order, specific phobia, GAD, social anxiety disorder, and panic disorder. ***Table 5*** displays the one-year prevalence of anxiety disorders, both overall and by subtype, in the NESARC and the Collaborative Psychiatric Epidemiology Surveys (CPES) of the United States. The prevalence of anxiety disorders is higher among women relative to men, and the prevalence of all anxiety subtypes decreases among persons 75 years of age or older. Previous studies have also reported ethnic differences in prevalence, such that Native and White Americans have the highest prevalence, and Hispanic and Asian Americans have the lowest prevalence of anxiety disorders [85]. Black Americans have a higher or lower prevalence of anxiety disorders depending on subtype; specific phobias and GAD are more prevalent, comparable to Native and White Americans, whereas panic disorder and social anxiety disorder are less prevalent, closer to levels observed in Hispanic and Asian Americans. The prevalence of anxiety disorders does not vary substantially by educational attainment or marital status.

INCIDENCE

The incidence of a disease is defined as the rate at which new cases occur. In contrast to prevalence estimates, which are based on single diagnostic assessments, incidence estimates require at least two diagnostic assessments. The reason for this is that anyone meeting criteria for an anxiety disorder at any time is counted as a case for the purpose of prevalence estimation, whereas only those individuals who did not have anxiety disorder at time one and who went on to be diagnosed with anxiety disorder at time two are counted as cases for the purpose of incidence estimation, showing that the individuals represent new occurrences of the disorder. The individuals at time one who do not meet criteria for an anxiety disorder are the "risk set" and form the denominator of the incidence ratio, and the individuals at time two or later who meet criteria for an anxiety disorder form the numerator over the period in which the diagnostic assessments were made.

Just as the prevalence of anxiety disorder is higher in older adults than other mental disorders, so too is the incidence, or the rate of newly diagnosed cases [86]. The subtypes with the highest incidence, in descending order, are specific phobia, social anxiety disorder, panic disorder, agoraphobia, and GAD [87; 88]. Data from the Epidemiologic Catchment Area (ECA) study and National Comorbidity Survey (NCS) in the United States, and the Netherlands Mental Health Survey and Incidence Study (NEMESIS) indicate that women have a higher incidence than men [88; 89]. Although anxiety disorder often peaks in young adulthood, there is a smaller but important second peak that occurs in older adulthood [88; 89].

COURSE

The chronicity of a disease refers to its persistence. Persistence is defined here as the percentage of respondents who meet diagnostic criteria for an anxiety disorder at baseline and who then meet criteria again at follow-up. Data from the NESARC indicate that approximately 30% of older adults (55 years of age and older) have persistent cases of anxiety disorder, or chronicity, assessed over a three-year follow-up period. The most persistent subtypes were specific phobia (25%) and GAD (20%), followed by social anxiety disorder (16%) and panic disorder (10%) [31].

There is high co-occurrence between anxiety and other mental disorders, particularly major depression [90; 92; 93]. Panic disorder and GAD have a particularly high comorbidity with mood and substance use disorders in adults [94]. Specific phobia has a strong association with social anxiety disorder and depression [95]. Finally, there are strong associations between social anxiety disorder, GAD, and bipolar disorder [91]. These patterns generally persist among older adults [54]. Anxiety subtypes also have high degrees of overlap [91; 94; 95].

EVIDENCE-BASED PRACTICE RECOMMENDATION

When assessing an adult with possible social anxiety disorder, the National Collaborating Centre for Mental Health recommends that clinicians be aware of comorbid disorders, including avoidant personality disorder, alcohol and substance misuse, mood disorders, other anxiety disorders, psychosis, and autism.

(https://www.nice.org.uk/guidance/cg159/resources/social-anxiety-disorder-recognition-assessment-and-treatment-pdf-35109639699397. Last accessed February 17, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Data from the NCS suggest that anxiety disorders are also associated with various physical conditions [96]. While panic attacks are associated with vascular conditions, specific phobias are linked with respiratory conditions, and social anxiety disorder with metabolic conditions. Among older adults, there are high rates of anxiety disorders in individuals who have chronic obstructive pulmonary disease (COPD) and/or cardiovascular diseases [35; 97]. The Baltimore ECA study reports an association between blood-injection phobia and vascular complications among individuals with diabetes, which suggests the possibility that fear of blood and injections may interfere with medical treatment [98]. Blood-injection phobia is also associated with respiratory conditions, similar to the data on overall phobias in the NCS sample [99]. The prevalence of blood-injection phobia ranges from 4% to 8% in older adults [36; 100].

CONSEQUENCES

As discussed, anxiety is diagnosed as a disorder only when it is deemed by the individual to be a cause of distress and/or to interfere with daily life. In the NEMESIS study, those with anxiety disorder at baseline had more suicidal ideation and suicide attempts at three-year follow-up, after adjustment for demographic characteristics and past history of mental disorders [101]. Similar associations were observed in cross-sectional studies of the NESARC and NCS-R samples of adults residing in the United States [102].

Importantly, the findings of a 2016 systematic review and meta-analysis of prospective, longitudinal studies suggest that a diagnosis of any anxiety disorder at baseline is not associated with increased risk of all-cause mortality at follow-up [5]. In fact, in a population study of Norwegians, high anxiety symptoms were associated with lower mortality among individuals with depression [103]. In a population study of a 1946 UK birth cohort, individuals who demonstrated lower levels of

trait anxiety in adolescence were associated with higher risk of accident mortality at follow-up [104]. Thus, low anxiety (but not high anxiety) is associated with increased mortality risk, and some degree of anxiety is beneficial for survival. Some anxiety likely encourages individuals to engage in preventive health behaviors. For example, women who worry about the possibility of breast cancer are more likely to seek routine screenings, people who are more worry-prone are more likely to vaccinate than those who worry less, and smokers with higher worries about their health have been found to be more likely to quit [105; 106; 107].

RISK FACTORS, RISK ASSESSMENT, AND PREVENTION

The two strongest risk factors for anxiety disorders among older adults are female sex and younger age [84; 108; 109]. However, other risk factors have also been identified. Cigarette smoking is shown to be a major risk factor of anxiety disorder onset, while smoking cessation is associated with reduced anxiety, suggesting that smoking interventions would have a significant effect on anxiety disorder onset [110; 111]. Another important risk factor of anxiety disorder onset in longitudinal studies is the occurrence of adverse life events, such as the ending of a relationship or the injury, illness, or death of a loved one [112; 113; 114].

The presence of adverse events at baseline is associated with an increased risk of overall anxiety disorder onset in older adults. In addition to female sex, history of any mood disorder, and cigarette smoking at baseline, lower levels of educational achievement are associated with higher risk of anxiety disorder onset at follow-up. Although previous studies have reported that excessive anxiety may be a result of licit or illicit substance use or abuse, this has not been replicated in more recent analyses [115; 116; 117]. The association between anxiety disorder and increased substance abuse (including prescription medication) observed in prior studies has been interpreted as evidence of self-medication for emotional distress [118; 119; 120]. A 2019 study assessed the longitudinal association of baseline social anxiety disorder and incident alcohol use disorder at 3- and 10-year follow-up periods in two national samples and did not find evidence of an association between social anxiety and self-medication with alcohol [121].

The prevalence of anxiety disorder is substantially higher in medical versus community settings, and there is a particularly high prevalence of anxiety disorder in individuals with Parkinson disease and among caregivers of older adults [51; 61; 122; 123; 124; 125]. Studies have demonstrated that, in part, the psychological distress (e.g., anxiety and depression) experienced by caregivers is linked to their patients' overall cognitive well-being, patient functional ability, and the reported caregiver burden [126; 127; 128; 129].

TREATMENT

This section will review the available evidence base for the treatment of anxiety disorders. First, preference is given to systematic reviews and network meta-analyses in the general population. However, individual studies are also used in discussion of specific phobia due to a lack of more rigorous research.

PANIC DISORDER

A 2016 network meta-analysis of 54 intervention studies assessed the effectiveness of eight methods of psychological interventions for treating panic disorder with or without agoraphobia [130]. These interventions included [130]:

- Psychoeducation
- Supportive psychotherapy
- Physiological therapies
- Behavior therapy
- Cognitive therapy
- Cognitive behavioral therapy (CBT)
- Third-wave CBT
- Psychodynamic therapies

Researchers found that not one of these treatments was supported as being more efficacious than the others, although any psychological treatment was generally mildly efficacious in comparison with a wait-list control condition [130]. In a subsequent study, the same investigators assessed whether particular components of CBT were associated with better responses to treatment. They reported that face-to-face administration (as compared to self-help) and graded interoceptive exposure to the physiological aspects of the panic response are the most effective features of CBT for treating panic disorder, although it is important to note that the principle of totality applies: the whole of a treatment is more than the sum of its parts [131]. Individual studies addressing treatments for late-life panic disorder have found that both psychological and pharmacological interventions tend to be less efficacious for older adults compared with younger adults [132].

SOCIAL ANXIETY DISORDER

Which classes of pharmacotherapy are the most effective in the treatment of social anxiety disorder?

A systematic review and network meta-analysis compared the effectiveness of seven classes of psychological interventions, five classes of pharmacological interventions, and three control groups [133]. Interventions included:

- Promotion of exercise
- Exposure and social skills
- Group CBT
- Individual CBT

- Other psychological therapy (including interpersonal psychotherapy, mindfulness training, and supportive therapy)
- Psychodynamic psychotherapy
- Self-help with or without support

Individual CBT was found to be effective for acute treatment compared with waitlist control groups. Pharmacologic interventions included anticonvulsants, benzodiazepines, monoamine oxidase inhibitors (MAOIs), noradrenergic and serotonergic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs). SSRIs and SNRIs were found to be the most effective class of pharmacological treatment compared with placebo control groups [133].

In this study, the promotion-of-exercise intervention was not found to be effective; however, this was not actually an exercise intervention. A 2020 systematic review and network meta-analysis assessing the efficacy of aerobic, resistance, and mind-body training regimens for treating depression reported that actual exercise interventions elicit high levels of treatment compliance and can be effective in reducing depressive symptoms [134]. Thus, similar treatments may also prove to be efficacious for treating anxiety disorders or subtypes.

GENERALIZED ANXIETY DISORDER

The results of two systematic reviews and meta-analyses suggest that psychological therapy has short-term efficacy for treating GAD [135]. A systematic review and network meta-analysis of 27 randomized, double-blind, placebo-controlled studies compared the relative effectiveness of nine pharmacologic treatments of GAD [136]. Although none of the treatments stood out as being clearly more successful than the others, it was concluded that fluoxetine may be preferred for response and remission and sertraline for treatment tolerance. Sertraline is also the most cost-effective pharmacologic treatment of GAD [137]. A separate systematic review and meta-analysis of 27 clinical trials assessed the effectiveness of psychological and pharmacologic treatments for late-life GAD [41]. In this study, benzodiazepines were found to be mildly efficacious relative to placebo, and psychotherapy was found to be mildly efficacious relative to waitlist control groups. A 2016 meta-analysis also reported that CBT is effective for treating GAD in older adults [138].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the National Collaborating Centre for Mental Health, the recommended high-intensity psychological intervention for persons with generalized anxiety disorder is cognitive-behavioral therapy (CBT) or applied relaxation.

(https://www.nice.org.uk/guidance/cg113. Last accessed February 17, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

SPECIFIC PHOBIAS

Exposure therapy is the treatment of choice for specific phobias [139; 140]. This includes in vivo (real-life) and virtual reality exposure to phobic stimuli or situations. Virtual reality exposure therapy was introduced in the 1990s, and although it may have some treatment benefit, it has not been found to have strong efficacy [141]. A one-session exposure therapy treatment for specific phobias was pioneered more than 30 years ago with a suggested duration of two hours and was subsequently used to treat various specific phobia subtypes [142; 143; 144; 145]. More recent studies suggest that one session does not always turn out to be adequate and that multiple sessions are generally more efficacious [140; 146]. However, there may be some cases where the single-session approach is viable.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Mental Health recommends against routinely offering computerized CBT to treat specific phobias in adults.

(https://www.nice.org.uk/guidance/cg159/resources/social-anxiety-disorder-recognition-assessment-and-treatment-pdf-35109639699397. Last accessed February 17, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Pharmacotherapy is not a common treatment for specific phobias. However, studies have sought to supplement exposure therapy using pharmacologic approaches. One such intervention administers cortisol to augment exposure therapy due to its role in interfering with memory for fearful scenarios [147; 148]. Although this treatment shows some efficacy, it does not seem to be particularly advantageous relative to exposure therapy alone. A second form of pharmacologic augmentation for exposure therapy, introduced more than 20 years ago, is the antibiotic D-cycloserine, which is thought to facilitate fear extinction due to its role as an *N*-methyl D-aspartate (NMDA) receptor agonist [149; 150]. D-cycloserine has also been used to augment exposure therapy for social anxiety disorder, with studies suggesting that this antibiotic can produce a marginal benefit for treating specific phobias and social anxiety disorder when combined with exposure therapy [151]. However, while these studies mention that the antibiotic is of a low dosage, they do not mention that this marginal benefit needs to be traded off against the risk of accelerating antibiotic resistance, which is a pressing global public health challenge. Computational studies suggest that increasing administration of low doses of antibiotics (as these studies suggest doing in conjunction with exposure therapy) accelerates resistance [152; 153].

Although the short-term efficacy of exposure therapy for specific phobias is moderately high, it is important to note that specific phobias are prone to high rates of relapse [139; 140; 154; 155; 156; 157]. Accordingly, studies have sought to eliminate conditioned responses to phobic stimuli over multiple contexts to make for a more successful extinction [158; 159; 160; 161; 162].

TREATMENT IMPLICATIONS

Given that anxiety itself is an adaptive trait, anxiety disorders are better seen as poorly regulated defenses than as defects. As decades of lesion studies indicate, a lack of anxiety may also create non-trivial problems for individuals' lives. Low levels of anxiety are associated with higher mortality risk, and those who report greater worries about particular health problems are likely to seek medical care and take preventative or corrective action [39; 103; 104; 105; 106; 107]. If some degree of anxiety is advantageous, then insufficient and excessive anxiety can both be considered maladaptive.

CONCLUSION

Anxiety facilitates the management of potential future hazards. Even though anxiety is effective at reducing danger, excessive anxiety is often a cause of significant distress and impairment, and anxiety disorders are the most prevalent mental disorders among older adults. Female sex and smoking are the strongest risk factors for late-life anxiety disorders, although adverse life events are also an important factor. About one-third of all cases have considerable chronicity, and therefore prevention is important. Interventions should focus on reducing anxiety to a sufficient, but not excessive, degree.

Customer Information/Evaluation insert located between pages 44–45.

Multimodal Pharmacotherapy for Pain Management

Includes 5 Pharmacotherapeutic/Pharmacology Hours

This course meets the Michigan requirement for 2 hours of Pain and Pain Symptom Management education.

Audience
This course is designed for nurses involved in the care of patients with pain.

Course Objective
The purpose of this course is to provide healthcare providers with a clear understanding of the concept of multimodal pharmacotherapy for pain relief, including available classes of analgesics.

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

1. Describe the underlying pathophysiology of pain.
2. Outline the different types of pain.
3. Discuss the mechanism of action and clinical use of opioids in the management of pain.
4. Compare and contrast other analgesic agents that can be used in a multimodal approach to pain management, including nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and local anesthetics.
5. Analyze approaches to multimodal pharmacotherapy for pain management.

Faculty
Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN, LTC US Army Nurse Corps (Retired), is a nurse anesthetist and prehospital registered nurse (instructor) who has published extensively in various areas of healthcare research while providing clinical care in arenas ranging from academic medical centers to austere environments in the third world during both wartime and peacetime. He has a bachelor's degree in nursing from Georgetown University, Master's degrees in education (Boston University) and nursing specializing in anesthesia (State University of New York in Buffalo and U.S. Army), and a PhD from the University of South Carolina. He is a retired lieutenant colonel in the U.S. Army Nurse Corps. He has taught nursing anesthesia, pharmacology, and physiology; mentored students in doctoral programs; and used advanced patient simulation to train students. Dr. Haas has worked in clinical, administrative, education, and research roles. He continues to work as an independent consultant, while taking more time to enjoy life with his wife of 45 years and their children and grandchildren.

Faculty Disclosure
Contributing faculty, Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN, LTC US Army Nurse Corps (Retired), has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Sharon Cannon, RN, EdD, ANEF

Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure
The division planner and director have 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.

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

AACN Synergy CERP Category A.

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

Mention of commercial products does not indicate endorsement.

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 07/29/2025); 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 12/31/2023); 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/MI23**.
- 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

Pain is one of the most potent safeguards to homeostasis. Experiencing pain allows humans to learn which activities or substances might cause irreparable damage to the body, and thus avoid engaging in those activities or ingesting those substances. However, this system is not perfect. Techniques to ameliorate pain have been actively sought since the earliest recorded history of science and medicine. Opioids, alcohol, mandrakes, and cannabis have all been used through the years in an attempt to mitigate pain [1].

From the 1860s until the 1950s, morphine was the pre-eminent opioid used for the control of pain. It was easily produced, especially as the pharmacotherapeutic industry became increasingly more refined and developed. In the 1950s, researcher Paul Janssen began his work on the synthesis of a new opioid called fentanyl [2]. In 1960, fentanyl was synthesized, and its use became widespread as a result of its safety and efficacy. Two derivatives of fentanyl followed in the 1970s: alfentanil (with a more rapid offset) and sufentanil (with increased potency) [2]. Opioids continue to be the mainstay of severe pain relief.

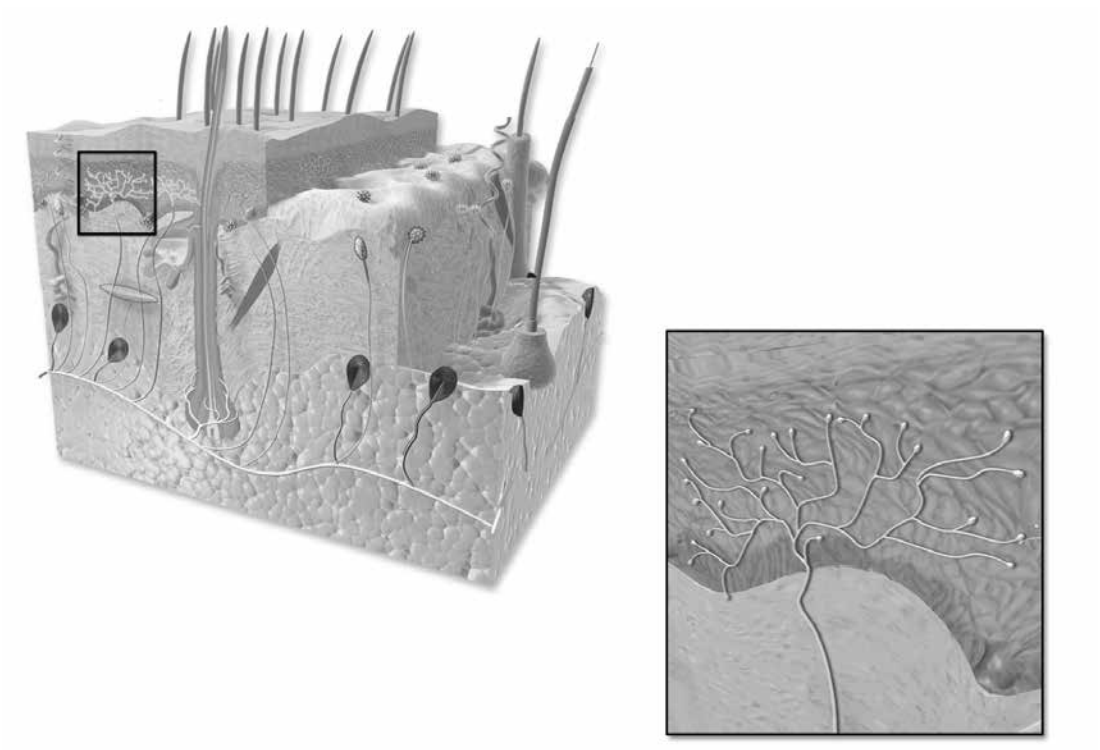
Even as researchers have lauded the effects of opioids for pain relief, they decried the problems with the use of opioids, particularly the risks of abuse and addiction. In the decade following their widespread use in the Civil War, physicians began to refer to opioid use disorder as the "soldier's disease" [3]. Unfortunately, knowledge of the problem has not led to an immediate solution. Problems with opioid abuse, including use disorder and diversion for illicit use, continue. At the same time, opioids (including fentanyl and its congeners) are widely used for the control of severe pain. There is evidence that even appropriate use of opioids may lead to use disorders and diversion in a subset of patients [4].

In an effort to decrease the use of opioids, it is vital for clinicians to first consider other agents to control pain. Combining various classes of drugs, in lower doses, can help control pain while decreasing side effects. One large dose of an opioid may be effective, but the preferred approach may be to use less or no opioid and to combine other agents, including anti-inflammatories, local anesthetics, alpha-2 receptor agonists, and others, to attain pain relief without the risks associated with opioids. This course will focus on the science behind multimodal pharmacologic pain management and its efficacy.

TYPES OF SENSORY RECEPTORS		
Type	**Function**	**Location**
Free nerve ending	Transmit pain and temperature	Skin, periosteum, arterial walls, joint surfaces
Pacinian (lamellar) corpuscle	Pressure	Skin
Meissner (tactile) corpuscle	Touch	Skin
Muscle spindle Golgi tendon apparatus	Stretch and pressure Stretch and pressure	Skeletal muscle Tendons
Kinesthetic receptor	Three-dimensional location (proprioception)	Joints

Source: Compiled by Author *Table 1*

FREE NERVE ENDING



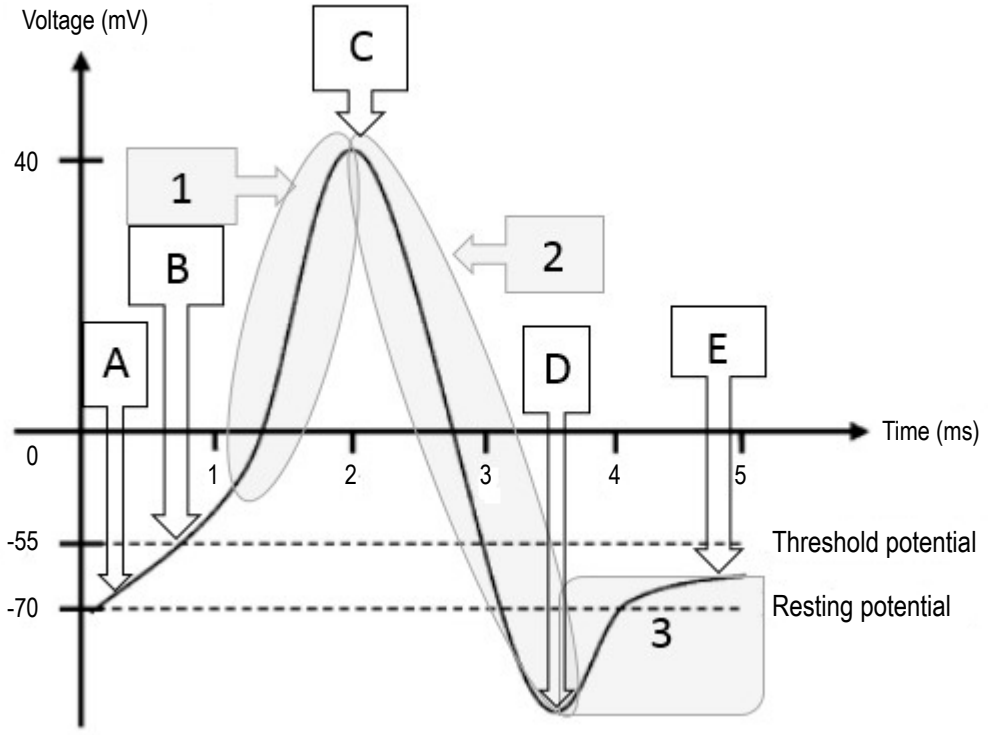
Source: Reprinted from Blausen.com staff (2014). Medical gallery of Blausen Medical 2014. WikiJournal of Medicine 1 (2). *Figure 1*

THE PHYSIOLOGY OF PAIN

Management of pain is a highly complex and patient-centered specialty. Clear understanding of the underlying anatomy and physiology is required to make the correct selection of pharmacologic interventions.

The human body has a number of specialized receptors in the skin, viscera, and periosteum of the bones that send impulses to the spinal cord and brain reporting the presence of pain (***Table 1***) [5]. Of particular interest to those treating pain is the free nerve ending (FNE) (***Figure 1***). There are several types of these unmyelinated nerve endings, and the ones most related to pain and tissue damage information processing are type IVa [6]. FNEs can send an impulse in the form of an action potential into the pain pathways as the result of tissue damage (secondary to trauma or heat) or tissue deformity (severe pressure resulting in tissue destruction). It is helpful to briefly review the concept of the action potential before moving on to an examination of the FNE.

ION MOVEMENT IN ACTION POTENTIAL FORMATION



Point A above shows the resting membrane potential of the nerve. At rest, a certain degree of leakage of both the sodium (Na+) into the cell and potassium (K+) out of the cell occurs. When a painful stimulus is experienced in the periphery, impulses will arrive at some point along a secondary nerve. Note the gradual upslope of the potential within the cell (the section between points A and B). In this example, painful impulses are coming into a section of nerve tissue from a free nerve ending, resulting in opening voltage-gated Na+ channels, resulting in an influx of Na+ that is faster than the outward leakage of K+, leading to an increasing membrane potential. Once membrane potential reaches threshold (point B), a large number of voltage-gated Na+ channels open, resulting in a large shift of Na+ ions from the extracellular fluid to the intracellular fluid, causing the initiation of an action potential (shaded area 1). Voltage-gated K+ and chloride (Cl-) channels then open, allowing K+ efflux and Cl- influx, dropping membrane potential (shaded area 2). The movement of K+ and Cl- is so great that an overshoot occurs, and the nerve hyperpolarizes (or falls below resting membrane potential, point D and shaded area 3). The Na+/K+ ATP-ase pump begins to work (shaded area 3) and equalizes Na+ and K+ gradients to result in a return to normal resting membrane potential.

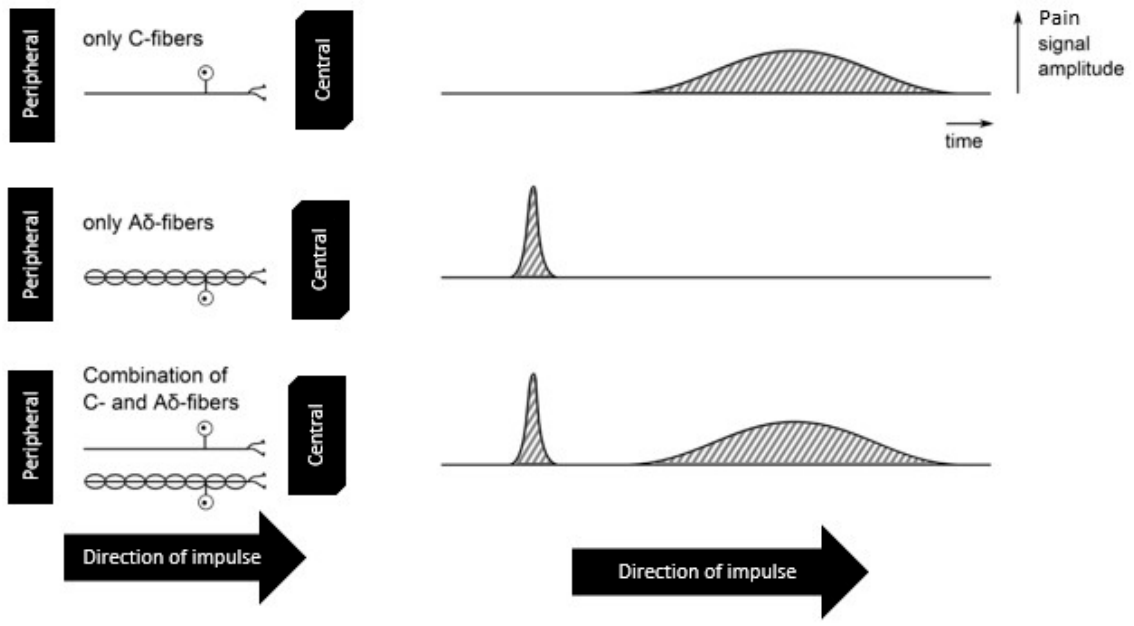
Source: [7] *Figure 2*

ACTION POTENTIAL

Action potentials are changes in polarity along a nerve based on ion flow into and out of the nerve cell. As the action potential travels down the length of the cell, it will end at a point in the nervous system that results in some form of output, either physical (muscle movement) or experiential (pain). ***Figure 2*** shows some of the details of an action potential and provides and extended explanation of their formation. Of particular importance is the quantity of ions moving at any specific time. The primary ions moving after stimulation and reaching threshold are Na+ (sodium, into the cell), K+ (potassium, out of the cell), and Cl- (chloride, into the cell). After the nerve has fired, the sodium/potassium adenosine triphosphate (ATP)-ase pump works to move sodium out of the cell and potassium back into the cell. A pump is needed because the ions are moving against their gradients, and energy is required in the form of ATP to power the pump.

A variable but set amount of nervous action potential impulses is required to reach threshold. The nerve must receive a sufficient number of input signals (or stimuli) to move its membrane potential above threshold and fire an impulse, sending, in this case, a message of pain along a nerve pathway. Understanding the science behind the action potential and its formation is crucial for the healthcare provider, as many analgesic drugs work by altering the transmissibility of signals sent along the nerve. If the action potential formed in the FNE can be blocked or altered, painful sensations can be mitigated or eliminated.

SIMPLIFIED PAIN PATHWAY



Source: Bettina Guebeli, licensed under a Creative Commons Attribution-Share Alike 4.0 International license. Modified by author.

Figure 3

FREE NERVE ENDINGS AND FIBER TYPES

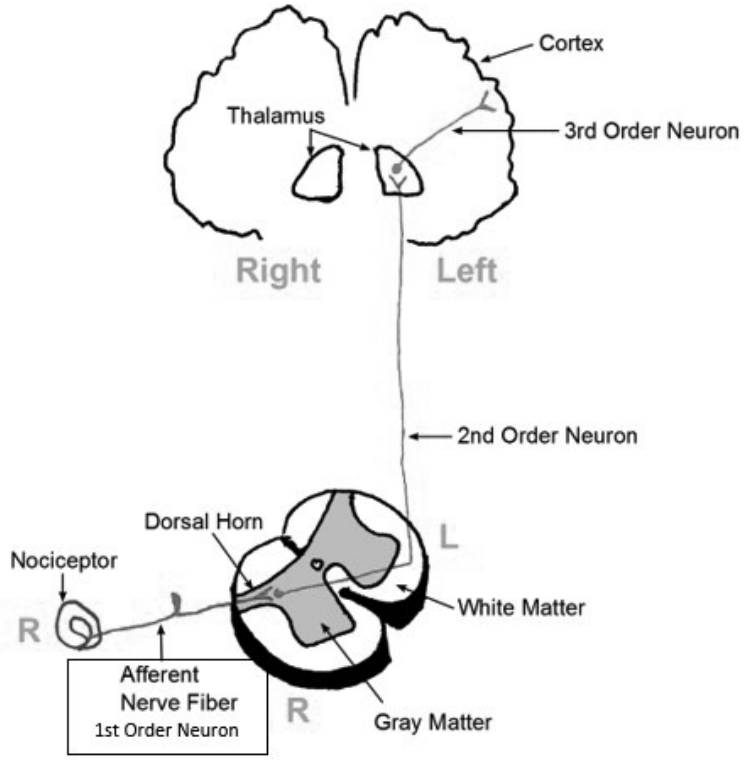
What are the two primary types of nerves that carry pain data elicited by stimulation of an FNE?

The FNEs are one of the sets of tissue receptors that can be stimulated to send impulses (action potentials) along the length of the nerve for further interpretation either in the spinal cord or various sections of the brain. Despite the study of FNEs over the past decade, the exact mechanism of action is still unknown. There are several postulations about how stimuli cause the firing of FNEs, initiating action potentials and resulting in the experience of pain. FNEs are also referred to as nociceptors. While nociceptors are often described as pain receptors, the purpose of the nociceptor is to alert the body to the presence of tissue damage [8]. FNEs are small structures, with a thin layer of Schwann cells surrounding them. They are branched in appearance and have small varicosities containing mitochondria, vesicles, and an axonal reticulum (analogous to the sarcoplasmic reticulum or endoplasmic reticulum in other cell types) [5; 9]. The vesicles contain numerous neuropeptides, including substance P and calcitonin gene-related peptide (CGRP), both of which are crucial in spreading action potentials during conditions of tissue destruction resulting in pain [9]. ***Figure 2*** illustrates varicosities in the distal ends of the FNE, but these structures are present throughout the FNEs until they reach larger nerves.

There are two primary types of nerves that carry pain data elicited by stimulation of an FNE: type Aδ or myelinated (fast) nerve fibers and type C or unmyelinated (slow) nerve fibers [5; 8]. Myelinated fibers are insulated with Schwann cells, but with gaps (nodes of Ranvier) in which the nerve fiber is exposed to the environment of the extracellular fluid. The myelinated fibers are also referred to as fast fibers because the action potentials can skip between the nodes of Ranvier in a process called saltatory conduction (rather than traveling the entire length of the axon). Sharp or acute pain, especially from traumatic injury, is usually processed in this fashion.

Type C fibers move impulses more slowly. While myelinated fibers can carry action potential impulses at speeds of 5–30 meters per second, unmyelinated fibers have speeds of 0.4–1.4 meters per second [8]. Most individuals have experienced this type of pain differential speed in their own lives: an acute accidental injury such as cutting one's finger while cooking results in an immediate response followed by an aching sensation. This is because both type A and type C nerve fibers travel in bundles together, and the stimulation of one nerve makes the stimulation of a nearby nerve easier. An example of this phenomenon is seen in ***Figure 3***. The solid line represents an unmyelinated nerve (type C), while the line with nodes represents a myelinated nerve (type Ad). If the nerves travel together from the site of injury, the patient experiences two waves of pain. Myelinated fibers carrying information about

FAST VS. SLOW PAIN TRANSMISSION



Source: Bettina Guebeli, licensed under a Creative Commons Attribution-Share Alike 4.0 International license. Modified by author.

Figure 4

pain tend to be highly localized, dependent on the density of FNEs in the area of injury. Unmyelinated fibers tend to carry information related to aching or less acute or localized pain. A significant amount of visceral pain tends to be carried by unmyelinated fibers, making diagnoses of this type of pain difficult.

PAIN PATHWAYS: GETTING THE INFORMATION FROM THE SITE OF PAIN TO THE CENTRAL NERVOUS SYSTEM

Pain pathways are complex routes over which action potentials are sent from the peripheral nerves to the central nervous system (CNS). An interruption of the pathway at any point tends to mitigate the degree of pain felt by the patient and, in some cases, may alleviate pain entirely. This can be accomplished by blocking some part of the pathway with a local anesthetic or by administering an agent(s) that drives the resting membrane potentials of neurons in a more negative fashion or interrupts the pathway within the brain. One of the key aspects of multimodal pharmacologic pain relief is to use smaller doses of various agents that work at different points along the pathway, minimizing adverse side effects while maximizing the number of sites of action.

Pain and other impulses originate in the peripheral nervous system (PNS), enter the dorsal horn of the vertebra, and then ascend to the brain along the spinothalamic tract. This is a three-neuron pathway containing first-, second-, and third-order neurons. In ***Figure 4***, the spinothalamic tract can be traced from the primary afferent nerve (receiving the pain signals at the site of injury) to the spinal cord, entering via the dorsal root of the cord. At this point, the first-order neuron synapses with a second-order neuron. Upon entry into the cord, the second-order neuron crosses from the right to the left (or left to right, if it enters the left dorsal root). This is referred to as decussation. The second-order neuron then rises up the cord in either the anterior or later spinothalamic tract, synapsing with a third-order neuron in the thalamus. This neuron leads to the sensory cortex in the brain, which in turn interprets the exact location and degree of pain.

SUBSTANCES AFFECTING THE TRANSMISSION OF IMPULSES IN FREE NERVE ENDINGS AND SOMATIC NERVES	
Substance	**Description**
Bradykinin	Bradykinin is a vasodilator that increases capillary permeability, increases migration of white blood cells, and increases free radicals in inflamed tissue and significantly excites pain receptors.
Calcitonin gene-related peptide (CGRP)	Stimulation of the free nerve endings results in the release of CGRP from the neuron, sensitizing it to stimuli and making the neuron hyperactive.
Norepinephrine	Pain stimulates the sympathetic nervous system, leading to the release of norepinephrine, which has an excitatory effect on the neuron.
Glutamate	Glutamate is an endogenous and highly excitatory neurotransmitter that binds at both the NMDA and AMPA receptors to excite the neuron and facilitate pain transmission.
Histamine	A ubiquitous substance throughout the body, histamine is released by mast cells and binds with excitatory receptors on the neurons and other cells.
Tachykinin	Tachykinins are a broad family of neuropeptides, including substance P, neurokinin A, and neurokinin B, released in response to pain or inflammation. They bind with neurokinin receptors, resulting in increasing excitatory stimulation of the neuron.
Serotonin (5-HT)	During inflammation, 5-HT is released from platelets in the area of injury. In turn, these bind with 5-HT2A and 5-HT3 receptors, resulting in excitation of the nerve.
Prostaglandin	One of the most crucial substances in pain management, prostaglandin sensitizes all aspects of excitatory phenomena in neurons. They are produced from the cell's arachidonic acid supply via the cyclo-oxygenase and lipo-oxygenase pathways.
Cytokine	Cytokines increase synaptic excitatory transmission in neurons and are represented by such substances as TNF and interleukins (e.g., IL-1b, IL-6).
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA = *N*-methyl-D-aspartate, TNF = tumor necrosis factor.	
Source: [5; 10; 11; 12; 13; 14; 15]	*Table 2*

Local Changes and Injured Tissue

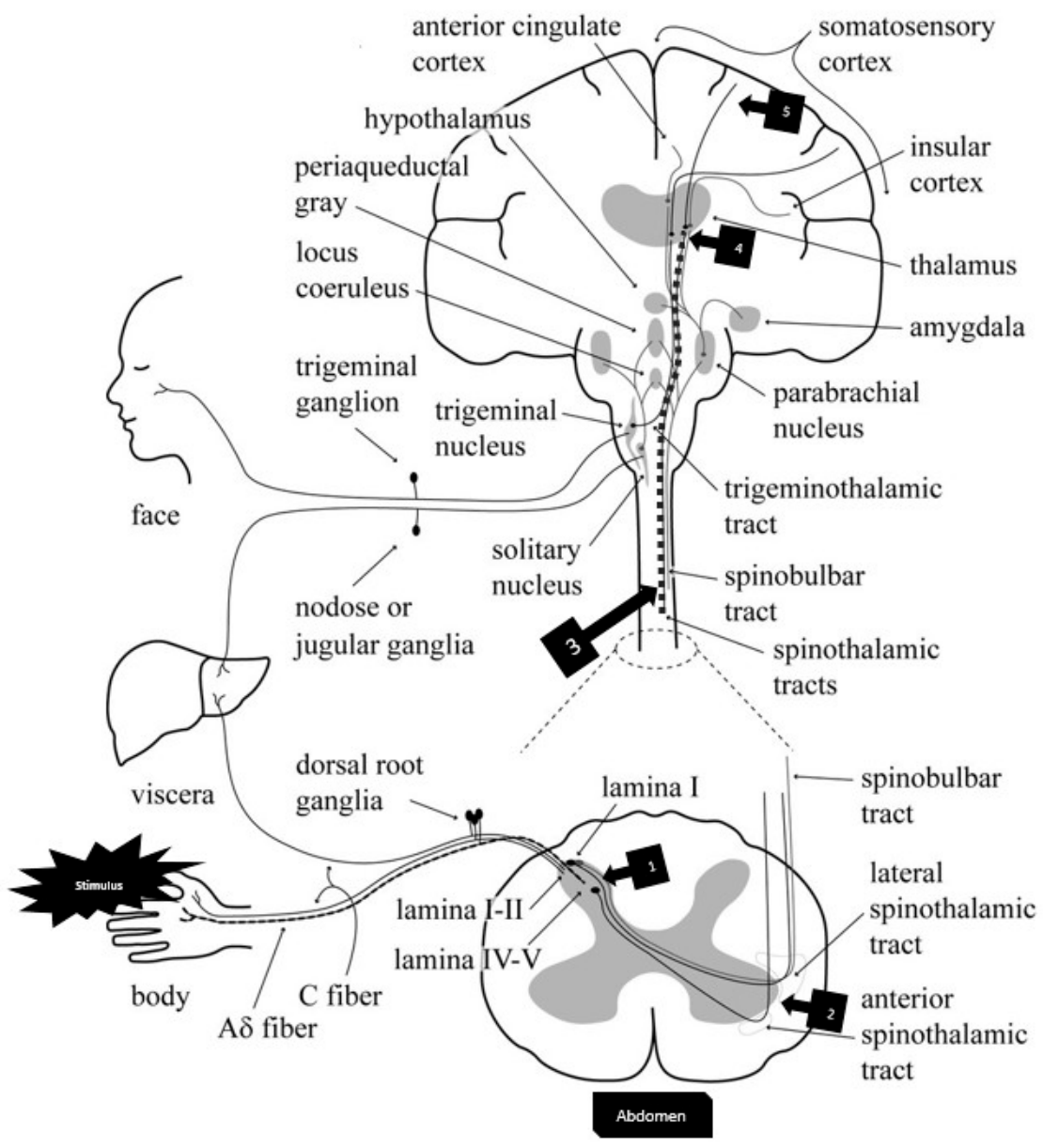
Because pain is adaptive in nature, it is important that signals are sent to the central nervous system to ensure the body responds to maintain homeostasis. As discussed, FNEs exposed to noxious stimuli send action potentials down a specific pain receptor pathway to insure its arrival in the central nervous system [9; 10; 11; 12]. Recall also that action potential generation is dependent upon the release of neurotransmitters, which in turn raise the nerve's membrane potential above threshold. While many neurotransmitters do this, a significant number function to lower resting membrane potential. This environment, in the presence of injury, has been referred to as "inflammatory soup," as a representation of the numerous and diverse substances involved in responses to pain [7]. ***Table 2*** provides a synopsis of most of these substances, focusing on those with the greatest impact in pain management. For nearly every substance, there is some form of pharmacologic antagonist available or in development to nullify its excitatory effect. While ***Table 2*** provides a brief glimpse at how neurons can be excited by local peptides and neurotransmitters, the actual mechanisms by which these changes are made are incredibly complex.

There is a large number of receptors on the neuron's cell membrane, most of which can bind with a specific molecular neurotransmitter. Nearly every drug administered in multimodal pain therapy interacts with one or more of these receptors.

Complex Ascending Pain Pathways

Figure 5 is a complex diagram of the ascending pain pathways. Starting in the lower left corner (with the stimulus), the pain pathway can be seen tracking along both Aδ and C fibers and entering the dorsal root of the spinal cord. The peripheral nerve synapses with a second-order nerve (Box 1) that decussates across the spinal cord; activating or inhibiting the interneurons in the lamina of the dorsal root can stop the impulse from propagating. The pain pathway then begins to ascend the anterior and lateral spinothalamic tracts toward the brain (Box 2). In the neck area of the diagram, the spinothalamic tract has been highlighted (Box 3), and it continues to ascend into the thalamus in the brain. The second-order neurons synapse in a special area of the thalamus called the ventrobasal complex (Box 4) [5]. The thalamus, when activated, is thought to cause the conscious perception of pain and provides an anatomic location for the cell bodies of the third-order neurons [5].

ASCENDING PAIN PATHWAYS



This is a cross-sectional view looking from the top of the head down toward the feet. As indicated by the box labeled abdomen, the patient is lying face down.

Source: Richard Lennertz, licensed under a Creative Commons Attribution-Share Alike 4.0 International license.
Modified by author.

Figure 5

The third-order neurons then ascend to the somatosensory cortex, allowing the patient to localize and quantify the painful stimulus (Box 5).

The thalamus also has neuronal branches that help to stimulate the reticular activating system, the portion of the brain responsible for sleep and waking [5]. The thalamus has numerous projections into other areas of the brain, including the prefrontal cortex and the amygdala, the latter of which is part of the limbic system [16; 17]. The projections of the neurons into the limbic system account for the suffering aspect of pain, where the sensation is overlaid with an emotional experience. As pain is important in preventing homeostasis damage, including an emotional response to pain (in addition to a sensory response) helps ensure the person experiencing pain will avoid the stimulus that led to the pain.

The hippocampus is another area that receives neuronal impulses during painful stimuli [17]. Previous studies have linked decreases in hippocampal volume to major depression; however, the hippocampus also helps process and modify nociceptive stimulation [18; 19]. Further, the hippocampus is the primary site for implanting memories [17].

Patients who are exposed to chronic pain or chronic stress may develop severe pain syndromes refractory to usual treatment. These pain syndromes have been associated with increased production of tumor necrosis factor-alpha (TNFα), a proinflammatory cytokine that sensitizes the patient to increased levels of pain secondary to local inflammation [19]. These inflammatory processes also atrophy the hippocampus, which has been associated with major depressive disorder [20]. It is not unusual, therefore, for unremitted or inadequately treated pain to co-occur with severe depressive disorders [21; 22].

Wide-Dynamic-Range (WDR) Neurons

At this point, it is appropriate to discuss the case of the wide-dynamic-range (WDR) neuron, a self-stimulating type of interneuron. As discussed, interneurons are found in the dorsal horn of the spinal cord and may act to facilitate or inhibit the transmission of nerve impulses, depending upon the receptors and neurotransmitters present. WDR neurons are associated with chronic pain states and are triggered by glutamate and glycine (excitatory neurotransmitters), which in turn activate *N*-methyl-d-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors [5; 12; 23; 24]. The NMDA receptor is a channel between the extracellular fluid and intracellular fluid embedded in the cell membrane. The dorsal horn of the spine has many glutamate- and glycine-releasing interneurons, and in an excitatory state, large numbers of glutamate and glycine neurotransmitters are released from neurons [25]. They have binding sites on NMDA receptors, which allows the movement of both Na+ and Ca2+ into cells, while a comparatively small amount of K+ exits [23; 25]. The NMDA receptor cannot open, even in the presence of glutamate and glycine, without first having the magnesium ion (Mg2+) blocker removed from the center of the channel. The interneurons containing the NMDA receptors, however, have other receptors, allowing them to become excited and fire an impulse. When the initial depolarization occurs, the Mg2+ obstruction is removed from the channel, and the rich environment of glycine and glutamate allows the membrane to continually depolarize. This increases the excitability of the second-order neuron, facilitating the passage of painful stimuli to the brain. As the nervous tissue becomes increasingly excited, further releases of glutamate and glycine occur, prompting more NMDA receptor opening in a positive feedback loop. This is called a windup phenomenon [26]. In other words, the area of injury becomes so excited that hyperalgesia sets in, and, in this state, even the smallest stimulus may result in severe pain. Wind-up phenomena result in a continual stimulation of neurons within the cord, with information processed there being sent to the brain. This is referred to as long-term potentiation and is quite difficult to treat [23; 24].

Knowledge of these pain pathways is necessary to achieve a sense of the many sites in the central and peripheral nervous systems where pain can be treated. As specific drug classes are described, one may return to these sections for a better these diagrams to understand how and where they act in the body.

TYPES OF PAIN

ACUTE PAIN

Pain pathways stimulate many areas of the brain. The brain responds by the release of many neurotransmitters and other hormones to provide a systemic response [10]. As discussed, pain impulses activate the amygdala, which triggers a sympathetic nervous system response, sometimes referred to as the "fight-or-flight" response. The release of norepinephrine and epinephrine results in, among other things, tachycardia, hypertension, and elevated blood glucose levels. Additionally, the local response to the stimulus produces the release of local neurotransmitters, such as substance P, glutamate, CGRP, and brain-derived neurotrophic factor (BDNF) [10; 11]. Of perhaps greater concern is the release of cytokines, which results in a profound inflammatory response. The inflammatory response is usually highlighted by hyperalgesia (exaggerated painful response to a painful stimulus) and allodynia (painful response from a non-pain-inducing stimulus). Take the example of a minor sunburn. If the skin is reddened and inflamed, a pat on the back becomes inordinately painful (hyperalgesia) and simply wearing a shirt may be intolerable (allodynia). In addition to these responses, untreated acute pain may lead to the expression of additional FNEs and nociceptors.

Acute pain usually has an easily recognized proximate cause and can be well-localized. The possible exception is intra-abdominal or pelvic pain, in which unmyelinated nerves are responsible for most nerve impulse propagation. However, even this hard-to-localize pain is often characterized to a general area ("My stomach hurts") rather than being poorly defined ("Everything aches").

In some cases, acute pain is associated with a medical procedure, such as routine surgery. For these patients, it is possible to visualize precisely where tissues have been manipulated and thus the location of the pain. The advantage of treating this form of acute pain is that treatment can be pre-emptive, with the administration of analgesics as part of the overall management plan [27].

CHRONIC PAIN

What is nociceptive pain?

Chronic pain is experienced by nearly one-third of the adult population of the United States and is associated with costs of more than $600 billion per year [11]. It can result in physical and emotional disability. It has become clear that chronic pain is far different from acute pain in its experience and treatment. While acute pain is related to a specific injury site, chronic pain is often centrally mediated and can therefore occur without the stimulation of a peripheral nerve [7; 11; 28]. Unfortunately, while acute pain can serve some adaptive purpose in protecting the person from harm, chronic pain is maladaptive in nature and typically has no beneficial biologic or systemic significance [11].

Historically, the initial approach to diagnosis and management of pain emphasized the identification of disease, lesion, or anatomic site of the pain, without reference to the underlying neural mechanisms or the application of this to treatment considerations [29]. Evidence now strongly supports combining the conventional etiology-based approach with a mechanism-based approach that classifies pain syndromes by the type of maladaptive nervous system alteration that has developed in reaction to the original insult. This approach provides a comprehensive dual therapeutic focus that targets the pathologic sustaining mechanism of the pain as well as the original disease, lesion, or tissue injury that has been the traditional focus of pain management [29; 30]. Such an approach is believed to optimize pain diagnosis and treatment by avoiding the limitations associated with the traditional etiology-based approach [31; 32; 33; 34; 35; 36].

Most pain syndromes involve multiple, often overlapping, neurobiologic mechanisms determined by the stage of the disease process. Current concepts of pain classify these into four main categories: nociceptive, inflammatory, neuropathic, and centralized [37].

Nociceptive pain is a physiologic response to tissue injury, the perception that arises from intense stimulation of specialized peripheral sensory neurons (nociceptors) that respond only to noxious (pain) stimuli. Nociceptive pain is subgrouped by location of involved tissues into somatic pain (muscle or connective tissue) and visceral pain (visceral structures) [38]. Nociceptive pain is considered adaptive during tissue healing but maladaptive and pathologic when it persists after healing has occurred.

Inflammatory pain occurs in response to tissue injury or infection that activates peripheral nociceptors and initiates the immune response. While the resultant production and recruitment of pro-inflammatory mediators to the injury site may serve to perpetuate discomfort, it also facilitates tissue repair; thus, this is considered an adaptive pain mechanism.

Neuropathic pain originates from peripheral or central nervous system injury. Unlike nociceptive and inflammatory pain, the mechanism of neuropathic pain has no adaptive function and is strictly pathologic [32; 39]. Acute pain from somatosensory damage is termed "acute neural injury." The term "neuropathic pain" implies pain that persists beyond the period of expected or actual tissue healing, and the underlying mechanism involves a maladaptive alteration in somatosensory nervous system function [35].

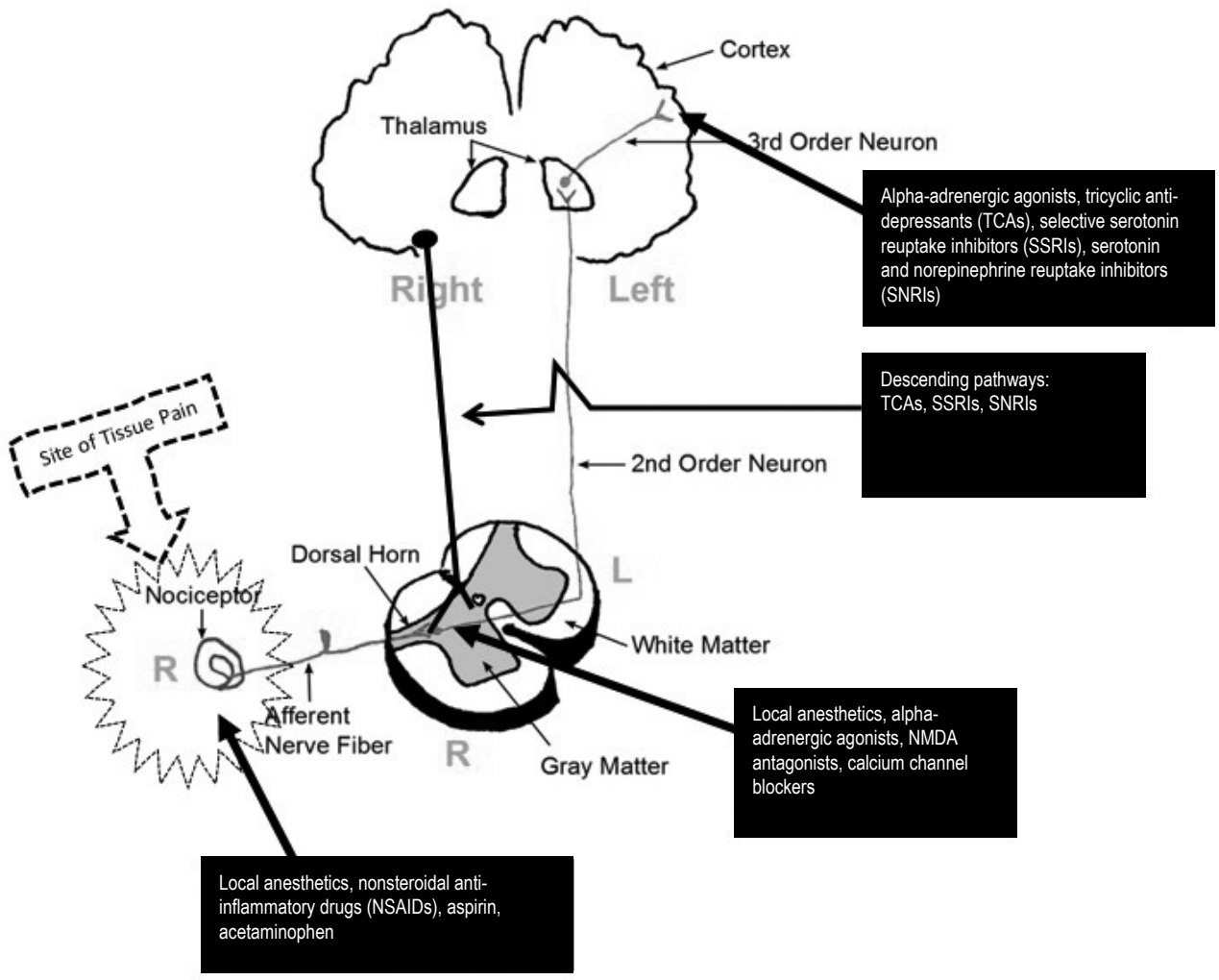
Centralized pain results from heightened nociceptive sensitivity in the absence of detectable peripheral stimulus and with negligible peripheral inflammatory pathology. The mechanism is poorly understood and is regarded as strictly pathologic as it lacks any evident adaptive function. Centralized pain disorders include conditions such as fibromyalgia, tension headache, and irritable bowel syndrome [32; 38; 40].

The persistence of acute nociceptive, inflammatory, or neural injury pain beyond tissue healing or repair reflects ongoing nociceptive activity that has become dissociated from peripheral nociceptive input to become maladaptive. Regardless of whether acute pain originates from tissue injury, tissue infection, or peripheral nerve injury, a similar process occurs by which nociceptive, inflammatory, and neuropathic pain signals are relayed from tissue injury site to the brain. This highly intense or prolonged pain signaling can lead to profound alteration in neuronal pathways that are further "upstream" from the peripheral tissue pain origin. Among these are increased ascending pathway signaling to the brain, reduced descending inhibitory signaling, expansion of pain receptive field, and induction of spontaneous and widespread pain. The resulting peripheral and central pathway hypersensitivity represents a state of abnormal nervous system function, amplified central nervous system sensory signaling, and abnormally low threshold pain response. The pain is no longer a symptom of peripheral insult, but a disease state of the nervous system [35]. This transition from acute to chronic pain occurs in discrete pathophysiologic steps involving multiple signaling pathways [41].

ANALGESIC AGENTS EMPLOYED IN MULTIMODAL PAIN MANAGEMENT

Figure 6 illustrates some of the sites and agents useful in the management of pain. Note that some agents act at more than one site along the pain pathway, and some of the agents enhance the utility of the endogenous descending pain pathways.

SITES AND AGENTS FOR MULTIMODAL ANALGESIA



Source: Bettina Guebeli, licensed under a Creative Commons Attribution-Share Alike 4.0 International license. Modified by author. *Figure 6*

OPIOIDS

What are the three primary opioid receptor types?

Opioid analgesics produce therapeutic and side effects by mimicking endogenous opioid activity, although some opioids produce analgesia by activity outside the opioid receptor complex. Opioids widely differ in levels of affinity and activation of opioid receptor subtypes. In addition, inter-individual variation in analgesic response and side effects is significant, largely driven by genetic factors [42]. The complex interaction between unique opioid properties and individual patient characteristics dictates that a patient-tailored approach is required for opioid selection, dose initiation, and titration to optimize safety, analgesia, and tolerability.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, there needs to be shared decision-making with the patient about reducing or eliminating opioids to avoid unnecessary complications from long-term opioid use. This involves following and re-evaluating the patient closely, with dose reduction or discontinuation as needed.

(https://www.icsi.org/wp-content/uploads/2020/01/PalliativeCare_6th-Ed_2020_v2.pdf. Last accessed October 20, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Naturally occurring opioid compounds are produced in plants (e.g., opium, morphine) and in the body (the endogenous opioids) [43]. Endogenous opioids are peptides that bind opioid receptors, function as neurotransmitters, and help regulate analgesia, hormone secretion, thermoregulation, and cardiovascular function. The three primary endogenous opioid peptide families are the endorphins, enkephalins, and dynorphins, and the three primary opioid receptor types are mu, kappa, and delta [44; 45]. A quick overview of this complex pain modulation system is helpful in understanding how opioid analgesics work.

Endogenous Opioid Peptides

Endogenous opioid peptides are neurotransmitter molecules in the opioid receptor complex that produce specific physiologic effects determined by neuronal distributions of the activated opioid receptor type [46]. The endogenous opioid peptides are cleaved from the pro-hormone precursors proenkephalin, pro-opiomelanocortin, and prodynorphin. The endogenous delta opioid receptor peptides are met-enkephalin and leu-enkephalin, cleaved from proenkephalin. Prodynorphin gives rise to kappa opioid receptor agonists dynorphin A and B. Pro-opiomelancortin encodes the peptide beta-endorphin, which has agonist activity at all three classical opioid receptors. Some endogenous opioid ligands lack specificity for opioid receptor subtypes, such as b-endorphin and the enkephalins [47; 48].

Endorphins

Endorphins are synthesized in the hypothalamus and the pituitary gland. Pain, strenuous exercise, excitement, and orgasm stimulate their release, binding, and activation. Endorphins are popularized as the "natural pain killers" from their ability to induce analgesia and a general feeling of well-being. They are thought to largely mediate analgesia from acupuncture, massage, hydrotherapy, and transcutaneous electrical nerve stimulation therapy [49].

Dynorphins

Dynorphin peptides are synthesized from the precursor pro-dynorphin and have primary affinity and binding at the kappa opioid receptor. Dynorphins are distributed throughout the CNS, with highest concentrations in the brain stem, hypothalamus, and spinal cord. Their physiologic actions are diverse, and their primary function is the modulation of pain response, appetite and weight, circadian rhythm, and body temperature. Dynorphins are linked to stress-induced depression and drug-seeking behavior, and drugs that inhibit dynorphin release are under evaluation for possible use in the treatment of depression related to drug addiction [49].

Enkephalins

Enkephalin peptides, derived from pro-enkephalin, are located throughout the brain and spinal cord and are involved in regulating nociception. Enkephalins inhibit neurotransmission in pain perception pathways, reducing the emotional and physical impact of pain. Enkephalins also reside in the gastrointestinal (GI) tract, where they help regulate pancreatic enzyme secretion and carbohydrate metabolism [49].

Opioid Receptors

Opioid receptors are expressed throughout the CNS and PNS on key nodes within the pain pathway and are highly concentrated in areas involved with integrating pain information [50]. Opioids vary greatly by receptor affinity, binding, and activity and can bind to produce agonist, partial agonist, or antagonist receptor activity [44]. As noted, the analgesic activity and the side effects result from mimicry of endogenous opioids, achieved by the beta-phenylethylamine group moiety shared by endogenous and exogenous opioid receptor ligands that facilitate opioid receptor binding [51].

Mu Opioid Receptors

Mu receptors are the primary mediators of analgesia produced by opioid analgesics in clinical use. Their greatest CNS concentration is in the thalamus, medulla, periaqueductal gray area, neocortex, amygdala, dorsal horn, inferior and superior colliculi, and brain stem [44; 49; 52]. PNS occupancy includes the peripheral sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, ileum, and proximal and distal colon. Mu receptors in non-neural tissue are found in the vascular and cardiac epithelium, keratinocytes, vas deferens, and Sertoli cells [53].

Mu opioid receptors in the amygdala and nucleus accumbens mediate opioid reward response (e.g., euphoria). In this brain region, opioids bind to and activate mu receptors, which inhibit gamma-aminobutyric acid (GABA) to increase dopamine transmission [50]. Mu opioid receptors broadly distributed in the limbic system mediate emotional response to pain and analgesia. In the medial thalamic nuclei, they relay spinothalamic inputs from the spinal cord to the cingulate gyrus and limbic structures [54].

Kappa Opioid Receptors

Kappa opioid receptors bind dynorphin as the primary endogenous ligand. In the CNS, they are highly concentrated in the caudate-putamen, nucleus accumbens, amygdala, brain stem, neural lobe of the pituitary gland, and hypothalamus. In the PNS, these receptors are found in the sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, ileum, and proximal and distal colon. They are primarily found in the limbic system, brain stem, and spinal cord. Their major effects include spinal analgesia, sedation, dyspnea and respiratory depression, dependence, and dysphoria [53]. The kappa opioid receptor subtype k3 is considered the primary analgesic mediator [55].

COMMONLY USED OPIOIDS			
Drug	**Functional Category**	**Route(s)**	**Comparison to Morphine[a]**
Morphine	Mu receptor agonist	IM, IV, PO, inhaled vapors	1
Hydromorphone (Dilaudid)	Mu receptor agonist	PO, SQ, IM, IV	10
Fentanyl (Actiq, Sublimaze)	Mu receptor agonist	PO, IV, buccal film, transdermal patch	100
Oxycodone (Roxicodone, OxyContin)	Mu receptor agonist	PO	1.5
Tramadol (Ultram, ConZip)	Mu receptor agonist	PO, IV	0.1
Hydrocodone (Hysingla ER)	Mu receptor agonist	PO	1
Oxymorphone (Numorphan)	Mu receptor agonist	PO, SQ, IM, IV	0.3
Meperidine (Demerol)	Mu receptor agonist	PO, IM, IV	0.1
Methadone (Methadose)	Mu receptor agonist	PO, SQ, IM, IV	Dose dependent
Codeine (Codeine)	Mu receptor agonist	PO	0.17
Buprenorphine (Belbuca, Butrans, Sublocade)	Partial mu receptor agonist	PO, buccal film, transdermal patch, IM, IV	30
Butorphanol (Stadol)	Mixed agonist/antagonist	Nasal spray, IM, IV	2
Nalbuphine (Nubain)	Mixed agonist/antagonist	SQ, IM, IV	1
Sufentanil (Dsuvia)	Mu receptor agonist	IV	1,000
Naloxone (Narcan)	Antagonist	IV, IM, SQ, nasal spray	~

[a]Assuming the pain relief value of morphine is 1, this is the comparative pain relief value of each agent.
IM = intramuscular, IV = intravascular, PO = oral, SQ = subcutaneous.

Source: [57; 58] *Table 3*

Delta Opioid Receptors

Delta receptors are mostly confined to CNS structures of the pontine nuclei, amygdala, olfactory bulbs, and deep cortex, but are also found in the GI tract and the lungs. They mediate spinal and supraspinal analgesia and the psychomimetic and dysphoric effects of opioid analgesics [49; 56].

Other Potential Opioid Receptors

Other opioid-like receptors have been identified in the CNS, including the opioid receptor like-1 (ORL-1). In contrast to the classic opioid receptors, the ORL-1 receptor is insensitive to the opioid antagonist naloxone. Opioids can bind to and activate the toll-like receptor 4 (TLR4), an innate immune pattern-recognition receptor [50].

Opioid Analgesic Mechanism

Opioid analgesia results from a complex series of neuronal interactions, largely mediated by the high density of opioid receptors in the dorsal horn of the spinal cord and in subcortical regions of the brain [46]. The analgesic effects of opioids result from two general processes: 1) direct inhibition of ascending transmission of pain signaling from the dorsal horn of the spinal cord, and 2) activation of descending pain control circuits from the midbrain to the dorsal horn of the spinal cord [49]. All three opioid receptor types mediate spinal analgesia. Supraspinal analgesia is primarily mediated by mu opioid receptor subtype 1. Opioid receptors are coupled to the superfamily of inhibitory G proteins. Receptor activation inhibits adenylate cyclase, reducing generation of cyclic adenosine 3,5 monophosphate and other second messengers. Potassium conduction is activated, inhibiting calcium influx to hyperpolarized target cells and reducing their response to depolarizing pulses. Neurotransmitter release is inhibited, and generation of postsynaptic impulses is decreased [46; 50].

Although drugs such as morphine are highly selective for mu opioid receptor and bind multiple mu receptor subtypes, mu opioid agonists greatly differ by interaction with different receptor variants and other opioid and non-opioid receptors [45]. A pharmacologically and clinically relevant classification approach is classifying opioid agents by functional interaction as mu receptor agonists, partial agonists, mixed agonists-antagonists, or antagonists (***Table 3***).

Spinal Level

The spinal cord dorsal horn is a primary analgesic site of opioids and is densely populated with mu (70%), delta (20%), and kappa (10%) opioid receptors. Opioid receptors are localized on presynaptic afferent fibers, interneurons, and postsynaptic projection neurons [50]. Opioids bind to and activate mu receptors, which inhibit the release of pain mediators such

as substance P, glutamate, and nitric oxide from nociceptive afferent neurons. Spinal level analgesia appears to elevate pain thresholds [46].

Supraspinal Level

At supraspinal levels, opioids produce analgesia by attenuation of the subjective evaluation of pain. After morphine is given for severe pain, patients report pain but without the associated anguish and distress. Conscious awareness and pain response are retained but modified by changes in emotional response to pain, mediated in part through opioid receptors in the limbic system [46].

Opioid receptors are highly concentrated in the medial thalamus, where incoming sensory information associated with intense and deep pain is filtered and then relayed to the cerebral cortex. This opioid effect on medial thalamus pain signal filtering greatly contributes to analgesia [46].

Opioid receptors are highly localized in subcortical brain regions where descending pain-modulating pathways originate. Normally, these pathways are inhibited by GABAergic neurons that project to descending inhibitory neurons of the brain stem. Opioid analgesics bind to and activate mu receptors on GABAergic neurons; this inhibits GABA to activate descending pain-modulating pathways [46; 50]. In addition, opioids activate ascending serotonin/norepinephrine pathways that project to forebrain centers to regulate the emotional response to pain [44].

The greatest factor that contributes to opioid analgesia is concentration of the drug on the mu receptor, which can be altered by pharmacokinetic processes that influence plasma concentration of the opioid by impacting its absorption, distribution, metabolism, or excretion. Intrinsic properties of the opioid, such as lipid solubility, also contribute to opioid receptor concentration [59].

Neuropathic Pain

Opioid analgesics have historically been considered less effective in neuropathic pain, but more recent evidence provides some support for their use. The extent of neuropathic pain reduction correlates with the duration of opioid therapy, possibly accounting for the mixed results in short-term studies [60; 61]. A 2011 study discovered previously unknown mu and kappa receptor expression on numerous peripheral tissues, immune cells, and joint capsules/synovium. The administration of opioids by injection into painful peripheral tissue sites results in pain relief in the absence of CNS activity, which supports the existence of localized peripheral opioid receptors [62].

Opioid effectiveness in neuropathic pain may be influenced by the capacity to inhibit voltage-gated sodium channels and individual channel type. Buprenorphine is more effective in blocking sodium channels than meperidine, lidocaine, and bupivacaine, possibly from greater lipophilicity, as this is a major factor in local anesthetic potency [61]. Sufentanil, fentanyl, and tramadol, but not morphine, are effective in blocking neuronal Nav 1.2 and may have greater clinical effect in some forms of neuropathic pain [63].

Inflammation enhances opioid anti-nociceptive action by peripheral mechanisms that activate during later (but not early-stage) inflammation, suggesting that timing of opioid administration contributes to analgesic efficacy in inflammatory pain [62]. Opioids are also effective in reducing the "air hunger" of dyspnea in patients suffering from cancer or respiratory or cardiovascular insufficiency [44].

Opioid Antagonists

A fourth group of opioids, opioid antagonists, bind and inactivate opioid receptors. Naltrexone and naloxone have traditionally been used to reverse potentially fatal overdose from opioid receptor agonists such as morphine or heroin. Opioid agonist molecules on mu opioid receptor are displaced, agonist effects on mu opioid receptor are abruptly halted, and opioid-dependent patients rapidly experience full alertness, analgesic loss, and opioid withdrawal [64].

Clinical trials with low-dose naltrexone have found unexpected and paradoxical enhancement rather than blockade of analgesia when co-administered with morphine and other opioid agonists in postoperative pain or severe intractable pain. Other evidence suggests analgesic efficacy as monotherapy in Crohn disease, irritable bowel syndrome, and fibromyalgia [65]. These findings led to the development and introduction of the peripheral-acting mu receptor antagonists alvimopan, methylnaltrexone, and naloxegol for severe opioid-induced constipation [66; 67].

In addition to opioid-induced constipation, opioid antagonists are U.S. Food and Drug Administration (FDA)-approved for the treatment of alcohol and opioid use disorder (naltrexone 50–100 mg/day oral) and opioid overdose (naloxone 0.4–1.0 mg/dose IV or IM). In pain medicine, the dose ranges of naltrexone and naloxone are substantially lower. Of the two, naltrexone is much more widely used, and published pain medicine studies have used dose ranges of 1–5 mg (termed "low-dose") or <1 mg in microgram amounts (termed "ultra-low-dose") [65]. For example, case studies have reported dramatic improvement in refractory pain with intrathecal administration of an opioid agonist combined with ultra-low-dose naloxone in the low nanogram range [68].

The mechanism of low-dose and ultra-low-dose opioid antagonists is not fully known and is the subject of investigation [65]. One explanation describes a sequential action, whereby binding and inhibition first occurs at excitatory receptors, followed by binding at inhibitory receptors. This decrease in excitation facilitates a broader clinical expression of inhibitory function, which potentiates analgesia and reduces adverse effects. For example, with opioid-induced hyperalgesia, ultra-low-dose naltrexone appears to act through excitatory blockade to promote analgesia and tolerability [69; 70].

COMMONLY USED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND ACETAMINOPHEN	
Drug	**Route(s)**
Meloxicam (Anjeso)	IV, PO
Ketorolac (Toradol)	PO, IM, IV, eye drops, nasal spray
Ibuprofen (Motrin, Advil)	PO, IV
Diclofenac (Cataflam, Voltaren)	PO, IM, IV, topical gel
Acetaminophen (Tylenol)	PO, IV, rectal
Naproxen (Aleve, Anaprox)	PO
Celecoxib (Celebrex, Elyxyb)	PO
Aspirin	PO
Source: [74; 75]	*Table 4*

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

How do NSAIDs alleviate pain?

NSAIDs alleviate pain by inhibiting the conversion of arachidonic acid to prostaglandins catalyzed by COX isozymes. Nonselective NSAIDs inhibit COX-1 and COX-2 and include ibuprofen, aspirin, and naproxen. The nonselective action inhibits the formation of both gastroprotective-mediating prostaglandins and pain-promoting prostaglandins, increasing the risk of serious toxicities such as GI ulceration and bleeding. This prompted the development of selective COX-2 inhibitors, which produce fewer GI side effects but are linked with an increased risk of cardio-renal morbidities [71]. To mitigate risk of GI adverse events, proton pump inhibitors are recommended for use in some patients using NSAIDs [72].

Acetaminophen is available over the counter and is also included in combination with many prescription opioids. Analgesia is achieved through central but not peripheral inhibition of prostaglandin. Although effective in mild pain, acetaminophen is not anti-inflammatory. The side-effect profile is relatively benign with intermittent use at recommended labeled dosing, but long-term or high-dose use can be hepatotoxic, and the daily dose should never exceed 4 g. Acetaminophen is recommended over NSAIDs as an analgesic in patients with GI, renal, or cardiovascular comorbidity [73].

While beneficial in the management of pain, some patients with reactive airway disease may develop bronchospasm, although this adverse effect is rare [5]. In addition, prostaglandins are vasodilators. A constitutive level of circulating prostaglandin is necessary to maintain adequate vasodilation in the afferent limb of the glomerulus to assure renal blood flow in the kidney. Overuse of NSAIDs may result in decreased glomerular blood flow, resulting in decreased elimination of toxins from the body and, in especially severe states, renal failure [5]. The most commonly used NSAIDs are listed in ***Table 4*** [74; 75].

LOCAL ANESTHETICS

Local anesthetics prevent the generation and propagation of nerve impulses in response to painful stimuli. The basic chemical structure of a local anesthetic consists of an aromatic ring (which enhances lipid solubility) and an intermediate ester or an amide chain and a terminal amine [8]. As such, all of these agents are classified as either an ester type or an amide type. The type of anesthetic used and the inclusion of a vasoconstrictor (e.g., epinephrine) will influence the duration of action. Certain factors, such as the presence of active infection in the area to be anesthetized, heightened patient anxiety, or inaccurate deposition of the agent, may affect the ability of a local anesthetic to achieve the appropriate level of anesthesia.

The local anesthetics lidocaine and bupivacaine block Na+ influx of voltage-gated ion channels in afferent neuron terminals, inhibiting depolarization and generation of action potentials, resulting in the transmission of fewer nociceptive impulses to the spinal cord. In clinical application, topical lidocaine is used for neuropathic pain to block hyperactive sodium ions in damaged peripheral nerves and inhibit transmission of ectopic impulses to the dorsal horn. This action interferes with peripheral and central sensitization and maladaptive neuroplasticity [71; 76].

Capsaicin defunctionalizes nerve fiber terminals through multiple mechanisms to produce analgesia. The initial reduction in neuronal excitability and responsiveness result from inactivation of voltage-gated sodium channels and direct desensitization of plasma membrane TRPV1 receptors. This is followed by extracellular Ca2+ entry of TRPV1 and release from intracellular stores to overwhelm the TRPV1 receptor intracellular Ca2+ buffering capacity, subsequent activation of calcium-dependent proteases, and cytoskeleton breakdown [77; 78]. The persistent effect involves extracellular Ca2+ entry of TRPV1 and release from intracellular stores to overwhelm TRPV1 receptor intracellular Ca2+ buffering capacity, subsequent activation of calcium-dependent proteases, and

MAXIMUM DOSES OF LOCAL ANESTHETIC[a]					
Local Anesthetic	**Ester or Amide**	**Maximum Dose Per Kilogram Plain**	**Maximum Dose Plain[b]**	**Maximum Dose Per Kilogram with Epinephrine**	**Maximum Dose with Epinephrine[b]**
Bupivacaine (Marcaine)	Amide	2 mg/kg	175 mg	3 mg/kg	225 mg
Levobupivacaine (Chirocaine)	Amide	2 mg/kg	200 mg	3 mg/kg	225 mg
Lidocaine (Xylocaine)	Amide	5 mg/kg	350 mg	7 mg/kg	500 mg
Mepivicaine (Carbocaine)	Amide	5 mg/kg	350 mg	7 mg/kg	500 mg
Ropivacaine (Naropin)	Amide	3 mg/kg	200 mg	3 mg/kg	500 mg
Prilocaine (Citanest)	Amide	6 mg/kg	400 mg	8 mg/kg	250 mg
Procaine (Novacaine)	Ester	7 mg/kg	1,000 mg	10 mg/kg	600 mg
Tetracaine (Amethocaine)	Ester	0.2 mg/kg	20 mg	N/A	1,000 mg
[a]Doses vary by country and institution, familiarize yourself with your local policies regarding maximum doses before administering [b]If administering a local anesthetic to a large patient, stop at the maximum dose, even if the mg/kg dose would exceed it.					
Source: [82; 83; 84]					*Table 5*

cytoskeleton breakdown [77; 78]. Capsaicin is available as a high-potency (8%) patch and as a lower-concentration cream. A single 60-minute application may provide up to 12 weeks of analgesia [76]. Capsaicin may initially cause pain because substance P is released from nociceptive terminals to initiate nociceptive firing. The analgesic response follows as nociceptive terminals desensitize to elevate pain threshold [79].

The use of local anesthesia has become more popular and may be more precisely administered being guided by ultrasonography. Ultrasound technology allows for optimized needle placement, resulting in fewer failed blocks and lower doses. These blocks can be performed before having a procedure performed. When administered before surgery, local anesthetic blocks allow for lower doses of anesthetic agent, along with prolonged postoperative pain relief. In one study, when a local anesthetic block was provided in addition typical analgesic therapy following total knee replacement, morphine doses, pain scores, and nausea were all significantly decreased compared with those who received usual treatment [80].

However, local anesthetics are not without drawbacks, and overdose resulting in local anesthetic systemic toxicity (LAST) is a concern [81]. Because local anesthetics are designed to cross phospholipid membranes, they easily enter the brain and heart, where the blockade of ion channels can have adverse effects. Normally, the first symptoms in patients who are conscious are a metallic taste and/or ringing in their ears (tinnitus). If left untreated, this can progress to excitatory symptoms, followed by drowsiness, coma, and even death [81; 82]. ***Table 5*** provides key information about commonly used local anesthetics, including maximum doses.

The closer to the vasculature the site of injection is, the more likely that the local anesthetic will undergo rapid vascular uptake and result in adverse effects. Mixing the agent with epinephrine, a vasoconstrictor, decreases uptake, thus prolonging the anesthetic effect and decreasing the likelihood of complications. As this is the case, it is possible to give more local anesthetic when it is mixed with epinephrine [82; 83; 84].

In the event of an accidental overdose, there is a specific protocol for treatment [81; 82]. As soon as LAST is detected, the patient should be administered an IV bolus injection of 20% lipid emulsion 1.5 mL/kg^{-1} over one minute. An infusion of 20% lipid emulsion should be started at a dose of 15 mL/kg^{-1}/hour. If after five minutes cardiovascular stability is not restored or the patient further deteriorates, a maximum of two repeat boluses may be administered, with five minutes between injections. At the same time, the infusion rate may be doubled. The infusion should continue until the patient has stabilized or the maximum dose of emulsion (12 mL/kg^{-1})

has been given. The use of lipids to rescue these patients is a relatively new development, so review is important for those in clinical areas with high use of local anesthetics [85].

CALCIUM CHANNEL BLOCKERS

The gabapentinoids, gabapentin and pregabalin, are widely used in the management of both postoperative and chronic pain relief. Their names may give the impression they interact with gamma-amino butyric acid (GABA), but this is not the case [86; 87]. Gabapentin and pregabalin are anticonvulsants that are also effective in a wide range of neuropathic pain conditions. Their mechanism of action involves selective binding to and blockade of the α2δ1 subunit of voltage-gated calcium channel in various brain regions and the superficial dorsal spine. This inhibits the release of glutamate, norepinephrine, and substance P to decrease spinal cord levels of neurotransmitters and neuropeptides [76; 88; 89]. The binding affinity of pregabalin for the calcium channel α2δ1 subunit is six times greater than gabapentin, which is reflected in the greater efficacy of pregabalin at lower doses. Because gabapentin possesses a shorter half-life and nonlinear absorption, pregabalin is easier to titrate and better tolerated [89].

While having a long history in the treatment of chronic pain, the use of these agents to prevent postsurgical pain is relatively new. In one study of 90 women scheduled for abdominal hysterectomy, a control group was compared to groups receiving either 300 mg pregabalin or 900 mg gabapentin administered one to two hours prior to surgery [86]. The average time until first request for analgesia was 31 minutes in the pregabalin group, 16 minutes in the gabapentin group, and 7 minutes in the control group. There was no difference in demographic variables, including length of surgery, across the three groups. In this case, preoperative administration of a gabapentinoid was shown effective in lengthening the duration of analgesia [86].

The locus coeruleus is activated during normal responses to painful stimuli. However, in patients with chronic pain, stimuli inhibit rather than activating the locus coeruleus, dampening analgesic response [90]. When gabapentin is administered to these patients, glutamate is released in the brain, which in turn stimulates the locus coeruleus, restoring its analgesic function [91].

ALPHA-ADRENERGIC AGONISTS

While more commonly associated with the autonomic nervous system and its functions, alpha-adrenergic agonists can also function in the relief of pain, as well as decreasing the sympathetic side effects which accompany pain, including hypertension and tachycardia. Antinociceptive activity of the α-2 adrenoceptor agonists clonidine and tizanidine includes modulating dorsal horn neuron function and norepinephrine and 5-HT release, potentiating mu-opioid receptors, and decreasing neuron excitability through calcium channel modulation [92]. Clonidine is available as a transdermal patch for use in neuropathic pain states. Local use enhances release of endogenous enkephalin-like substances. Intrathecal or epidural administration with opioids and/or local anesthetics is favored in treating neuropathic pain because the synergistic effect improves pain control. Tizanidine is used as a muscle relaxant and antispasticity agent; its use in the management of musculoskeletal pain is off label [76; 79].

Dexmedetomidine was originally approved as a short-term sedative analgesic for mechanically ventilated patients in the intensive care unit [93]. Dexmedetomidine is far more selective as an alpha-adrenergic agonist and has the same central action around the locus coeruleus [93]. As time passed since its introduction, the use of dexmedetomidine has increased, especially among patients with comorbidities (e.g., heart and vascular disease, morbid obesity). Its cardiovascular stability, along with its minimal effect on respiratory drive after the infusion is terminated, have made this agent popular in both the intensive care unit and the operating room. Aside from its use as a sedative or aesthetic agent, use of dexmedetomidine has been explored in patients with refractory end-of-life pain. In a case study, a male patient, 58 years of age, with chronic pancreatitis secondary to alcoholism reported inadequate pain relief despite receiving a combination of oxycodone, nortriptyline, and lorazepam. Increased inpatient intravenous opioids and ketamine still brought the patient no relief, and dexmedetomidine was attempted as a last resort. An infusion of dexmedetomidine brought the patient's pain under greater control, to the extent that he was able to sit in a recliner and visit with family [94]. Based on this and other reports, dexmedetomidine is being explored as a possible option in palliative care.

Alpha-adrenergic agonists are also found in the area of the brain where projections from the locus coeruleus inhibit an inhibitory portion of the brain responsible for arousal. When alpha-adrenergic agonists act in this area of the brain, they block the ability of the nerves projecting from the locus coeruleus to inhibit the second-order neuron. Thus, these agents, in sufficient doses, render the patient somewhat drowsy [95]. This is important to remember, as the drowsiness associated with the original alpha-adrenergic agonists made their use problematic.

ANESTHETIC DRUGS

Anesthetics are powerful agents typically used in the operating room to reduce the capacity for consciousness and diminish the pain associated with surgery. Two examples are ketamine and nitrous oxide. These agents are quite different; the first is an injectable dissociative anesthetic with variable effects depending on the dose, and the second is an inhaled vapor with profound analgesic effects [18; 96; 97].

Ketamine

Ketamine is a phencyclidine anesthetic given parenterally, neuraxially, nasally, transdermally or orally in subanesthetic doses to alleviate a variety of pain conditions, including severe acute pain, chronic or neuropathic pain, and opioid tolerance [79]. The mechanism of analgesic effect primarily involves NMDA receptor inhibition. Thus, patients with NMDA-mediated central sensitization are likely to realize significant benefit from treatment with ketamine. Ketamine also has activity on nicotinic, muscarinic, and opioid receptors and exerts both anti-nociceptive and anti-hyperalgesic effects, with the latter produced at lower dose ranges [98].

Ketamine is one of very few therapies demonstrating substantial and durable pain reduction of treatment-refractory chronic regional pain syndrome [99]. Potentially distressing adverse reactions (e.g., hallucinations, disturbing dreams, out-of-body experiences) and unwanted changes in mood, perception, and intellectual performance have limited its clinical use in pain control. However, trials have effectively controlled these side effects with high-dose co-administration of midazolam or lorazepam combined with either clonidine or ondansetron [100; 101].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists recommend that subanesthetic ketamine infusions be considered for patients undergoing painful surgery and patients undergoing surgery who are opioid-dependent or opioid-tolerant.

(https://rapm.bmj.com/content/rapm/43/5/456.full.pdf. Last accessed October 20, 2022.)

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

Ketamine, however, also has its down sides. One of the most concerning is the formation of psychotomimetic behaviors, and the presence of hallucinatory phenomena after its administration. Fortunately, these are dose dependent in nature and rarely occur at the doses required to treat pain [102; 103]. It has also become a drug of abuse and misuse. Most notoriously, ketamine became known as a "date-rape drug," because it was administered in drinks to unknowing victims who were subsequently sexually assaulted by their predators. Because ketamine causes amnesia, victims have little or no memory of what occurred to them, although they often experienced after-effects, such as pain. As a result of this growing criminal use, Congress passed the Drug-Induced Rape Prevention and Punishment Act of 1996. During this period and the decade following, there was increased awareness of the dangers of ketamine and other drugs that were used in a similar manner, such as flunitrazepam (Rohypnol) and gamma hydroxybutyric acid (GHB) [104]. As a result, ketamine developed a stigma, and this negative view may persist in many minds.

Today, ketamine is increasingly being used to treat patients with treatment-refractory major depressive disorder, which frequently co-occurs in those with chronic pain. The agent appears to actually increase the size and volume of the hippocampus, thus treating the cause of depression [18; 105]. In patients who are imminently suicidal, short-duration doses have been found to significantly reduce suicidal ideation [106].

Nitrous Oxide

Nitrous oxide (chemical formula N_2O) is a component familiar to many, as it is commonly used today to facilitate comfort and address anxiety in dental settings. Historically, it has been used in both dental and medical interventions. Nitrous oxide is a compressed gas and is one of the oldest anesthetic agents in use, with its origins dating back to 1772 [96]. Unlike the inhaled hydrocarbons commonly used as part of a general anesthetic, nitrous oxide has potent analgesic properties. It is thought that nitrous oxide works to enhance the endogenous descending pathways to the alpha-2 and GABA-A neurons in the spinal cord, decreasing the ability of the second-order neurons to depolarize and carry painful stimuli to the brain. When administering nitrous oxide, it is crucial to ensure that oxygen is added to prevent the administration of 100% nitrous oxide to the patient, which would rapidly result in hypoxia and death. All certified nitrous oxide delivery devices have lockout systems to preclude this from happening.

Nitrous oxide is given as a percentage of total inhaled gas flow. The route of administration is inhalation via a mask secured to the patient's nose. For analgesic purposes, the concentration is typically 50% to 70% nitrous oxide with oxygen. Onset of action can occur in as quickly as 30 seconds, with the peak effects seen in five minutes or less. Nitrous oxide diffuses into the alveolus very quickly, accounting for its rapid uptake and circulation to the brain. Nitrous oxide is not metabolized in the body. It is eliminated via respiration within minutes after 100% oxygen is inhaled at the conclusion of the intervention [107].

Repeated doses can be problematic, as extended use of nitrous oxide has been linked to vitamin B12 deficiency [108]. As such, serum vitamin B12 level may need to be measured before and after treatment. Of more concern is the continuous exposure of hospital or clinic staff to chronic low doses of nitrous oxide [96]. Limits of nitrous oxide in the ambient environment are strict and tightly regulated by the by the National Institute for Occupational Safety and Health (NIOSH) [109]. The maximum recommended level of exposure is 25 parts per million per procedure over an eight-hour period [109]. Sufficient fresh air flow in the procedural area is required, along with a secure fitting of the delivery mask. Nitrous is highly diffusible and will enter into closed spaces very easily.

For a short period, prehospital paramedics were using 50% nitrous oxide as an analgesic during stabilization and transport of patients to the hospital; however, this use did not gain traction, and nitrous oxide is not a universal requirement for emergency medical vehicles [110].

As with other analgesics, nitrous oxide tanks should be secured, as there is a potential for abuse and diversion, particularly in locations in which small tanks are used and can easily be removed and transported. Nitrous oxide also enhances combustion, so care should be taken when using it around lasers and electric cautery. This agent is associated with increased rates of postoperative nausea and vomiting, but the risk decreases with the duration of administration.

ANTIDEPRESSANTS

Antidepressants, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), are now a mainstay of pain management. Each of these agents increases the circulating level of neurotransmitters (e.g., norepinephrine, serotonin, dopamine, acetylcholine) in the brain [111]. Note that while these agents have been used for pain management in some cases for decades, this use is often still considered to be off label [111].

Antidepressants act in the brain at the periaqueductal grey, the amygdala, the prefrontal cortex, the thalamus, and the somatosensory cortex, among other places [112]. However, they also work in the periphery, primarily by blocking voltage-gated Ca2+ channels, especially in the dorsal horn of the spinal cord. As discussed, when Ca2+ cannot enter a neuron, then exocytosis of neurotransmitters onto the receptors of the next order neuron cannot take place. This, in turn, blocks the transmission of the action potential and thus the painful stimulus [112]. Antidepressants also increase the effectiveness of endogenous GABA, an inhibitory neurotransmitter. The various antidepressant classes have different effects on pain pathways.

Tricyclic Antidepressants

TCAs are widely used in neuropathic pain. A TCA's mechanism involves blocking pre-synaptic reuptake of norepinephrine and serotonin; inhibition of neuronal membrane ion channels by reducing neuronal influx of calcium or sodium ions; and activity with adenosine and NMDA receptors [79]. A primary site of analgesic action is the descending modulatory pathway, where monoamine reuptake inhibition elevates norepinephrine and serotonin levels to enhance endogenous nociceptive inhibition. The secondary amines nortriptyline and desipramine are favored over the tertiary amines amitriptyline and imipramine due to more benign side effect profiles [113; 114]. Amitriptyline is often the treatment of choice for neuropathic pain [79]. Unfortunately, TCAs have numerous side effects, including xerostomia (dry mouth), tachycardia, urinary retention, and drowsiness [111].

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs were designed to treat depression by increasing the amount of circulating serotonin in the brain. This increased amount of serotonin results in down-regulation (decreased number and density) of the 5-HT receptors, which allows for an increased firing of serotonergic neurons in the brain [111]. Compared with the other antidepressants, SSRIs have limited utility in treating pain and are seldom prescribed for this purpose.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

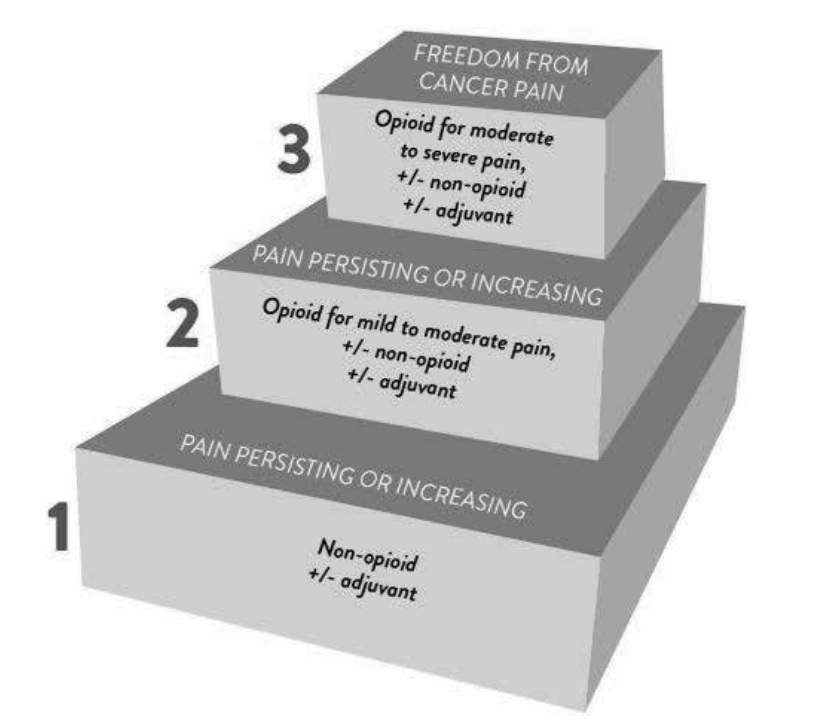
The dual serotonergic and noradrenergic re-uptake inhibitors (SNRIs) duloxetine, venlafaxine, and milnacipran are widely used in the treatment of neuropathic pain conditions. Duloxetine is used in painful diabetic neuropathy, with demonstrated efficacy at 60–120 mg/day. Venlafaxine behaves like a SSRI at doses of ≤150 mg/day and like an SNRI at doses >150 mg/day; a dose ≥150 mg/day is often necessary to achieve pain control [76]. Of the three available SNRIs, milnacipran has the greatest affinity for norepinephrine, duloxetine has the greatest potency in blocking serotonin, and venlafaxine selectively binds to the serotonin but not the norepinephrine transporter [115].

SNRIs are better tolerated than TCAs because they lack affinity for cholinergic, histaminic, and adrenergic receptors [89]. The anti-nociceptive effect of the SNRIs duloxetine and milnacipran primarily involves increasing serotonin and norepinephrine concentrations in descending inhibitory pain pathways, which enhances the suppression of afferent spinal inputs and reduce pain [113].

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs work by irreversibly degrading the monoamine oxidase enzymes responsible for degrading norepinephrine. These agents, however, have numerous side effects, including hypotension, dizziness, headache, xerostomia, palpitations, and weight gain [116]. One potential issue is the interaction of MAOIs with tyramine and tryptophan. With oral ingestion, MAOIs inhibit the catabolism of dietary amines. When foods containing tyramine (e.g., red wine, aged cheeses and meats, soy sauce, tap beer, smoked or pickled fish, sauerkraut) are consumed, the individual may suffer from hypertensive crisis. If foods containing tryptophan (e.g., milk, poultry, tofu, nuts, seeds) are consumed, hyperserotonemia may result. The amount required to cause a reaction varies greatly from individual to individual and depends on the degree of inhibition, which in turn depends on dosage and selectivity. These side effects limit the utility of MAOIs in pain management [116; 117].

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



Source: [118] *Figure 7*

USING MULTIMODAL PAIN THERAPY: EXAMPLES FROM THE PROFESSIONAL LITERATURE

Which agents are appropriate for mild pain according to the WHO analgesic ladder?

With a clear understanding of the pharmacologic tools available to help manage pain, clinicians can begin the process of creating and supporting a pain management plan for each patient's unique needs. The World Health Organization (WHO) analgesic ladder, introduced in 1986 and disseminated worldwide, remains recognized as a useful educational tool but not as a strict protocol for the treatment of pain. It is intended to be used only as a general guide to pain management [118]. The three-step analgesic ladder originally intended for management of cancer-related pain designates the type of analgesic agent based on the severity of pain (***Figure 7***) [118]. Step 1 of the WHO ladder involves the use of nonopioid analgesics, with or without an adjuvant (co-analgesic) 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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Orthopaedic Trauma Association Musculoskeletal Pain Task Force recommends the use of multimodal analgesia (MMA) as opposed to opioid monotherapy for pain control. MMA may include NSAIDs, acetaminophen, gabapentinoids, and immediate-release opioids.

(https://journals.lww.com/jorthotrauma/fulltext/2019/05000/clinical_practice_guidelines_for_pain_management.11.aspx. Last accessed October 20, 2022.)

Strength of Recommendation/Level of Evidence: Strong recommendation, moderate-quality evidence

The pharmacologic treatment of pain involves selecting the right drug(s) at the right dose, frequency, and route, and managing side effects As with any healthcare action, it is vital to assess patients and to attempt to identify underlying cause(s) prior to the initiation of treatment. Specific evaluative steps should be taken to determine the nature of a patient's pain and to assess the possibility and impact of adverse effects. The WHO ladder is also accompanied by guiding principles [118; 119]:

- Believe the patient's report of pain. This sounds simple, but it can be difficult for clinicians to avoid becoming jaded over time, especially if they care for patients in drug-seeking environments.
- Initiate discussions of pain by asking specific questions and observing behaviors, such as groaning, a furrowed brow, and elevations in pulse or blood pressure.
- Get the facts about the pain. A helpful mnemonic taught to prehospital providers is OPQRST:
  - **O**nset
  - **P**rovocation or palliation
  - **Q**uality
  - **R**egion (of the body) and radiation
  - **S**everity
  - **T**iming
- Evaluate the patient's psychological state.
- Perform a detailed physical assessment.
- Obtain further testing if one is not sure, including radiologic and laboratory tests.

With these data, the provider is now ready to plan and carry out multimodal analgesia. The following examples are presented as examples of the applicability and efficacy of multimodal approaches in research studies.

EXAMPLE 1

In one study, 150 patients were assessed for breakthrough pain following shoulder surgery [120]. The first group (75 patients) was given a standard course of opioid and acetaminophen combination (hydrocodone 10 mg/acetaminophen 325 mg) or 5–10 mg of oxycodone every 4 hours [120]. They also received a single-shot interscalene regional nerve block with 0.5% ropivacaine (local anesthetic). Finally, intravenous hydromorphone was also available as a rescue intervention. In the second multimodal group (75 patients), patients received preoperative 300 mg celecoxib, 600 mg gabapentin, and 1,000 mg acetaminophen. They also received the same regional nerve block. For postoperative pain, group 2 received naproxen 500 mg every 12 hours with food, gabapentin 300 mg every 8 hours, acetaminophen 1,000 mg orally or IV, followed by 500 mg orally every 6 hours. For breakthrough pain, this group could receive 5–10 mg of hydrocodone, as needed [120]. There were no differences in the demographic makeup of the two groups. On postoperative day zero (the day of surgery), pain scores were significantly lower in group 2 when compared with the standard group [120]. On postoperative days 1 and 2, the multimodal group continued to have lower scores, but the differences were not statistically significant. Opioid consumption, measured in mg of morphine equivalent, were significantly decreased in the multimodal group on all three measurement days. The length of in-patient stay for the multimodal group was significantly lower (1.4 days +/- 0.7) compared with the opioid group (1.9 days +/- 1.1 days), resulting in an average cost savings of $1,000 for the multimodal group [120].

EXAMPLE 2

In this study, patients with unresectable hepatocellular carcinoma received transarterial chemoembolization, a primary palliative treatment [121]. This group of patients have chronic pain, and transarterial puncture is associated with a lower degree of surgical pain. In this example, patients are provided with a therapeutic procedure that can partially mitigate the pain and then supported with other analgesic agents. The study involved a total of 84 patients, with half assigned to the multimodal group and the other half assigned as a control group [121].

The multimodal group received 40 mg intravenous parecoxib sodium 30 minutes before the beginning of the procedure. In the control group, patients received 5 mg dezocine (an opioid) preintervention. All patients underwent a percutaneous puncture of the femoral artery after having the site numbed with 10 mL 2% lidocaine (total dose: 200 mg lidocaine). After the procedure, the multimodal group was provided with a patient-controlled analgesia pump; the intravenous pain solution was a combination of sufentanil 100 mcg and dexmedetomidine 200 mcg diluted in 100 mL normal saline. The pump was programmed to provide 2 mL of the solution (2 mcg of sufentanil and 4 mcg of dexmedetomidine) as a first dose, a background infusion rate of 2 mL/hour, and 2 mL bolus doses on demand with a lockout period of 5 minutes (maximum: about 12 doses per hour) [121]. This sufentanil dose is below the usual administered for general anesthesia. The dose of dexmedetomidine tracks closely to that needed for intensive care unit (ICU) sedation [122]. Using the two agents together provides central sedation via two routes (one from the opioid, the other from the alpha-2 agonist) while simultaneous providing pain relief throughout the spinal cord.

The control group received 100 mg flurbiprofen (an NSAID) every 12 hours for the first 48 hours postprocedure and 100 mg tramadol (a combination opioid agonist and SSRI) for breakthrough pain [121]. Mean visual analog scale (VAS) pain scores were measured at 0, 2, 4, 6, 12, 24, and 48 hours after the procedure. Patients in the multimodal group had statistically lower VAS pain scores at 0, 2, 4, 6, and 12 hours after the procedure. From a qualitative viewpoint, more than 95% of the multimodal patients reported good satisfaction with their pain control. In the control group, 69% reported good satisfaction, and 11.9% reported a "fairly bad experience" of pain control [121].

CASE STUDIES

The following case examples detail how specific patients were cared for and the logic behind analgesic decision-making. This should serve as a starting point that will result in further self-exploration.

CASE STUDY 1

Note that this first example is directed toward the management of acute pain, and the interventions take place in the hospital or surgical facility. Many people, however, suffer chronic pain and self-medicate to treat it. In either case, multimodal analgesic techniques may still be used.

Patient A is scheduled to receive a total knee replacement arthroplasty [123]. Preoperatively, the patient is counseled regarding what pain might be expected with this surgery and how it might be treated. After the patient has been worked up, she receives acetaminophen 1,000 mg and celecoxib 400 mg by mouth [123]. This is referred to as pre-emptive analgesia and is done to ensure that the processes needed to, in this case, block the inflammatory effects of prostaglandins released by surgery are beginning to function prior to initiation of surgery [124].

The patient is next taken to a block room and receives local anesthesia in the knee area. In other cases, surgeons may inject local anesthesia at the end of the case.

During surgery, the patient receives a spinal anesthetic with local anesthesia. The anesthetic is placed in the subarachnoid space with local anesthesia. Because the local anesthetic is deposited so close to the nerves, a very small dose can provide several hours of anesthesia.

After surgery, the patient begins to receive several pain management interventions almost immediately, the first of which is cryotherapy. Next, as the body is responding with an inflammatory process releasing prostaglandins and other neurotransmitters in response to an injury (albeit a therapeutic one), the patient receives 1,000 mg of acetaminophen every six hours around the clock [123]. This patient tolerated oral analgesics, but acetaminophen can be administered intravenously for those experiencing problems with postoperative nausea and vomiting. The patient is also started on celecoxib 200 mg twice per day for up to five days. At this point, Patient A begins to question the need for NSAIDs when she is "having no pain." The nurse describes the importance of reducing inflammation in simple terms. He also explains that the long-acting local anesthetics will wear off over time, and it is important to pre-emptively control pain. Despite these interventions, some patients will experience postoperative pain exceeding the ability of NSAIDs to mitigate. For these individuals, an opioid rescue (oxycodone tablet 5 mg and intravenous hydromorphone 0.2 mg) every four hours as needed will help bring most pain under control [123].

CASE STUDY 2

Patient B is an elderly man (85 years of age) with chronic and unremitting pain. Initial assessment of the patient's pain remains important. While Patient B is experiencing chronic pain, he may also have an unresolved injury or illness causing the pain. In such a case, treatment of the underlying pathology could result in mitigation of pain [125].

Therapeutic intervention for Patient B begins with the use of NSAIDs and COX-2 inhibitors, especially for a pathology such as osteoarthritis, which is quite common among the elderly. As part of the assessment in this example, remember that elderly patients tend to have less total body water, decreased muscle tone, increased fat stores, and normal age-related degeneration of the liver and kidneys [125]. Unless there are other factors (e.g., current opioid use disorder), the best approach is to start low and titrate slow—use the smallest dose possible and increase it incrementally in small doses. The elderly often experience depression as part of their chronic pain; this should not be surprising, as living with unresolved pain each day can be psychologically taxing. Antidepressant agents, such as an SNRI, may be added to the care plan, with the caveat that there is an increased risk of falling [126]. Gabapentinoids may replace the antidepressant if the pain is neuropathic in nature, and opioids can be added on an as needed basis, though it is crucial to start at the low end of the dosing scale [126]. This follows the WHO guidance of NSAIDs first and opioids last.

While it is fine to conduct mental exercises with imaginary patients, the guiding standard for the clinician is whether the analgesia works. This is an important question, so at this point a small number of studies will be presented for your review.

CASE STUDY 3

In this example, Patient C, a man 71 years of age, presents with a severe case of recurring right sciatic pain [127]. On history and examination, the patient describes persistent pain at a scale of 8 out of 10, starting in the lumbar area of his back and running down his right thigh. Further comorbidities include chronic obstructive pulmonary disease (COPD) and previous right-side neck surgery to remove a buccal tumor. An MRI is ordered, revealing spondylolisthesis, which causes pain in lower back or legs at L5–S1, and the patient was also identified as having degenerative disk disease at L5–S1, and disk herniations at L3–L4, L4–L5, and L5–S1 [127]. This patient is taking 20 mg oxycodone daily in an effort to mitigate his pain.

The pain control team begins to titrate back the patient's oxycodone with tramadol and offers surgical decompression. After the patient refuses surgical intervention, the team decides to administer an ultrasound-guided caudal epidural steroid injection of triamcinolone 40 mg and 2% lidocaine 20 mg (local anesthetic) mixed in 12 mL of normal saline [127]. The mixture of normal saline is necessary because epidural injections require a greater volume to ensure the nerve roots are all bathed in the solution.

After the injection, Patient C's walking distance increases from 20 meters to 200 meters, and his pain score reduces from 10 to 7. One month later, the patient remains improved, but the team decides to add 5 mg oxycodone (25% of the original dose) as needed back to the patient's regimen. By his third month post procedure, the patient's pain score has dropped to 2. The multimodal plan, when compared with the singular large dose opioid plan, proved to be life-changing for this patient [127].

CONCLUSION

It is important to remember that pain is an adaptive mechanism to protect the body from comprise and prevent future involvement with the pain-generating stimulus. Modern medicine has many options to identify causes of pain and to treat the underlying problem while providing relief from pain [27]. However, pain management is an elusive goal for many patients. In the 1990s and 2000s, in an effort to address this problem, opioids were prescribed more freely. Unfortunately, this corresponded with an increase in opioid misuse and use disorder. In order to both assure that patient pain is managed and reduce the risks associated with opioids, numerous types of analgesics and techniques can be carefully mixed to decrease side effects while optimizing pain control.

It is crucial for all practitioners to carefully evaluate patients who are in pain to determine the extent to which the pain can be repaired or relieved. All available tools should be explored to treat the causes of pain at the local peripheral levels, the spinal cord levels, and the brain processing level. Familiarity with the pathophysiology of pain can guide good pharmacologic decisions and restore the patient's quality of life.

Customer Information/Evaluation insert located between pages 44–45.

Pathophysiology: Muscles, Joints, and Connective Tissues

Includes 8 Pharmacotherapeutic/Pharmacology Hours

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

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

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

1. Describe the structure and function of the muscles, joints, and connective tissues.
2. Discuss the pathophysiologic influences that may affect the muscles, joints, and connective tissues.
3. Outline the role of subjective data in completing a full nursing assessment of the muscles, joints, and connective tissues.
4. Describe objective data compiled during a nursing assessment of the muscles, joints, and connective tissues.
5. Identify imaging and diagnostic studies used in the identification and classification of muscles, joints, and connective tissues.
6. Discuss genetic conditions manifesting in the muscles and connective tissues.
7. Evaluate the presentation and differential diagnosis of inflammatory muscle and connective tissue disorders.
8. Describe the clinical presentation and treatment of immunologic disorders of the muscles and connective tissues.
9. Review the assessment and treatment of traumatic conditions of the muscles and connective tissue.
10. Discuss disorders of the joints with multifactorial origin.
11. Analyze the manifestations and therapeutic approaches for degenerative joint diseases.
12. Outline the presentation, treatment, and nursing considerations for patients with immunologic joint conditions, such as rheumatoid arthritis.
13. Compare and contrast the various joint diseases with an infectious origin.
14. Describe cancers of the joints, muscle, and connective tissues.
15. Evaluate the appropriate assessment and management of traumatic joint injuries.

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

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

Division Planner
Sharon Cannon, RN, EdD, ANEF

Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure

The division planner and director have 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 15 ANCC contact hours.

NetCE designates this continuing education activity for 8 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 07/29/2025); 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 12/31/2023); 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/MI23**.
- 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.

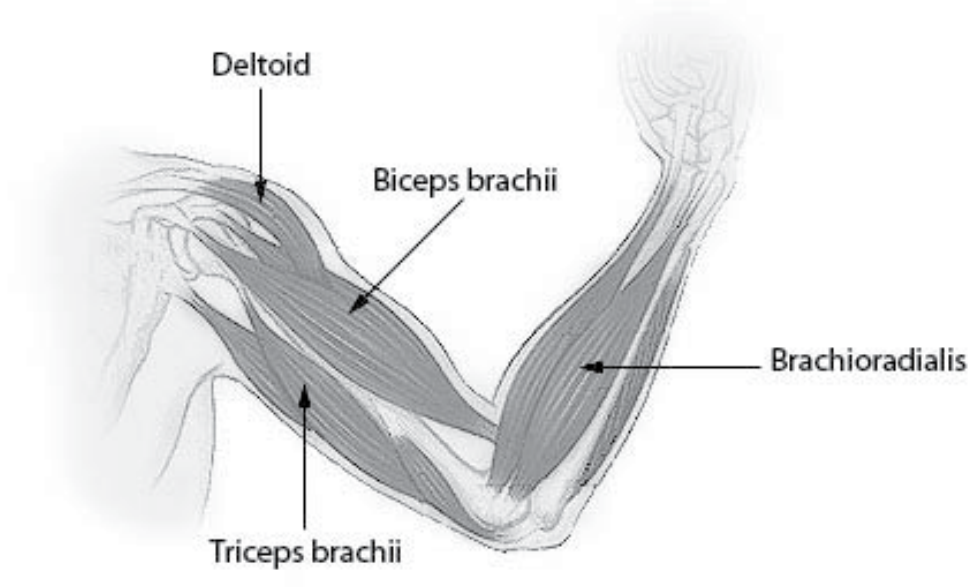
INTRODUCTION

Along with the bones, muscles, ligaments, tendons, cartilage, and the joints provide the body with a supportive framework that allows flexibility of movement and protects the internal organs. These tissues also give shape to the body and act partially as a storage and supply area for minerals. When the tissues are unable to perform their usual functions because of trauma or rheumatic, inflammatory, or degenerative conditions, a person's physical support, protection, mobility, and ability to carry out activities of daily living are affected.

MUSCLES, JOINTS, AND CONNECTIVE TISSUES: STRUCTURAL AND FUNCTIONAL INTER-RELATIONSHIPS

The musculoskeletal system is composed of many anatomical structures that work together to produce movement, support, and protection of the body and its parts. These structures include the bones and joints of the skeletal system; the skeletal muscles; and the tendons, ligaments, and other elements that connect these tissues. This course will focus on the components of the system excluding the bones.

MUSCLES OF THE UPPER EXTREMITY



Source: National Cancer Institute *Figure 1*

STRUCTURE AND FUNCTION OF SKELETAL MUSCLES

Contraction of skeletal muscle is its primary function, with the intent of moving the bones of the skeleton. Bone serves as a lever, the joint serves as a fulcrum upon which the bone pivots, and the muscle provides the force that moves the lever. A second function of skeletal muscles is maintenance of body posture. A residual amount of contraction in the muscles, known as muscle tone, serves to keep the body erect. A third function is heat production. To combat hypothermia, small, rapid contractions of skeletal muscle (shivering) produce body heat [1].

Producing Skeletal Movement

A typical skeletal muscle is anchored at each end to bone by a tendon. The muscle often stretches across a joint. The muscle's attachment to the less movable bone is called its origin, and its attachment to the more movable bone is called its insertion. When the muscle contracts, one bone remains more or less stationary, forcing the other bone to move [2].

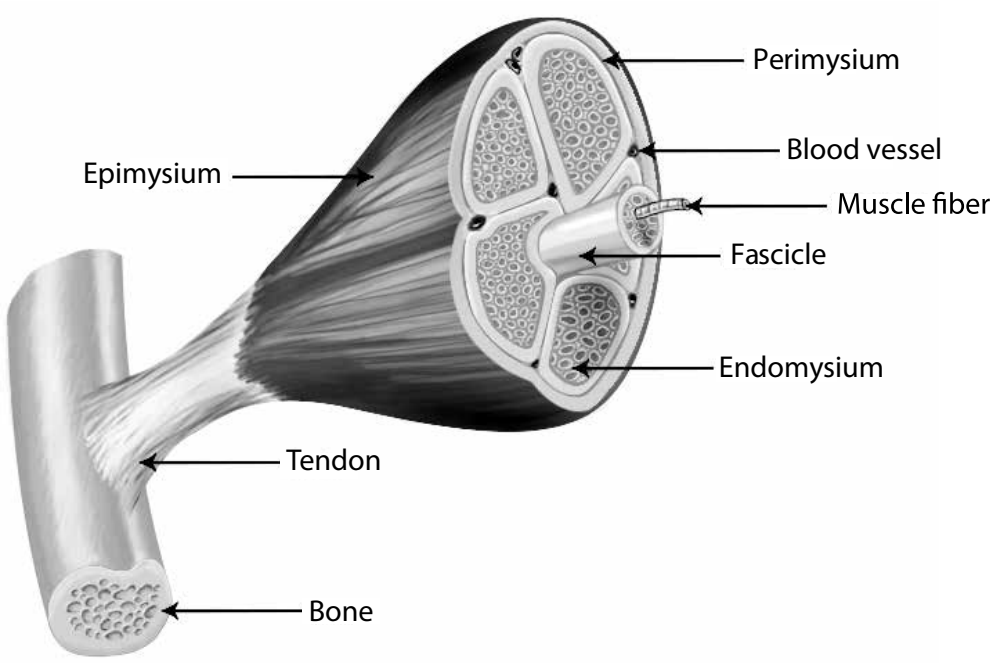
Most skeletal muscles work in groups. The prime mover is the muscle that contracts to produce the movement. Synergists are muscles that work with prime movers to assist in performing the movement. Antagonists are muscles that work opposite prime movers by relaxing during their contraction or by producing an opposite effect. For example, the arm is flexed by contracting the biceps brachia, which acts as the prime mover; at the same time, the triceps brachii on the opposite side of the humorous relaxes, acting as the antagonist (***Figure 1***). When the arm is extended, the roles of the biceps and triceps are reversed. An isotonic contraction occurs when a muscle shortens during contraction. An isometric contraction occurs when a muscle becomes tense while remaining the same length [2].

Skeletal Muscle Structure

Muscle—skeletal, smooth, and cardiac—is made up of elongated cells called fibers (***Figure 2***). The fibers contain strands of contractile protein called myofibrils that extend the length of the cell. At the neuromuscular junction, the chemical acetylcholine creates the stimulus for muscle-nerve conduction of movement. Skeletal muscle fibers are multinucleated, and their myofibrils have striations: light and dark bands perpendicular to the long axis of the cell. The dark bands (anisotropic or A strands) are composed of the protein myosin, and the light bands (isotropic or I strands) contain the protein actin. A sense fibrous line called the Z line crosses the center of each I band and divides the myofibrils into a series of repeating units called sarcomeres. The bands are visible to the unaided eye and give skeletal muscle its alternate name: striated muscle. Smooth and cardiac muscles are made up of uninucleated cells. They further differ from skeletal muscle in that smooth muscle has tapered fibers with no striations and cardiac muscle has branched fibers [2].

Muscle fibers are bound together by connective tissue into small bundles called fascicles, visible to the unaided eye. Fascicles are bound into larger bundles, which collectively form the muscle. The entire muscle is enclosed by a connective tissue covering called the epimysium, which is continuous with the connective tissue surrounding the fascicles and fibers. The epimysium is also continuous with the tendon or other connective tissue at attachment of muscle to bone. Thus, there is a continuous network of connective tissue extending from

STRUCTURE OF A SKELETAL MUSCLE



Source: National Cancer Institute *Figure 2*

individual muscle fibers to the tendon. Blood vessels and nerves penetrate the connective tissue of the muscle, so muscle has sufficient blood supply to furnish nutrients and oxygen and to remove the waste products of muscular activity [2; 3].

OTHER CONNECTIVE TISSUE STRUCTURES

What is a bursa?

Tendons are cords of connective tissue that attach muscles to the periosteum of the bones. During muscle contraction, the muscle pulls the tendon, which pulls the bone to which it is attached, producing movement. Flexion, extension, adduction, and abduction are normal movements of muscles and bones.

Ligaments, made of fibrous connective tissue, connect bones to one another. They have the ability to stretch while providing stability. The knee joint, for example, is stabilized by ligaments, such as the anterior and posterior cruciate ligaments, which bind the femur to the tibia within the joint capsule, and by the medial and lateral collateral ligaments outside the joint capsule [4].

A bursa is a fluid-filled sac that facilities motion of structures that move against each other. It can be found between skin and bone, muscle and bone, tendons and bone, ligaments and bone, and between muscles. The bursae function as padding between structures to reduce friction caused by moving parts [4].

Connective tissue, in the broad sense of the term, include all tissues made up of cells in a matrix, including bone, cartilage, blood, and lymph. However, the term is used in a more limited sense when discussing diseases of the connective tissues. In this sense, connective tissue means the binding and covering tissues of the body, inducing tendons, ligaments, muscle fascia, and the deep layers of the skin. This kind of connective tissue (sometimes called "connective tissue proper") is essential in holding together all the components of the musculoskeletal system. Also included are intervertebral discs (or intervertebral fibrocartilage), which serve as "shock absorbers" to cushion the spine and help it move [4; 5].

THE PROCESS OF SKELETAL MUSCLE CONTRACTION

Skeletal muscle contraction begins with the stimulus of a muscle fiber by a motor neuron. Every motor neuron ends in many fine branches, with each branch connecting with an individual muscle fiber. A group of muscle fibers activated by a single motor neuron is called a motor unit. Motor units range in size from a single muscle fiber in muscles controlling fine, skilled movements to over one hundred fibers in muscles involved in gross movements. All the fibers of a motor unit contract together when the neuron is stimulated [6]. There are two types of motor units in skeletal muscle, Type 1 and Type

2. Type 1 has a small cell diameter, with a high excitability and fast conduction velocity. It has an oxidative profile with moderate contraction velocity and low fatigability. There are few muscle fibers of this type. In contrast, Type 2 has a large cell diameter, with low excitability but a very fast conduction velocity. Type 2 fibers are numerous in quantity, with a glycolytic profile and high fatigability. The small motor units, with Type 1 (also known as "slow-twitch") fibers, are recruited first and are frequently active, while the large motor units, with Type 2 ("fast-twitch") fibers, are used infrequently, in forceful contractions. Maximal efforts, in which fast motor units are recruited, cannot be sustained because of the rapid depletion of glycogen.

When a nerve impulse reaches the end of a motor neuron, small vesicles in the ends of the nerve branches release acetylcholine, which increases the permeability of the muscle cell and causes an influx of calcium ions into the cell. The calcium ions cause structural changes in the myofilaments that allow them to slide past each other, causing contraction. The structural changes also allow breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) to provide energy for the contraction. The muscle relaxes as a result of the action of the enzyme cholinesterase, which breaks down acetylcholine, allowing the muscle to return to its resting state [6].

At the beginning of muscle contraction, ATP is formed from creatine phosphate stored in the muscle. The supply of creatine phosphate is limited, however, and even with mild muscle activity, additional ATP must be formed from ADP. The energy for forming this additional ATP is supplied by respiration. The first step in respiration is glycolysis, or anaerobic respiration, which produces lactic acid and small amounts of ATP. Under normal conditions, the lactic acid is broken down further by aerobic respiration, which requires an oxygen supply. The final products of aerobic respiration are carbon dioxide, water, and large amounts of ATP [6].

During sustained strenuous exercise, the blood cannot supply enough oxygen to keep pace with glycolysis, and lactic acid accumulates in the muscle, causing an oxygen debt. Muscle contractions continue for a short time using the small amount of ATP produced by glycolysis, but soon the demand exceeds the supply and the muscle is fatigued. The contractions decease in strength and then stop. The pain of muscle fatigue is the result of accumulated lactic acid. Oxidation of excess lactic acid occurs after exercise, when the person breathes deeply to pay off the oxygen debt [6].

The effects of exercise on the body's cells are significant. Physical activity increases the size and number of mitochondria, increases muscle's ability to use fat as a source of energy, increases the size of muscle fibers, and increases the content of myoglobin in muscle fibers. Exercise also results in increased fat oxidation. All of these increases lead to hypertrophy of the muscle, which leads to an increase in strength of the muscle. The wasting of muscle due to lack of use is assessed as atrophy

PATHOPHYSIOLOGIC INFLUENCES AND EFFECTS

The primary function of the musculature and connective tissues of the body is to provide body movement. When disease or trauma alters the system, the individual's ability to move and ambulate can be affected, which can profoundly affect a person's lifestyle. Movement is often still possible, but not without pain or difficulty [7].

INFLAMMATION

Inflammation may occur in muscle or connective structures as a result of excessive or repeated strain or pathogenic invasion. Restricted motion and pain usually result. One such example is rotator cuff injury, when the patient is unable to abduct the arm because of pain and muscle spasms. Other connective tissues of the body may be affected by inflammation, resulting in changes in other organs as well as the musculoskeletal system. Many of these connective tissue disorders are believed to be associated with immune processes [7].

DEGENERATIVE CHANGES

What musculoskeletal structure is most frequently influenced by degenerative disease?

The joint is the musculoskeletal structure most frequently influenced by degenerative disease. Changes are most often associated with aging, excess weight, trauma, and inflammatory conditions. In the presence of these factors, articular cartilage softens, thins, and ulcerates, and the joint surfaces become rough. There may be a narrowing of the joint space and swelling of adjacent soft tissue. The normal smooth-gliding joint action is diminished, and the periosteum becomes irritated by friction, stimulating the growth of bone spurs at the joint margins. The effects of this destruction include joint pain, stiffness, and joint deformity, which can result in slight to moderate limitation of movement. Crunching or grating sounds, called crepitus, may be heard upon movement [8; 9].

The intervertebral discs can also be affected by degeneration. The water content of the discs decreases with age, causing them to become thinner. The surrounding ligaments also change with age, so the disc becomes unstable. These changes along with increased bone resorption cause decreased height and painless restriction of spinal movement in the elderly. In some cases, the condition becomes more severe, with pressure on nerves causing pain and neurologic deficits [8; 9].

Somewhat akin to degeneration is the process of atrophy. Muscle can atrophy as a result of disuse. As noted, the normal strain on muscles contributes to their development and to the maintenance of their size, shape, strength, and composition. Through disuse, muscle cells become reduced in size and weakened, and the muscle mass becomes more fibrous. Inactivity can also lead to joint contracture; the muscle fibers become shortened and fixed, and the joint's range of motion becomes

limited. These conditions are reversible with the resumption of activity. However, contractures can progress to an irreversible state without treatment [8; 9].

INFECTION

Musculoskeletal structures, such as joints and bursae, can be infected by pathogens entering from penetrating wounds or via the circulation. Pain and restricted motion are common in these cases [10].

NEOPLASIA

Malignant neoplasms of the bone, muscle, and cartilage are called sarcomas. Cancer affecting the muscle is called rhabdomyosarcoma; chondrosarcoma originates in the bones but can extend to the cartilage [11]. Depending on the specific cancer and location, patients may experience a temporary limitation in mobility (e.g., following surgery for tumor removal) or permanent limitation due to extensive surgical intervention, such as amputation [11].

TRAUMA

Skeletal muscle can be injured by trauma. Fortunately, skeletal muscle fibers can regenerate, but when the damage is extensive, the fibers are replaced by scar tissue. Trauma to the musculoskeletal structures supporting the joints is common. Muscle fibers may be injured due to overuse, overstretching, forcible twisting and other abnormal movement. The fibers may be torn, or stretched too far, and joint surfaces may dislocate, that is, separate partially or completely. Associated blood vessels and nerves may be damaged in the process. Pain and limited motion are the result [12].

Direct muscle trauma, overuse, or exposure to high temperatures can induce rhabdomyolysis. Rhabdomyolysis is a complex syndrome involving the rapid dissolution of damaged skeletal muscle, resulting in the leakage of intracellular contents to such an extent that it results in organ (particularly kidney) damage.

RELATED INFLUENCES AND EFFECTS

NEUROLOGIC AND VASCULAR PROBLEMS

Neurologic and vascular problems can cause or contribute to connective tissue and muscle disorders. Because muscle functioning is the result of the combined effect of muscle fibers and motor nerves, neurologic damage or interference can impair muscle functioning, causing atrophy and paralysis. Likewise, disruption of the vascular supply to these tissues can limit the nutrient and oxygen supply to cells and interfere with removal of cellular waste products. Prolonged interruption of circulation leads to necrosis [13; 14].

Connective tissue disorders can also give rise to neurologic or vascular problems, which may in turn cause further musculoskeletal damage. Pressure from bandages, traction devices, tumor growth, and poor positioning are a few problems that can hinder nerve and blood vessel functioning. Trauma to muscles causes edema and hemorrhage in soft tissues, increasing the pressure within a confined space. Pressure on nerves and blood vessels in the area can become so great as to produce irreversible necrosis of the muscle tissue. A permanently disabling contracture of the limb may occur, as well as loss of motor and sensory functioning [13; 14].

OCCUPATION AND LIFESTYLE

A person's occupation and lifestyle can contribute to alterations in the muscular and connective tissues. Interest in physical fitness has prompted many people to become active in athletic endeavors. Highly athletic activities, including weightlifting, distance running, and more intense sports, are associated with an increased risk for injury, particularly with improper conditioning and training [15].

Sport injuries can generally be categorized as acute or overuse. Acute injuries occur most often in contact sports and include strains, sprains, and dislocations. Overuse injuries are usually a result of repetitive motions or excessive intensity or duration of exercise. Acute injuries are typically traumatic (e.g., ligament tears), while the most common overuse injuries are tendinosis and osteoarthritis [15].

With muscle and connective tissue disorders, patients may be unable to continue their usual recreational activities. Further, roles within the family may change to accommodate impaired ability to conduct usual activities of daily living. Occasionally, it may be necessary to use assistive devices or to modify the environment, which requires a period of adjustment [15].

NURSING ASSESSMENT: ESTABLISHING THE DATA BASE

The nursing assessment of patients with muscle, joint, and/or connective tissue disorders requires special emphasis on the musculoskeletal, neurologic, and vascular systems [16].

SUBJECTIVE DATA

As part of any nurse assessment, patients should provide important information about what they are experiencing as a result of their conditions.

Pain

Pain, in some cases severe, is a common manifestation of joint, muscle, and connective tissue problems. Patients should be asked to describe their pain thoroughly, including location, intensity, quality, duration, radiation, precipitating factors, and successful relief measures. Some patients ache all over and should indicate each of the areas involved. Knowing the quality of pain may help pinpoint a specific problem, but the patient may require help in describing the pain. All these data are helpful in reaching a diagnosis [16].

Some patients experience pain so severe they cannot tolerate moving or being touched. Others have learned to live with chronic pain. It is important to pay attention to descriptions of pain that seem unusual or excessive for the patient's condition; such complaints warrant a thorough assessment. Changes in pain status may indicate a new or undiagnosed condition [16].

Paresthesia

Some patients with musculoskeletal conditions will experience paresthesia, such as tingling, numbness, and/or and diminished or absent sensation. The affected area should be defined as precisely as possible. Paresthesia is an indication of a neurologic problem and requires an in-depth assessment [16].

Changes in Activities of Daily Living and Mobility

Nurses can obtain additional subjective data by asking the patient how the problem affects activities of daily living and mobility. Changes in normal activities may be from pain alone or from other effects of their illness, including fatigue, weakness, stiffness, or decreased mobility of a particular body part. Some patients may have abandoned activities or made adjustments to maintain independence. Patients should be encouraged to discuss their view of the situation to bring insights and misconceptions to the surface [16].

Assistive Devices

Patients should be asked about any assistive devices used to help maintain independence, including aids for walking, eating, dressing, bathing, or toileting. These may not be devices designed specifically for the tasks; some are creative and adaptive in finding new ways to meet their daily needs [16].

History of the Injury

Subjective data are particularly helpful in the case of injury when the patient can describe the traumatic event and the action taken. This information can help the healthcare team determine what tissues and structures were inured as well as anticipate potential problems.

OBJECTIVE DATA

Physical Assessment

Objective data include the results of physical assessment and of laboratory and other diagnostic tests. When assessing patients with musculoskeletal disorders, vital signs, posture, muscle strength and tone, ability to ambulate, and neurologic status should all be included in the patient assessment [16].

Vital Signs

Assessment of vital signs is of particular importance in cases of musculoskeletal trauma. Hyperthermia may accompany inflammation and is common with an infection. Observing respiration is essential when injury occurs to the face, neck, or chest. Patients with spinal or chest changes may also have abnormal respirations [16].

Inflammation and Swelling

Inflammation is an immune response to infection, physical trauma, or autoimmune reaction. Swelling occurs as inflammatory exudate forms to defend the tissues from the injury. Edema may also be present. Inspection and palpation are used when assessing patients for swelling and inflammation and comparing one extremity to the other for size, warmth, and erythema. A joint will appear swollen when there is an increase in synovial fluid or when blood or purulent material is present in the joint capsule. This swelling is known as effusion. Effusion in the knee is detected by displacing the fluid with an upward stroke along the medial side of the knee and then pressing on the lateral side. The fluid will return and form a bulge (the bulge sign).

It is important to be gentle when assessing inflamed areas because they are usually tender. It is best to start palpating at the distance from the obvious tender area and work toward it, letting patients know when and where they will be touched and reassuring them that the touch will be gentle [16].

Skin Integrity

Injury or disease processes may cause changes in the skin. Discoloration results when trauma to soft tissues causes ecchymosis (bruising). The skin may be broken or torn as result of injury. Describe any lesions completely: include the occasion, length, depth, and appearance of the involved tissue. If there is any drainage, describe the amount, color, type, and odor [17; 18].

Rashes are common in connective tissue disorders. Look for changes in the skin such as discoloration, dryness, scaliness, and lesions. With some types of arthritis, the hair, skin, and nails may show signs of changes. Discoloration, usually redness, may occur in the palms, over joints, and at the distal ends of the toes and fingers. Normal pigmentation may also be altered. Characteristic nodules may be noted when palpating and observing the skin [17; 18].

Structural Changes

Heberden nodes are associated with what condition?

Joints may be assessed for changes by observation and palpation. Heberden nodes may be noted on the distal interphalangeal joint of patients with osteoarthritis. Likewise, rheumatoid nodules may be noted need the joints of patients with rheumatoid arthritis, even in the absence of other signs. Joints may be compared bilaterally to assess symmetry, position, and changes in alignment [17; 19].

The curvature of the spine should be assessed to identify the presence of scoliosis (lateral curve), kyphosis (convex curve of the thoracic spine), or lordosis (concave curve of the lumbar spine). Patients with skeletal changes may shift another body part in the opposite direction to compensate for the imbalance; for example, the pelvis may tilt to compensate when one leg is shorter than the other [17; 18].

Range of Motion

What is normal elbow flexion?

Range of motion can be measured with an instrument called a goniometer. Placing the arms of the goniometer parallel to the axis of the bones that form the joint, the examiner measures the angle for the typical positions of the joint. The elbow's normal flexion, for example, is 160°, whereas its normal extension is 0°. To determine what is normal for a patient, compare a joint with an apparently impaired range of motion to the corresponding joint in the other extremity, if possible. Patients can have differences in range of motion for a variety of reasons, particularly as they age, so it is vital to assess typical range of motion on an individualized basis. Dexterity is usually assessed by asking the patient to pick up an object from a flat surface [17; 18].

If a patient is unable to move an extremity, range of motion may be determined through passive movement. Joints should not be moved beyond the point of comfort, and if possible, assessments should not include acutely inflamed joints, which may be tender [17; 18].

During the assessment of range of motion, note joint stiffness, instability, and changes. Boney crepitation may be heard or felt during movement when there is a rough surface of the articular cartilage or when broken bone ends rub together. A limitation of motion may be due to a contracture. Early detection of signs movement limitation can allow for the implementation of measures to improve range of motion and prevent further limitations [17; 18].

Posture

Observe the patient's standing posture for abnormalities. Posture can be affected by structural changes or differences, muscle weakness, or trauma. In addition, patients may hold themselves in positions that relieve or decrease pain. Patients should be observed for symmetry. Posture is also an indication of energy and muscle tone. Normally, posture is erect but not rigid [16].

Muscle Strength, Size, and Tone

Assessment of muscle strength, size, and tone can support the diagnostic process, but it can also provide information about the amount of assistance necessary for ambulation and participating in activities. Muscle strength is assessed by asking the patient to resist movements or to move against resistance [16].

Muscles should be observed and palpated bilaterally to check their size and asymmetry. If there seems to be a significant discrepancy in size, the limb circumferences should be measured [16].

Muscle tone is assessed by moving the extremities passively. While the patient is relaxed the examiner moves the extremity through the ranges of motion, noting resistance to movement. A muscle with diminished tone is described as flaccid. When the muscle is tight and tense from involuntary contraction, it is said to be spastic [16]. Function of the muscles depends on proper function of the nervous system. Muscle abnormalities noted during the assessment may be due to disorders of the nervous system rather than musculoskeletal disorders.

Ability to Ambulate

To assess the ability to ambulate, the patient should be asked to get up to walk across the room, turn around, and come back. Any difficulties rising to standing, starting or stopping walking, or turning should be noted. In a typical gait, the feet are 2–4 inches apart, and the body shifts from side to side about 1 inch. The posture is erect, with toes pointed straight ahead and shoulders in a straight line; the arms swing back and forth at the person's sides, and movement is smooth with good balance [16].

There can be a variety of irregularities in gait, with an equally diverse underlying etiology. A limp can occur from differences of leg length, joint motion, muscle strength, or other causes. The gait may appear stiff, unsteady, or wide-based; the feet may drag, or the steps may be very short. The body may lurch to the side as the individual shifts weight from one leg to the other. An irregular gate can cause fatigue because of the extra energy needed for walking. Ambulation may also be affected by pain, fear of falling, and loss of balance and coordination. As adults age, walking speed and balance may decrease. Steps may be short and shuffling, without the confidence and poise of youth [16].

DIAGNOSTIC STUDIES

Diagnostic studies provide information useful in diagnosing and following the course of the disease process.

Serum Enzyme Tests

Blood tests performed to detect presence of muscle disease measure levels of enzymes released when muscle tissues are destroyed or injured. These enzymes are creatine phosphokinase or creatine kinase, lactic dehydrogenase (LDH), and serum glutamic-oxaloacetic transaminase (SGOT), also known as aspartate amino-transaminase (AST). The same tests indicate cardiac muscle destruction in the patient with a myocardial infarction [20].

Serum Tests for Antibodies and Antigens

The antinuclear antibody (ANA) test is the most specific and sensitive test for lupus and is therefore the most commonly used autoantibody test. Ninety-seven percent of patients with lupus have a positive ANA blood test. The titer and patterns of the blood sample are reported. A titer greater than 1:80 is usually considered positive [21]. It is important to note that a positive ANA test is found in 97% of patients with lupus, but alone, it does not indicate a conclusive diagnosis of lupus [21]. A positive ANA test, although not always found, satisfies one of the four typical clinical characterizations required for a definitive diagnosis of lupus. ANA tests may also be positive in patients with other connective tissue diseases, chronic infectious diseases, and autoimmune diseases [21].

The 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) joint working group recommends several laboratory tests for the diagnosis of rheumatoid arthritis, including rheumatoid factor, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anti-cyclic citrullinated peptide (anti-CCP) antibody [22]. A positive rheumatoid factor is the most specific and sensitive laboratory marker of rheumatoid arthritis, as it is seen in about 70% to 80% of patients [23; 24; 27]. It is also present in many healthy individuals, patients with other rheumatic diseases, and individuals with chronic infections [26]. The anti-CCP antibody test is a specific blood test available for diagnosing rheumatoid arthritis and distinguishing it from other types of arthritis [24; 27]. The anti-CCP antibody test is a marker of anti-citrullinated protein antibody (ACPA) and is positive in about 80% to 90% of patients; it can also be present in other diseases, including active tuberculosis, and is especially useful in early synovitis. While rheumatoid arthritis differs from person to person, individuals with rheumatoid factor, the anti-CCP antibody, or subcutaneous nodules tend to have more severe forms of the disease [24; 26; 27]. However, biomarkers for the initial tissue processes that cause joint damage in rheumatoid arthritis lack prognostic accuracy and are therefore inadequate as stand-alone tests. As such, they are typically used to help rule out other causes of arthritis when a patient has clinical features of rheumatoid arthritis [28].

The presence of human lymphocyte antigen B27 (HLA-B27) is used to help diagnose or rule out ankylosing spondylitis and reactive arthritis. This antigen is present in 90% of those with these conditions, but it can also be found in those without pathology, so it is not diagnostic [20].

Serum Uric Acid

Serum uric acid is elevated during an acute episode of gout but may be normal during remission. Serum uric acid level is also used to assess kidney function [20].

Erythrocyte Sedimentation Rate and C-Reactive Protein

The ESR is a test in which the settling of red blood cells in uncoagulated blood is timed. This is a nonspecific test, and elevations in ESR are indicative of generalized inflammation. Changes in the ESR give an indication of improvement or worsening of the condition [20].

CRP is also associated with disease activity, and the CRP value over time correlates with radiographic progression in patients with rheumatoid arthritis [24; 26; 29]. ESR is typically ≥ 30 mm/hour, and CRP level is typically ≥ 0.7 pg/mL.

Synovial Fluid Analysis

In certain instances, clinicians may perform an arthrocentesis in order to differentiate rheumatoid arthritis from other arthropathies [30]. Findings from synovial fluid aspiration that support a diagnosis of rheumatoid arthritis include straw-colored fluid with a significant number of fibrin flecks, synovial fluid ability to clot at room temperature, and 5,000–25,000 white blood cells/mm^3 (5–25 × 10^9/L) with 85% polymorphonuclear leukocytes [23; 24]. In addition, bacterial cultures are negative, no crystals are present, and the synovial fluid glucose level is low [23; 24].

X-ray

Examination by x-ray helps diagnose joint problems; it also allows following of the progress of a condition and its response to treatment. X-rays are able to show joint changes, such as erosion of joint margins, joint space narrowing, bone spurs, loose bodies, and dislocation. Specific injuries to soft tissues such as tendons and ligaments do not show on x-rays, but soft tissue swelling may be obvious [20].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with chronic extremity joint pain and suspected rheumatoid arthritis, the American College of Radiology recommends x-ray as the imaging study of choice for evaluation.

(https://acsearch.acr.org/docs/3097211/Narrative. Last accessed September 26, 2022.)

Strength of Recommendation: 9 (Usually appropriate)

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) can produce a detailed and highly useful image of the joints and soft tissues. As such, it is usually the best option when evaluating major joints, the spine and the muscles, tendons, and ligaments of the extremities. MRI has a role in the diagnosis of a variety of musculoskeletal disorders, including osteoarthritis, back pain, tears in the connective tissues of the joints, congenital disorders of the joints, and occupational/sports-related injuries [31].

Musculoskeletal Ultrasound

For what conditions is ultrasound an essential component of diagnosis?

Because it is readily available and avoids the use of radiation, ultrasonography is often a good option in the assessment of musculoskeletal disorders and injuries. Ultrasound allows for the visualization of joints, tendons, muscles, bursae, ligaments, cartilage, nerves, fascia, and related soft tissue and can have a role in diagnosis and/or evaluation of disease progression for a variety of conditions. The American Academy of Physical Medicine and Rehabilitation indicates that ultrasound is an essential component in the diagnosis of tendinopathies/tendon tears, nerve entrapments (e.g., carpal tunnel syndrome), and acute or chronic muscle injury [32]. It may also be involved in the evaluation of ligamentous injury and joint instability syndromes, subluxations/dislocations, and fascia injury or inflammation. When joint aspiration is necessary, it may be guided by ultrasound, as may therapeutic injections.

Electromyogram

The electromyogram is a test to measure the electric currents produced by muscles, at rest and during contraction. Small needle electrodes are inserted into the muscle being tested and then connected by wires to an electromyography machine. Changes in muscle electrical activity may be helpful in diagnosing neuromuscular disease, and the test is particularly useful in differentiating muscular disease from neurologic disease [20].

Biopsy

Various biopsies may be performed on the musculoskeletal system. Skin samples, obtained by a punch biopsy, may be examined to diagnose certain connective tissue disorders. Muscle biopsies are usually operative procedures done to evaluate muscle disease. The synovial membrane can be biopsied, and analysis can be useful in diagnosing different types of arthritis. Buccal mucosa may be biopsied to help diagnose Sjögren syndrome, and the temporal artery may be biopsied to diagnose temporal arteritis [20].

SPECIFIC DISORDERS OF CONNECTIVE TISSUE AND MUSCLES

Injury to connective tissue and muscle may arise from congenital or acquired disease or from trauma. Diagnosis and treatment/management of these conditions are specific to the disorder.

GENETIC DISORDERS

Genetic disorders of connective tissue are structural connective tissue changes present at birth. Most of these disorders are transmitted by a single autosomal dominant gene. Although there are many congenital connective tissue disorders, most are rare; two more widely known conditions are Marfan syndrome and Ehlers-Danlos syndrome. The obvious manifestations of these disorders may not appear until the second decade of life or later [33].

Both syndromes are serious and require collaborative assessment and treatment by the entire healthcare team. Healthcare providers should gather careful family histories detailing the patterns of disease transmission so families can see the degree of risk [33].

Marfan Syndrome

Marfan syndrome is one of the most common inherited (autosomal dominant) disorders of connective tissue, occurring in 1 in every 10,000 to 20,000 individuals [34]. It is the result of mutations in the *FBN1* gene. *FBN1* mutations are associated with a broad continuum of physical features ranging from isolated features of Marfan syndrome to a severe and rapidly progressive form in newborns.

Clinical Manifestations

What is the most common ocular symptom of Marfan syndrome?

There is wide variability in clinical symptoms in Marfan syndrome, with the most notable occurring in eye, skeleton, connective tissue, and cardiovascular systems. The most common symptom is myopia. Ocular problems are a result of defective supporting tissue of the lens, which can cause bilateral subluxation or total dislocation of the lens. The dislocation is usually upward, but slit-lamp examination is done to detect more subtle variations. Complications such as reduced visual acuity, uveitis, glaucoma, cataracts, and retinal detachment may also occur [33].

Cardiovascular complications of Marfan syndrome are potentially life-threatening and commonly involve the aorta. Marfan syndrome causes degeneration of the elastic fibers of the aortic media, which can lead to dissecting aneurysm. Aortic regurgitating may occur, producing a diastolic murmur. Mitral valve prolapse, thickening of the coronary arteries, conduction system abnormalities, and aortic coarctation have also been associated with this condition [33].

Echocardiogram is useful in following aortic and mitral valve abnormalities. Patients with valve involvement are at risk for endocarditis. These patients should be prescribed antibiotic prophylaxis for any dental work causing bleeding or for any other invasive procedures, to prevent bacteremia [33].

The most obvious skeletal manifestations in patients with Marfan syndrome are extreme height and long extremities. These patients are usually much taller than other members of their families and have excessively long arms and legs in relation to their bodies. The measurement from fingertip to fingertip with the arms outstretched is typically greater than the body height. Arachnodactyly (extremely long fingers) is commonly noted. The sternum may bulge outward (pectus carinatum, or pigeon breast), or it may be depressed (pectus excavatum, or funnel breast). If the chest differences are extreme, the echocardiogram becomes unreliable [33].

Kyphoscoliosis may be quite severe because of the weakness of the ligaments and other supporting connective tissues. Other skeletal manifestations include a long and narrow skull, with a high, arched palate, and flat feet. Joints and ligaments are hyperextensive, leading to recurrent dislocations of the knees and hips [33].

Therapeutic Measures

Therapeutic approaches in Marfan syndrome are directed toward the specific manifestations. Corrective lenses are almost universally necessary, and yearly ophthalmologic examinations aid in early detection of retinal detachment and lens dislocation [33].

Because cardiovascular problems are the major cause of mortality, most diagnostic and treatment efforts are directed here. Echocardiograms are done yearly, unless the diameter of the aorta exceeds the upper limits by 50%, in which case echocardiogram is performed every six months [33]. Beta blockers are used to decrease the stress on the aorta at the time of diagnosis or when there is progressive aortic dilatation. There is some evidence that angiotensin receptor blockers may be used, and clinical trials are underway to evaluate this use. Surgery to repair the aorta is done when the aortic diameter is greater than 5 cm in adults and older children, when the aortic diameter increases by 1.0 cm per year, or when there is progressive aortic regurgitation [34].

Kyphoscoliosis is the most deforming and disabling skeletal manifestation of Marfan syndrome. Patients should be examined biannually, and therapy (e.g., bracing, physical therapy, spinal fusion) should be initiated as soon as possible to prevent or slow further changes [33]. In more severe cases, the thoracic cavity in patients with kyphoscoliosis can be so reduced that cardiac and respiratory function are compromised. These patients are particularly susceptible to upper respiratory infections and should be treated aggressively if an infection occurs [33].

Prepubertal girls are often given estrogen and prepubertal boys given androgens to decrease height and help prevent kyphoscoliosis. While these hormones induce early epiphyseal closure, they also trigger the physical and psychosocial changes of puberty, which can create additional psychosocial stresses.

While Marfan syndrome is not always inherited, it is always heritable. Approximately 75% of cases are inherited, and the offspring of patients with Marfan syndrome have a 50% chance of developing the syndrome. In addition, patients with Marfan syndrome who become pregnant are at risk for potentially dangerous aortic changes resulting from cardiovascular overload and increased intra-abdominal pressure [33].

Specific Nursing Measures

The health history is extremely important in patients with congenital disorders such as Marfan syndrome. Particular attention should be paid to the patient's coping abilities in terms of living with a chronic disease that involves numerous changes in body image [7; 35].

At each visit, the patient should be thoroughly assessed, with particularly attention to the eyes, cardiovascular system, and musculoskeletal system [7; 35]. When examining the patient's eyes, look for tremor of the iris as it is moved horizontally. This is an indication of subluxation of the lenses. These patients may also have myopia and blue sclera (due to the presence of thin sclera through which the vessel-rich choroid can be seen).

Patients may display early diastolic murmurs of aortic regurgitation. This consists of a high-pitched blowing sound, heard best with the stethoscope over the second right or third left intercostal space. Increased pulse pressure and collapsing (water-hammer) pulse may also be evident. Occasionally, a midsystolic click indicative of mitral valve prolapse may be auscultated.

Nursing interventions for these patients will focus on supportive symptomatic care and education needs. The nurse should be prepared to discuss the nature and course of the disease and the importance of genetic and pregnancy counseling. The patient should be urged to keep current with biannual exams. Patients should also be counseled to avoid trauma, including contact sports, and invasive surgical procedures (when possible) [7; 35]. They are also advised to avoid medications and foods that can lead to chronic increases in blood pressure and stretch the connective tissue in the cardiovascular system.

Ehlers-Danlos Syndromes

Ehlers-Danlos syndromes are a group of rare genetic disorders of connective tissue that affect the skin, joint, and hematopoietic systems. It is usually transmitted by an autosomal dominate gene, but it may also be recessive or an X-linked recessive gene [33].

Clinical Manifestations

The major manifestations of Ehlers-Danlos syndromes are fragile and increased elasticity of skin, hyperextensible joints, and fragility of blood vessel walls [33]. In the 2017 classification system, 13 types of Ehlers-Danlos syndrome were identified, including rarer forms [36]. They are generally organized according to the dominant system(s) involved, severity, and mode of transmission.

The skin of most patients with an Ehlers-Danlos syndrome is very smooth and hyperextensible; it can be pulled away from the body but returns to its original shape. Fragility and bruising are often evident. Minor cuts cause gaping wounds with little bleeding. Even the slightest trauma may cause purpura or hematomas that calcify, particularly over pressure points such as knees and elbows [33].

An unusually large range of joint movement (hypermobility) occurs in most forms of Ehlers-Danlos syndrome, and it is a hallmark feature of the hypermobile type. Dislocations, effusion, and hemarthrosis of the hip, patella, and shoulders may occur. Kyphoscoliosis, flat feet, and hyperextensible knees are often present. Thoracic changes are not as common but do sometimes occur, as does a forward slipping of the lower lunar vertebrae (spondylolisthesis) [33].

The patient may have episodes of bleeding, including spontaneous epistaxis; bleeding into the joints (hemarthrosis); blood in the sputum (hemoptysis); dark, tarry stools (melena) indicating bleeding in the digestive tract; and bleeding gums. It is not known whether the abnormal bleeding is from weakness in blood vessel walls or abnormal interactions of platelets with collagen [33]. Patients with Ehlers-Danlos syndrome who become pregnant are at risk for uterine rupture.

Abnormalities of the heart and blood vessels occur in patients with the cardiac-valvular type. These include mitral valve prolapse, right bundle branch block, and other conduction abnormalities. Patients with this type of Ehlers-Danlos syndrome have friable arteries, increasing the risk for adverse events during invasive angiography [33].

Other manifestations of Ehlers-Danlos syndrome can include spontaneous bowel rupture, pneumothorax, and diaphragmatic hernias or diverticula. In rare instances, a patient may have glaucoma, retinal detachment, or corneal abnormalities [33].

Specific Nursing Measures

Care for patients with an Ehlers-Danlos syndrome is limited to symptomatic treatment and support; there is no curative treatment. The main concern is to protect the patient's skin and joints from cuts, bruises, and dislocations. At each visit, the patient should be assessed for bleeding gums, melena, hemoptysis, and nosebleeds. Inadequate wound healing or wound dehiscence after a surgical procedure should be noted. Assessment of the lungs for pneumothorax, particularly following surgery, is important [35].

As with any chronic condition, the nurse needs to teach patients and their families about the nature and course of the disease. The patient should also be referred to a genetic counselor, as there are varying modes of heritability. A patient with Ehlers-Danlos syndrome who becomes pregnant is at risk for abortion, preterm birth, exacerbation of joint problems, increased bruisablity, abdominal hernia, and varicosities. Serious complications may arise with cesarean deliveries, because sutures do not hold well and wound dehiscence may result [7].

INFLAMMATORY DISORDERS

Many pathologic conditions involve inflammation of connective tissue. In this section, most of the inflammatory conditions are related to alterations in the immune system [37].

Bursitis, Tendinitis, and Tendinosis

Bursitis is an inflammation of the synovial membrane lining a bursa; tendinitis is an inflammation of a tendon. These inflammations may result from trauma, or they may be secondary to disease. Although both conditions are usually acute, they can become chronic and disabling with repeated injury or inadequate care [37]. Note that tendinitis is distinct from tendinosis, which is the result of a noninflammatory condition characterized by degeneration of the tendon in response to chronic overuse.

Bursitis and tendinosis develop from prolonged overuse of a particular muscle group that can eventually damage a bursa or tendon. Overuse may be due to repetitive work movements or to a sports activity. Because the vascular supply of tendons is poor, their healing is limited and inflammation can become chronic, resulting in tissue damage and persistent pain. Often, the patient becomes unable to continue performing the movements that led to the condition, potentially impairing their ability to continue working.

Calcium deposits in tendons or bursae may also be the cause of inflammation. Tendon sheaths may become inflamed secondarily to systemic disease, such as gout, rheumatoid arthritis, or scleroderma [37].

Clinical Manifestations

Which conditions should be included in the differential diagnosis of bursitis and tendonitis?

The major symptom of bursitis/tendinitis/tendinosis is pain, often so severe that the patient is unwilling to move the affected part. Swelling may be present, and this alone may keep the patient from moving the joint. Any of the body's many bursae and tendons can become inflamed, but some joint areas are more commonly affected than others. Differential diagnosis of acute pain and erythema in joint areas should include infection, gout, and rheumatoid arthritis [37].

Bursitis and tendinitis/tendinosis of the shoulder involve the subacromial and subdeltoid bursa (different sections of the same large bursa) and the tendon of the supraspinatus muscle. The onset of bursitis or tendinitis in the shoulder usually follows activities involving repetitive movements of the whole arm, such as sanding, painting, sawing, throwing, or repeated lifting. Pain in the deltoid area increases when the patient lies on the shoulder or actively abducts the arm. A classic sign of bursitis/tendinitis/tendinosis of the shoulder is the "painful arc" between 80° and 120° of active arm abduction. The patient is often unable to support the weight of the arm at these angles. Further abduction causes no pain, and the examiner can perform assisted range of motion. If passive range of motion causes pain, capsulitis, rather than a periarticular disorder, is suspected [37].

Inflammation of the elbow region most often involves the olecranon bursa and the medial and lateral epicondyles. "Tennis elbow" is generally lateral epicondylitis, and "pitcher's elbow" is medial epicondylitis. These conditions cause pain that radiates from the elbow down to the forearm. The patient may drop heavy objects because of a feeling of decreased strength, although there is no real loss of strength or range of motion. Palpation of the involved epicondyle causes pain. Activities involving lower arm movement, such as tennis or hammering, may precipitate an attack. Olecranon bursitis usually is caused by leaning or falling on the elbow. There may not be severe pain, but swelling is often extensive [37].

Tenosynovitis involves inflammation of the tendon and tendon sheath and is also known as de Quervain tenosynovitis of the wrist [38]. When the tendons at the base of the thumb become irritated or inflamed this causes the tunnel around the tendon to swell and results in pain and difficulty grasping and holding objects. Overuse is the most common cause [38]. New repetitive activity, hormonal fluctuations associated with pregnancy and breastfeeding, and wrist fractures also are possible causes of de Quervain tenosynovitis [39].

Stenosing tenosynovitis, also referred to as "trigger finger," occurs when the pulley/tendon relationship between the hand and fingers is restricted by thickening or swelling at the base of the fingers. This creates pain and a distinctive catching, popping, or locking action in the finger or thumb. A cycle of triggering, inflammation, and swelling is common. Like carpal tunnel syndrome, stenosing tenosynovitis has been associated with other health conditions, such as gout, diabetes, and rheumatoid arthritis. In many cases, the actual cause is not clear [40].

The most common inflammatory problem of the hip is trochanteric bursitis. Pain, which is distributed over the lateral aspect of the hip and thigh, may inhibit ambulation. An increase in pain is seen with abduction and internal rotation against resistance. The patient feels tenderness with palpation over the greater trochanter. Patients who have leg length discrepancy may develop this inflammation in the hip of the longer leg [37].

Four bursa in the knee can cause significant discomfort for the patient when inflamed [37]:

- Prepatellar bursa
- Superficial infrapatellar bursa
- Deep infrapatellar bursa
- Pes anserine bursa

Prepatellar bursitis ("housemaid's knee") results from the combined action of excessive kneeling and leaning forward, as when gardening. Superficial infrapatellar bursitis ("clergymen's knee") can result from excessive kneeling. Deep infrapatellar bursitis and pes anserine bursitis are secondary to excessive weight bearing or unusually strenuous exercise [37].

Achilles tendinitis is a painful inflammation of the tendon of the ankle with or without swelling. This injury often results from a single episode of overuse. It can also occur in runners who wear shoes with rigid soles. Recurrent episodes of Achilles tendinitis, when a patient resumes activity before complete healing has occurred, can result in progressive scar formation, which may require surgical repair [37].

Therapeutic Measures

The measures employed for relief of bursitis and tendinitis vary according to the patient's age and the location, cause, and severity of the injuries. Recommendations usually include [37]:

- Short-term immobilization, particularly during differential diagnosis
- Ice packs applied to the affected area
- Physical therapy and structured exercise after the initial period of rest
- Anti-inflammatory medication

Occasionally, local corticosteroid injections are administered to the inflamed bursa or tendon area. While this approach is relatively widespread, it is not supported by well-designed systematic reviews [41].

Physical therapy and increasing return to activities is the best practice for these patients. Physical therapy consists of a four-step approach [42]:

1. Pain reduction and load management (isometric loading and avoiding positions of compression)
2. Isotonic loading (heavy-slow resistance through concentric-eccentric phases)
3. Energy-storage loading (plyometric loading)
4. Return to activity/sport

Exercise is crucial in the rehabilitation process, and active movement is started early. For example, in bursitis of any bursa of the knee, quadriceps-setting exercise is begun as soon as pain allows. When pain and tenderness have completely subsided, range of motion and full quadriceps activity are initiated. Physical therapists are often involved in designing and implementing exercises for patients, according to their individual needs. Occupational therapists may also participate if the nature of the problem involves a modification or change in job [15].

In some cases, fluid may be aspirated from the bursal space to relieve the symptoms. Any fluid obtained should be cultured and inspected. X-rays of joints are usually normal, but in some instances, calcium deposits can be identified as the precipitating factor. Arthrography is indicated in specific types of shoulder trauma to rule out any disruption of the joint capsule. Surgery is rarely used for bursitis or tendinitis unless rupture of the tendon occurs [37].

Specific Nursing Measures

Goals of nursing care are to relieve the patient's pain, maintain maximum mobility, and prevent joint contracture. Assessment of pain and range of motion is important both initially and after treatment to measure improvements. Reassurance and support can contribute to the relief of pain, so it is helpful to assure the patient that the pain of bursitis or tendinitis/tendinosis is usually of short duration [35].

Instrumental to the success of treatment is comprehensive patient education. Patients should receive instruction on physical therapy exercises (including frequency), pain management techniques, and return to activities; written instruction should also be provided. If pain is relieved with pharmacotherapy, the patient may be tempted to use the affected area too soon. It is important to caution patients to refrain from early resumption of activity to avoid reinjury and/or the creation of scar tissue [35].

Polymyalgia Rheumatica

Polymyalgia rheumatica is an immune-mediated inflammatory disorder characterized by muscle stiffness, pain, and weakness around the neck, shoulders, and hip. While this is an inflammatory disorder, the cause of trigger is unclear; genetic, infectious (e.g., Epstein-Barr virus, parvovirus), and gut health-related etiologies have all been suggested, with varying levels of evidence [43]. The incidence increases with age, with the greatest incidence in White patients older than 50 years of age; the average age at diagnosis is 70 years.

Clinical Manifestations

As noted, the characteristic symptoms of polymyalgia rheumatica are pain and stiffness in the shoulders, neck, upper arms, and hip area. The pain and stiffness are usually worse upon waking in the morning or after resting, and usually last an hour or more. Patient may experience difficulty performing normal activities, including rising from bed or a chair, dressing, and brushing hair. Many patients will have difficulty raising their arms above the shoulders [44]. Less common signs and symptoms include flu-like symptoms (e.g., low-grade fever, weakness, loss of appetite, weight loss) and swelling of the wrists or joints in the hands. Onset of symptoms is typically over the duration of a few days but may be as short as overnight.

Diagnosis is typically based on the presence of elevated inflammatory markers, particularly ESR and immunoglobulin G (IgG). In addition, these patients will display a decreased number of circulating B cells compared with healthy adults [43].

A significant portion of patients with polymyalgia rheumatica are also diagnosed with giant cell arteritis, and research indicates the co-occurrence of these conditions is common even without the presence of symptoms [43].

Therapeutic Measures

The EULAR and the ACR have issued a joint guideline for the management of polymyalgia rheumatica [45]. The cornerstone of treatment is at least 12 months of glucocorticoid therapy. This typically consists of 12.5–25 mg prednisone, although a lower dose may be preferred in patients at risk for glucocorticoid-related adverse events (e.g., those with osteoporosis, glaucoma, diabetes). Drug therapy should be tapered up to effective dose and tapered down when discontinued.

Care of patients with polymyalgia rheumatica includes monitoring for and preventing (when possible) the adverse effects of long-term steroid therapy. This can include vitamin D and calcium supplementation as well as bisphosphonate prophylaxis for those at increased risk for fracture [43]. Because close monitoring is necessary, patient education should include the necessity for keeping all follow-up appointments.

IMMUNOLOGIC DISORDERS

The disorders in this section are believed to have an autoimmune etiology. As with many autoimmune disorders, there are a variety of potential initiating factors, including viral infections, genetic predisposition, and exposure to toxins [46].

Autoimmune disorders may be generally classified as organ-specific or generalized. Autoimmune connective tissue diseases are generalized, usually involving a progressive degradation of collagen in connective tissue throughout the body. Rheumatoid arthritis is among autoimmune disorders but will be discussed later in this course, because joint involvement is the major problem [46]. Some autoimmune disorders result in musculoskeletal manifestations but have an etiology in another body system. For example, fibromyalgia is characterized by widespread musculoskeletal pain and fatigue, but it is believed to be the result of nervous system dysfunction.

Autoimmune connective tissue disorders can be associated with significant morbidity mortality. However, early diagnosis and treatment have improved prognosis, though they remain chronic (incurable) conditions. Successful therapy for patients with autoimmune disease requires an interprofessional team approach in order to ensure the best outcomes for patients [46].

Familiarity with each disorder will prepare the nurse to be alert for manifestations, exacerbations, and patient education needs. Because patients are often prescribed several medications to help manage the disorder, nursing management often includes medication management. Comfort measures are another important aspect of nursing care during acute phases or exacerbations. Proper positioning, use of splints, and small comfort measures (e.g., backrubs, smoothing wrinkled sheets, creating a calm environment) all contribute to the patient's well-being [46].

The nurse will explain to patients how they can try to prevent exacerbations of specific manifestations of their disease and how to cope with them when they do occur. Prevention measures may include avoiding stress, cold, sun, or certain drugs [46].

Systemic Lupus Erythematosus

Which type of lupus mainly affects the skin?

Four different forms of lupus have been identified: cutaneous lupus erythematosus, drug-induced lupus, neonatal lupus, and systemic lupus erythematosus (SLE) [47]. Cutaneous lupus mainly affects the skin. It is associated with chronic skin eruptions that, if left untreated, can lead to scarring and permanent disfigurement. Drug-induced lupus is associated with ingestion of various drugs that result in lupus-like symptoms. Neonatal lupus is a rare, non-systemic condition affecting infants of women with lupus. SLE, which affects multiple organ systems as well as the skin, is considered the most common of the four forms.

SLE, often referred to simply as lupus, is a chronic inflammatory autoimmune disorder of the connective tissue, primarily affecting the skin, joints, blood, and kidneys [47; 48; 49]. In this autoimmune disorder, antibodies are formed within the body that target healthy body systems, causing inflammation and structural changes. The word lupus means "wolf" in Latin, while erythematosus means "redness." The disease is named for the characteristic red rash that appears on the face and is thought to resemble a wolf's face [47; 49]. The term "lupus erythematosus" was coined in 1851 by Pierre Cazenave, a French dermatologist, but writings describing lupus date to ancient Greece [49; 50].

Lupus has been characterized as a multidimensional, unique, complex, challenging, unpredictable, and often elusive disease [47]. It is a non-organ-specific systemic disease with a varying prognosis that can be mild, serious, life-threatening, or even fatal. The disease is characterized by recurring remissions and exacerbations, often called flares, that occur most commonly in the spring and summer [48; 51]. Periods of remission vary considerably among those diagnosed with lupus [47].

The number of reported cases of lupus varies based on different sources; it is believed that there are at least 1.5 million affected individuals in the United States [52; 53]. More than 90% of SLE cases occur in women, with most women developing symptoms in their childbearing years (15 to 45 years of age) [54]. New diagnoses of lupus in women older than 45 years of age are uncommon [49]. SLE is most common among African Americans, with African American women having three times the incidence of White American women [54]. The incidence of lupus is also greater in Hispanic, Asian, and Native American women when compared to White women [55]. Statistics show that Black and Hispanic women tend to develop the disease at a younger age, are more likely to develop more serious complications (particularly cardiovascular complications and kidney disease), and tend to have a higher mortality rate from the disease as compared to White women [54].

The exact cause of lupus remains a mystery, but researchers believe that it results from multiple factors [49; 56]. Possible causes may be interrelated and include immunologic dysfunction, genetic factors, hormones, and environmental influences [50; 51].

Immune dysregulation, in the form of autoimmunity, is thought to be the prime cause of lupus. In patients with lupus, the body produces an accelerated inflammatory response, resulting in the production of autoantibodies, causing immune complexes (antigens combined with antibodies) [49; 56]. These autoantibodies and complexes assault the body's own healthy cells and tissues [47; 49; 50; 51]. Symptoms of SLE are the result of the damage to the body's tissues secondary to the immunologic response. One of the hallmark indicators of lupus is the formation of autoantibodies, and the presence of autoantibodies in the blood is a key factor to the diagnosis of lupus [47; 49; 51].

The strong hereditary component of lupus is supported by the fact that first- and second-degree relatives of patients with lupus are at a greater risk for developing lupus [57]. Estimates indicate that 5% to 13% of relatives will develop lupus, but only 5% of children whose mothers had lupus will develop the disease [57]. For those with a genetic predisposition, environmental factors may trigger lupus [47]. Environmental factors that may precipitate or exacerbate lupus include physical or emotional stress, streptococcal or viral infections, exposure to sunlight, immunizations (live vaccines), surgery, smoking, chemical agents (drugs, metals, or toxins), certain foods or supplements, and other environmental irritants [47; 50; 58]. Further, female sex hormones are believed to have a potential role, as women in their reproductive years are most susceptible to lupus.

Diagnosis

The diagnosis of lupus may be a challenge for the healthcare provider as well as the patient. In 2019, the EULAR and the ACR published updated classification criteria for lupus (***Table 1***) [59]. The EULAR/ACR criteria classifies a person as having lupus if they meet entry criterion of an ANA titer of >1:80, followed by additive weighted criteria (seven clinical and three immunologic) in which the patient must meet one clinical criterion and ≥10 points between the clinical criteria and immunologic criteria [59].

Clinical Manifestations

No two people with lupus will experience identical symptoms. The onset of lupus may be acute or insidious, vague, or even nonspecific. On average, individuals with lupus have symptoms of the disease for two to three years before a diagnosis is made [49]. Symptoms are the result of the inflammatory and immune response of the individual's body to the disease process [49]. Repetitive cycles of exacerbations and remissions of symptoms are a hallmark of the lupus disease process.

CLASSIFICATION CRITERIA FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS		
Domain	**Criteria**	**Weight**
Entry Criterion		
Positive antinuclear antibody (ANA) titer	ANA titer of >1.80 on Hep-2 cells or an equivalent positive test (ever)	Must be positive to continue to additive criteria
Additive Criteria, Clinical		
Constitutional	Fever	2
Hematologic	Leukopenia Thrombocytopenia Autoimmune hemolysis	3 4 4
Neuropsychiatric	Delirium Psychosis Seizure	2 3 5
Mucocuteanous	Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	2 2 4 6
Serosal	Pleural or pericardial effusion Acute pericarditis	5 6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria >0.5 g/24h Renal biopsy Class II or V lupus nephritis Renal biopsy Class III or IV lupus nephritis	4 8 10
Additive Criteria, Immunology		
Antiphospholipid antibodies	Anti-cardiolipin antibodies OR Anti-ß2GP1 antibodies OR Lupus anticoagulant	2
Complement proteins	Low C3 OR low C4 Low C3 AND low C4	3 4
SLE-specific antibodies	Anti-dsDNA antibody OR Anti-Smith antibody	6

Source: [59] *Table 1*

Common symptoms of lupus include fever, weight loss, malaise, fatigue, skin rashes, polyarthralgia, vasculitis, Raynaud syndrome (discussed in detail later in this course), patchy alopecia (hair loss), and painless ulcers of the mucous membranes [51]. Fatigue is probably the most universal symptom, described as a persistent complaint of a paralyzing fatigue that normal rest may not relieve [47]. Vague symptoms of lupus include aching, fatigue, low-grade or spiking fever, chills, and malaise. Episodic fever is reported by more than 80% of all patients with lupus, with a low-grade fever most often noted [47]. Infection is certainly a major concern and is a potential symptom for patients with lupus. Those with lupus are more susceptible to opportunistic infections due to alterations in their hematologic system, especially in white blood cells. Women with lupus may also experience irregular periods or amenorrhea due to the disease process [47; 49].

Skin rashes are very common among patients with lupus; approximately 80% of patients report skin involvement [47]. A red, raised rash over the nose and cheeks characterizes the classic "butterfly rash" of lupus. The butterfly rash is reported by 55% to 85% of all patients with lupus at some point during their disease process [47]. Discoid lupus lesions may also be seen. Ultraviolet light often aggravates skin eruptions, and approximately one-third of all patients with lupus are found to be photosensitive [47; 60]. Oral, nasal, and vaginal ulcers may occur. Conditions such as alopecia, pruritus, alteration in wound healing, and bruising are other common dermatologic symptoms.

Polyarthralgia (pain in multiple joints) occurs in more than 90% of lupus cases [47]. The joint pain associated with lupus is similar to that experienced by rheumatoid arthritis patients and is often called lupus arthritis. Most patients complain of morning joint stiffness and pain. The pain is typically symmetrical, and joints may become tender, warm to the touch, and swollen. The dominant extremities are usually more inflamed. Joints commonly affected include the toes, ankles, fingers, wrists, elbows, and knees [61]. Joint pain is often one of the first and most common complaints of those with lupus and is often what initially brings them to a healthcare provider [50]. Additional musculoskeletal symptoms that may occur include subcutaneous nodules, tendonitis, tendon rupture, and carpal tunnel syndrome [47].

Anemia and cardiopulmonary abnormalities are relatively common among patients with SLE, affecting 50% of patients [47; 49; 62]. The most common cardiac complication of lupus is pericarditis, while pleurisy is the most common respiratory complication [47; 49].

Nervous system involvement secondary to lupus is common and can range from mild to severe. Central nervous system involvement may result in cognitive disorders, including confusion, fatigue, memory impairment, and difficulty in articulating thoughts [49]. Cognitive dysfunction is estimated to occur in up to 90% of patients with lupus and is not associated with lupus disease activity [63].

Renal damage is one of the most serious complications of lupus, often causing such symptoms as hematuria, proteinuria, urine sediment, cellular casts, urinary tract infections, and fluid/electrolyte imbalance. Renal involvement has the potential to cause renal failure, affecting up to 50% of patients [47]. Renal disease is a leading cause of death in patients with lupus [47].

Ophthalmic disease affects approximately 20% of patients with lupus [47]. Ophthalmic symptoms associated with lupus may include a lupus rash on the eyelids, conjunctivitis, dry eyes, glaucoma, and cataracts [47]. In severe cases, retinal exudates or blindness may occur.

Therapeutic Measures

There is currently no cure for lupus, and long-term disease management is required. Due to the variability of lupus symptoms, treatment protocols differ for each individual. The range of treatments, however, are increasing in number and becoming more effective; thus, the disease can be controlled reasonably well in most people. The ultimate goal of treatment is to suppress immune system abnormalities, prevent disease flares, and reduce inflammation and other complications secondary to lupus [51].

Treatment is based on such factors as symptoms and severity, overall general health, activity level, school and/or family schedule, age, family and social situations, other medical conditions, and financial and insurance considerations [50].

Although there is no cure for lupus, there are several types of drugs available to aid in the treatment and management of secondary symptoms. Among these drug classes are nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarials, biologics, and immunosuppressives. In cases of severe lupus kidney disease not helped by pharmacologic intervention, dialysis or kidney transplant may be necessary.

Specific Nursing Measures

Nurses may see patients with SLE in both inpatient and ambulatory care settings. Discovering early symptoms and signs of exacerbations and complications is important in prolonging the life of patients with SLE. Carefully monitor all diagnostic study reports to remain well informed about the patient's progress [46].

Individuals diagnosed with lupus are encouraged to do all of the following [47; 49; 50; 51]:

- Get plenty of physical and emotional rest.
- Maintain a healthy diet.
- Establish an exercise regimen.
- Avoid sunlight.
- Seek prompt treatment of infection.
- Limit stress.
- Set realistic goals and priorities.
- Maintain effective communication with their healthcare providers.
- Develop a support system, including family, friends, healthcare professionals, community organizations, and organized support groups.
- Avoid triggering or aggravating factors.
- Seek regular health care.

Eight to 10 hours of sleep per night along with naps are recommended for patients with lupus. In addition, individuals with lupus should minimize stress to reduce emotional distress, as well as avoid direct prolonged sunlight, especially during the hours between 10 a.m. and 4 p.m. The use of a sunscreen with a sun protective factor (SPF) of 15 or greater that protects against both ultraviolet A and B rays is recommended along with protective clothing such as long sleeves and a hat [47]. Routine exercise is important to reduce fatigue and maintain joint mobility.

Social support can have a positive impact on individuals diagnosed with lupus. However, seeking and gaining social support can be difficult when one is experiencing a chronic illness such as lupus, because tremendous energy is necessary to maintain social networks [64]. Lupus symptoms, as well as treatment side effects, can present a challenge for individuals in maintenance of their pre-illness social relationships and activities. Furthermore, to gain necessary support, individuals with lupus should understand and then communicate to others what they need to assist them in managing their disease.

Keller noted similar findings in her research on social support and psychologic distress in women with lupus. She concluded that "younger women with lupus were more psychologically distressed than older women with lupus and that women with shorter duration since diagnosis were more distressed" [65]. Keller also found that the perception of having social support and being satisfied with the social support were more important than the number of social supports [65]. Thus, perception of and satisfaction with social support has been found to reduce psychologic distress.

One important potential source of assistance can be support groups. It has been noted that "participating in a support group can provide emotional assistance, boost self-esteem and morale, and help to develop or improve coping skills" [51]. Successful support groups can assist patients to gain insights into how to live with their lupus [66]. Darner found that women with lupus who had been diagnosed for longer periods of time had a healthier psychosocial adjustment [67]. Therefore, those newly diagnosed with lupus may require more support and interventions to aid in psychosocial adjustment.

Systemic Scleroderma

Systemic scleroderma, also called sclerosis, is an autoimmune connective tissue disorder that causes fibrous changes in the skin, synovium, and small arteries of the digits, as well as in various internal organs, most notably the esophagus, intestines, heart, lungs, kidneys, and thyroid. The disease occurs in various forms, ranging from a primarily skin condition (localized scleroderma) to the CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, which is thought to be more benign, to involvement of visceral organs (systemic scleroderma). Some patients with mild-to-moderate types of scleroderma can progress to the visceral and more extensive cutaneous lesions associated with systemic scleroderma [46].

In all forms of the disease, there is vascular injury at the level of small arteries and capillaries, and the resulting decrease in circulation is the cause of the tissue changes. The precipitating factor for the onset of systemic scleroderma is not clear, although there is some evidence that genetic and environmental factors play a role. Silica and certain organic solvents are recognized as risk factors of occurrence of systemic scleroderma. In addition, the prevalence of the disease is 13 times higher in first-degree relatives of patients than in the general population [68]. The result is an activation of the immune system, causing blood vessel damage and injury to tissues that result in scar tissue formation and the accumulation of excess collagen.

There are no definitive tests to diagnose systemic scleroderma, and diagnosis is primarily based on clinical evaluation. Autoantibodies occur in this disorder, and the ESR may be elevated. As part of the diagnostic workup, the following tests may be performed [68]:

- Nailfold capillaroscopy
- Screening for antinuclear antibodies (mainly anti-centromere and anti-scl70/anti-topoisomerase antibodies)
- Transthoracic echocardiography
- High-resolution computed tomography (CT) of the chest
- Diffusing capacity of the lung for carbon monoxide and spirometry
- Hand x-ray
- Esophageal manometry

Clinical Manifestations

The most frequent presentation in systemic scleroderma is the clinical triad of skin changes, Raynaud phenomenon, and esophageal hypomotility. However, manifestations are often present in other organ systems, requiring continual monitoring [46].

The most typical changes in all types of scleroderma occur in the skin. Typically, skin changes begin with swelling of the hands and gradual thickening, tightening, and hardening of the skin of the fingers (sclerodactyly). The fingers become tapered and in severe cases claw-like, with impaired mobility. Ulcers may develop on fingertips and over knuckles as the skin becomes taught. Skin changes can progress proximally at a slow rate, eventually affecting the face. In these cases, the skin of the face becomes tight and shiny, with a loss of normal wrinkles and skin folds. The nose may become beaked, and sometimes radial furrowing is seen around the mouth. Patients may experience an impaired ability to fully open their mouths. In extreme cases, the face becomes expressionless [46].

Most patients with systemic scleroderma have Raynaud syndrome, and this is often the first symptom to appear. With Raynaud syndrome, there is diminished blood flow to the digits secondary to vasoconstriction of the digital arteries, typically triggered by cold, vasoconstriction drugs, or emotional states. The initial sign is digital pallor, which progresses to cyanosis, then to erythema on rewarming [46].

The patient may have pain and stiffness in both small and large peripheral joints. Occasionally, patients develop arthritis and synovial effusion. Contracture and atrophy of the fingers may eventually occur [46].

Hypomotility of the esophagus occurs in most patients with systemic scleroderma. This typically presents as gastroesophageal reflux, with resulting heartburn and stricture, and potentially difficulty swallowing. In some cases, patients require esophageal dilation. Gastrointestinal involvement can progress to the intestine and colon, with development of hypomotility of the small intestine and wide-mouth diverticula [46]. In patients with gastrointestinal involvement, impaired nutrition is common.

Systemic scleroderma can also cause cardiopulmonary problems. Dyspnea may develop as a result of pulmonary hypertension and interstitial fibrosis. The examiner may hear fine dry rales or crackles at the bases of the lungs, and spirometry is often abnormal. Manifestations involving the heart are primarily the result of lung complications, but dysrhythmias, conduction disturbances, pericarditis, and pericardial effusions uncommonly occur [46].

In some patients, the kidneys can be seriously affected, with malignant hypertension rapidly producing renal failure, the leading cause of death for these patients. High renin levels and proteinuria are signs of kidney involvement [46].

Hematologic problems, in addition to a mild normochromic, normocytic anemia, include vitamin B_{12}/folic acid deficiency anemia, which may occur secondary to bacterial overgrowth in an atonic small intestine. There is also a risk for gastrointestinal bleeding and resultant iron-deficiency anemia [46]. Other manifestations include thyroid disease, biliary cirrhosis, trigeminal sensory neuropathy, and Sjögren syndrome [46].

Therapeutic Measures

Treatment of systemic scleroderma is symptomatic and driven by the stage and organ involvement of the disease. In its 2017 guideline for the treatment of systemic scleroderma, the EULAR has established guidelines for the management of manifestations, organized by affected body system [69]. For patients with systemic scleroderma-associated Raynaud phenomenon, evidence supports nifedipine to reduce the frequency and severity of attacks. As such, oral nifedipine should be considered as first-line therapy. Phosphodiesterase-5 (PDE-5) inhibitors should also be considered [69]. For patients with severe disease who do not improve on oral therapy, intravenous iloprost is the recommended approach.

Intravenous iloprost is also recommended for patients with systemic scleroderma who experience digital ulcers [69]. PDE-5 inhibitors have been proven to expedite healing and prevent the development of digital ulcers and should be considered for these patients. Patients who do not respond to calcium channel blockers, PDE-5 inhibitors, or iloprost therapy, may be prescribed bosentan, which has been shown to reduce the number of new digital ulcers in patients with systemic scleroderma. Physical therapy for the hands is important to prevent contractures. For patients with Raynaud phenomenon, biofeedback is sometimes useful for controlling temperature in the hands and feet [46].

For patients whose systemic scleroderma is characterized by pulmonary arterial hypertension, EULAR recommends treatment with endothelin receptor antagonists (e.g., ambrisentan, bosentan, macitentan), PDE-5 inhibitors (e.g., sildenafil, tadalafil), or riociguat [69]. In cases of severe disease, intravenous epoprostenol is the first-line option. In cases of malabsorption by the small intestine, absorption often improves with the use of tetracycline, which destroys the bacterial overgrowth that occurs with hypomotility [46].

Hypertension is treated aggressively with angiotensin-converting enzyme (ACE) inhibitors to prevent irreversible renal damage [46]. The risk for scleroderma renal crisis in increased in patients taking glucocorticoids, and these patients should be closely monitored [69].

Arthritis responds to NSAIDs, and the dry eyes (sicca syndrome) of Sjögren syndrome are helped by artificial tears. A patient with dry mouth (xerostomia) should have frequent dental exams, because this condition predisposes patients to severe dental caries [46].

Specific Nursing Measures

Patients with known or suspected systemic scleroderma should be thoroughly assessed, including the skin, joints, and cardiovascular, pulmonary, and gastrointestinal status. The eyes and mouth should be evaluated for adequate lacrimal and salivary gland secretions. It is important to closely monitor blood pressure and review laboratory results. Venipuncture in the antecubital area may be difficult because of skin changes; further, finger sticks should be avoided. If only a small amount of blood must be drawn, the earlobe may be the best site [35].

Patient education should include a clear explanation of the nature and course of systemic scleroderma, including signs of more serious involvement. For some patients, demonstration of range-of-motion exercises to prevent joint contracture may be warranted. Patients should be encouraged to use moisturizing lotions to decrease dryness [35].

Patients with Raynaud phenomenon are advised to avoid cold, ergotamine, and amphetamines. They should be cautioned to take precautions against cold weather, including the use of warm gloves and socks. The use of nicotine should be avoided, as it is associated with pronounced peripheral vasoconstriction, which markedly aggravates Raynaud syndrome [35].

Patients with esophageal dysmotility should be advised to eat small, frequent meals and to chew their food thoroughly; meals should be followed with water. Proton pump inhibitors (PPIs) and antacids after meals and at bedtime can help to help to relieve gastroesophageal reflux disease. Resting and sleeping with the head of the bed elevated may also help to relieve symptoms [35].

The face and hands often undergo considerable changes in scleroderma, which alters the patient's appearance and manual dexterity. The facial skin becomes taut, the nose may become beaked, and telangiectasias may appear on the face. Tapering of the fingers, with tightness of the overlying skin, occurs as flexion contractures may be present [35]. These physical changes may cause varying levels of disability, but they can also have a negative effect on the patient's self-esteem and self-worth. Referral to mental health care and participation in support groups can be helpful.

TRAUMATIC DISORDERS

Sprains and Strains

Traumatic injuries to the soft tissues surrounding joints—muscles, ligaments, and tendons—are called sprains and strains; chronic injury is joint instability. The acute injury may arise from blunt trauma to the muscle or joint; excessive exercise; or twisting, stretching, or forcible extension of a joint (e.g., "twisting" the ankle). Surgery is seldom needed unless complete rupture occurs, but the pain of such an injury can be severely limiting [70].

A sprain is an injury to a ligament caused by forcing a joint beyond its normal range of motion. The ligament may be stretched or actually torn. Sprains usually occur following a blunt blow during sports activities or falls. A strain is an injury to a muscle and/or tendon at any location from origin to insertion.

Strains are associated with excessive stretching of a muscle or muscle unit; they usually do not occur because of a blow or direct trauma. Poor conditioning, improper warm-up before activity, muscle fatigue or weakness, and strength imbalance can all contribute to muscle or tendon strain. Both strains and sprains have a high incidence of recurrence [70].

Clinical Manifestations

A sprain causes pain, swelling, local hemorrhage, spasm of the muscle that moves that joint, and disability. Pain occurs with passive movement of the joint, and there is intense pain over the involved ligament itself. Sprains are graded according to damage to the ligaments and the resultant joint instability [70]. A Grade I sprain is characterized by slight stretching and microscopic tearing of the ligament fiber, mild tenderness, and swelling around the joint. A Grade II sprain is identified by partial tearing of the ligament, moderate tenderness and swelling, and an abnormal looseness in the joint. The most severe is a Grade III sprain, which consists of a complete tear of the ligament, significant swelling and tenderness, and substantial instability.

The most common sprains affect the ankle and occur when inversion of the foot tears a ligament, usually the anterior talofibular ligament. Knee sprains cause swelling, hemarthrosis, significant decrease in range of motion, and joint laxity. Often the person hears a "pop" when the injury occurs and later describes the knee as feeling as it is going to "give way." The medial collateral ligament is most commonly involved [70]. Following the acute injury, patients are usually able to bear weight.

Strains cause pain, swelling, muscle spasm, and hemorrhage into the muscle. Discoloration and weakness may also be present. Pain increases with active flexion or passive stretching, which helps in differentiating strains from sprains. Strains are graded according to loss of muscle strength [70; 71]:

- Grade 1: A mild injury with no appreciable tissue tearing and no substantial (less than 5%) loss of function or strength
- Grade 2: A moderate injury with nearly half of muscle fibers torn, reduced strength, and some residual function
- Grade 3: A severe injury resulting from the complete rupture of the muscle, severe swelling and pain, and complete loss of function

Therapeutic and Specific Nursing Measures

Approaches to the treatment of strains and sprains are similar. Before initiating treatment, a thorough assessment and history to determine the nature and cause of the injury as well as any significant health problems that may influence the treatment. When a suspected strain or sprain occurs, the first-line treatment consists of five components known by the acronym PRICE:

- **P**rotection: The affected joint or muscle should be covered to minimize the risk of additional traumatization.
- **R**est: The patient should take steps to avoid use of the joint, tendon, or muscle to allow time for repair and healing.
- **I**ce: The application of cold will reduce pain and swelling (by causing vasoconstriction), and patients should be instructed to apply cold compresses up to several times per day, but to limit duration to 20 minutes or less.
- **C**ompression: In order to reduce diapedesis and promote lymphatic drainage, the area may be bandaged. Patients should be instructed that wrappings should not be so tight as to restrict circulation.
- **E**levation: The affected limb should be elevated to the level of the heart (or as close as possible) to promote venous return and reduce inflammation.

The PRICE regimen is usually continued for one week after injury, though there is some controversy about whether cold or heat is used after the first 24 hours. Cold is usually recommended for five to seven days because of its anti-inflammatory and analgesic effect. Then, wet heat may be used to aid in muscle relaxation and promote blood flow to the area [35].

With a second- or third-degree sprain, an x-ray should be taken to rule out fracture. Patients with sprains are usually immobilized for one week. When all pain on motion has ceased, patients can begin active range-of-motion and muscle-strengthening exercises. NSAIDs are the treatment of choice [35].

The PRICE regimen and NSAIDs are also appropriate for management of a strain. Emphasis is placed on prevention of recurrence through the use of muscle-strengthening and stretching exercises. Patients should be advised to engage in warm-up exercises before engaging in strenuous activity. For example, for patients with chronic ankle sprain/instability, slow stretching of the Achilles tendon daily can effectively reduce the incidence of recurrent sprain. Surgical intervention is recommended only in cases of complete muscle rupture [35].

Rhabdomyolysis

Rhabdomyolysis is a condition that develops as a result of the rapid dissolution of damaged or injured skeletal muscle [72]. Though not strictly a traumatic disorder, the most common cause of rhabdomyolysis is direct trauma to the skeletal muscle. However, any trigger of muscle destruction can theoretically result in rhabdomyolysis, and additional causes include infection, drugs/toxins, electrolyte disorders, endocrine disorders, extremes of body temperature, and excessive exertion [73].

As discussed, the function of skeletal muscle relies on ATP metabolism, electrolyte exchange, and intact myocytes. When these factors break down, the intracellular components of the muscle (e.g., electrolytes, creatine kinase, lactate dehydrogenase, myoglobin) are released into the body and enter the bloodstream. In more severe cases, this can lead to acute kidney injury, electrolyte imbalances, renal failure, and even death.

Clinical Presentation

The presentation of rhabdomyolysis is typically believed to consist of muscle pain, weakness, and discolored (reddish-brown) urine. Though this is considered the "classic" triad of symptoms, less than 10% of patients will present with all of these symptoms [73]. More than half of patients present only with myoglobinuria.

Diagnosis of rhabdomyolysis depends on detection of plasma creatine kinase. A diagnostic level has not been definitively identified, but most experts use a concentration five times the upper limit of the normal reference range (1,000 IU/L) [72].

Therapeutic Measures

What is the standard of care for patients with rhabdomyolysis?

Treatment of rhabdomyolysis focuses mainly on prevention of kidney damage and acute renal failure. Therefore, fluid therapy to increase urine output (and dilute urine) is the standard of care. The American Society of Nephrology has identified an ideal fluid regimen for these patients consisting of half isotonic saline (0.45%, or 77 mmol/L sodium), to which 75 mmol/L sodium bicarbonate is added [74]. At least 3–6 L should be administered per 24 hours; however, up to 10 L (or more) may be given if continuous supervision is possible. If necessary, 10 mL/hour of mannitol 15% may be added to further increase urine output. In cases that have already progressed to overt renal failure, extracorporeal blood purification is warranted [74].

In addition, supportive treatment of resultant hypovolemia and electrolyte imbalances (e.g., hyperkalemia, hypocalcemia) is necessary. Measures to help stabilize temperature are often necessary. Patients' input and output should be monitored and documented. Pain management is often necessary, and patients should be assessed for severity and quality of ongoing pain.

SPECIFIC DISORDERS OF THE JOINTS

Because of their location and constant use, joints are particularly susceptible to stress, injury, and inflammation. In addition, many autoimmune disorders manifest in the joints.

DISORDERS OF MULTIFACTORIAL ORIGIN

A wide variety of joint conditions are multifactorial in origin, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, gout and pseudogout, low back pain, scoliosis, Charcot arthropathy, and carpal tunnel syndrome [37; 75].

Joint disorders of multifactorial origin can disrupt normal life activities, and families and job security can be negatively affected unless patients seek proper medical attention and counseling. Among the disorders discussed in this section, only gout can be cured, but the other disorders can be controlled to varying degrees so that in most instances the patient can maintain a fairly normal lifestyle [37; 75].

Psoriatic Arthritis

Psoriasis is often associated with inflammatory arthritis and a negative rheumatoid factor. Psoriatic skin lesions usually precede the development of arthritis, and in most cases, there is correlation between joint flares and skin flares. However, some patients with psoriatic arthritis have very mild or no psoriatic skin lesions. Heredity is the most specific risk factor, but environmental factors also play a role; the exact etiology is unknown [76].

Clinical Manifestations

The manifestations of psoriatic arthritis vary from patient to patient. Some have distal joint involvement, while others have widespread deformity, ankyloses, and joint destruction. The disease can be symmetrical or asymmetrical, and some patients have spondylitis, sacroiliitis, eye problems, or a combination. Nodules are not present with psoriatic arthritis [76].

In patients with psoriasis, silver-white scaly patches develop on the elbows, legs, scalp, and back. Nails are often pitted (20 pits or more per nail), and arthritis is more common with nail changes than with skin lesions. Onycholysis is common [76].

Joint symptoms usually begin with the acute onset of pain and swelling of distal interphalangeal (DIP) joints. A gout-like symptom in the great toe often gives a "sausage" appearance to the joint, but the disability is usually not as great as with rheumatoid arthritis. Spondylitis is often found in families with a strong background of psoriatic arthritis. Upon x-ray

examination, some people show marked articular destruction with resorption of bone. A shortening of the middle phalanx of the DIP joints of fingers and toes has a characteristic cuplike appearance, and in some cases, an entire phalanx is destroyed. Extra-articular symptoms include conjunctivitis, episcleritis, or uveitis [76].

Laboratory studies of patients with psoriatic arthritis reveal mild anemia, an elevated ESR, negative rheumatoid factor, positive ANA, and an elevated uric acid level. Clinical diagnosis is made by considering nails, peripheral arthritis, and spinal involvement. Nail and skin changes in psoriatic arthritis may be hard to differentiate from those in reactive arthritis [76].

Therapeutic Measures

Therapeutic measures for psoriatic arthritis are aimed at both the arthritis and the psoriasis [76]. Nonpharmacologic approaches include physical and occupational therapy, exercise, smoking cessation, weight loss, and massage therapy. Symptoms may be controlled with NSAIDs and/or glucocorticoids (oral or injection). In treatment-naive patients with active psoriatic arthritis, a tumor necrosis factor (TNF) inhibitor is recommended over oral, small-molecule drugs (OSMs) as a first-line option. However, OSMs may be used instead of a TNF inhibitor in patients without severe disease, particularly if they prefer an oral treatment option [77].

Gout

Gout is a metabolic disorder associated with elevated urate levels in the body and is the most common cause of inflammatory arthritis in the United States. Gouty arthritis is characterized by recurring episodes of acute, usually monoarticular, arthritis that tend to remit over several days to weeks; however, undiagnosed, untreated patients are at risk for developing a chronic deforming arthritis. An estimated 9.2 million adults in the United States are affected [78]. Gout is rarely encountered in persons younger than 30 years of age, with the predominant age range being 30 to 60 years. However, onset may occur in men in their early 20s who have a genetic predisposition and lifestyle risk factors. The peak age of onset in women is the sixth to eighth decade of life [78]. The estimated prevalence of gout is 5.9% in men and 2.0% in women [78]. The prevalence and incidence of gout has increased over the past several decades [78; 79].

Gout develops in persons with hereditary or acquired chronic hyperuricemia or in those with marked perturbations in serum urate associated with such factors as alcohol consumption, drug use, eating foods high in purines, overweight/obesity, and myeloproliferative disorders [78; 80]. The normal serum urate is generally considered to be ≤6.8 mg/dL. The majority of patients at the time of an acute flare have demonstrable hyperuricemia (in excess of 7 mg/dL); however, about 20% do not. The presence of hyperuricemia in the absence of symptoms is not diagnostic of gout [78]. In all cases, the hyperuricemia is caused by some dysregulation in the balance between production and excretion of urate. An estimated 80% to 90% of gout cases are due to urate underexcretion and not overproduction [78]. Hyperuricemia can occur without precipitating gout, and in the absence of symptoms, it may not warrant intervention [78; 81].

The American College of Rheumatology conditionally recommends that patients with gout limit their consumption of purine-rich foods (e.g., meat and seafood), alcohol, and high-fructose corn syrup (particularly in sweetened soft drinks and energy drinks).

(https://www.rheumatology.org/Portals/0/Files/Gout-Guideline-Final-2020.pdf. Last accessed September 26, 2022.)

Certainty of Evidence: Low or very low

Uric acid is a final metabolic product of purine nucleotides found in many foods and in human tissue. Intermediary processes of purine metabolism include the initial breakdown of purines to inosine and then to hypoxanthine. Hypoxanthine is metabolized to xanthine, and xanthine to uric acid, with both stages catalyzed by the enzyme xanthine oxidase (the primary site for pharmacologic intervention by allopurinol) [82].

The human body is limited in its capacity to excrete a heavy urate load. In the setting of persistent hyperuricemia, often combined with stress to weight-bearing joints such as the great toe, monosodium urate crystals precipitate within joint synovial fluid, producing an intense inflammatory reaction. With chronicity, adjacent tissues may become saturated with urate, leading to deposits within articular, periarticular, bursal, bone, auricular, and cutaneous sites. These deposits, termed tophi, are detectable on physical exam or by radiographs and are a cardinal pathognomonic feature of gout. The presence of crystals, within joint fluid or in tissue, activates monocytes and macrophages to clear the crystals through phagocytosis. The release of proinflammatory cytokines and chemokines into the immediate area triggers an acute inflammatory reaction and influx of neutrophils into the joint space [83; 84; 85].

Clinical Manifestations

The clinical presentation of gout is typically one of arthritis and intense pain, and patients may exhibit inflammation and edema in the afflicted joint. Although the great toe is the most common site, other joints and their surrounding tissue can be affected, including the insteps, ankles, heels, knees, wrists, fingers, and elbows [78]. Gout may be confused with other causes of arthritis as all forms share the cardinal signs of inflammation: pain, redness, warmth, tenderness, and swelling [80; 86]. While gout initially manifests in severe, discrete episodes of pain, the condition may progress to more frequent attacks

with shorter asymptomatic periods between attacks [78; 86]. Synovial fluid analysis is the gold standard for diagnosing gout, confirmed by the presence of monosodium urate.

Therapeutic and Nursing Measures

Gout is perhaps the most easily treated, and preventable, form of arthritis. This is due to widespread understanding of its underlying mechanisms and the availability of effective treatment [80]. It is managed by controlling the current acute attack and preventing future attacks. Medications addressing the underlying pathophysiology include the xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat and the uricosuric agents probenecid, fenofibrate, and losartan [80; 87]. (Note: The use of fenofibrate and losartan for the treatment of gout is off label.)

The initial steps include patient education, testing to rule out other causes of hyperuricemia, and evaluation of the disease burden to determine appropriate treatment. All patients with hyperuricemia and established gout should be advised to begin dietary modification. This involves avoiding organ meat high in purine content, high-fructose corn syrup, and excessive alcohol use. Portions of high purine-content seafood, sugar, and salt should be limited. The ideal diet will include low- or non-fat dairy products and vegetables. Other lifestyle modifications can also assist in managing gout, including weight loss in overweight patients, regular exercise, smoking cessation, and adequate hydration [83; 87; 88].

The acute pain of gout may be treated with NSAIDs, a cyclo-oxygenase-2 (COX-2) inhibitor, systemic corticosteroids, or oral colchicine monotherapy in mild-to-moderate disease (≤6 on a 10-point pain scale). Combination therapy (i.e., colchicine and NSAIDs, oral corticosteroids and colchicine, or intra-articular steroids with each of the other options) may be used in cases of severe disease with intense pain and polyarticular presentation. Intramuscular triamcinolone acetonide is recommended in patients unable to take oral medication or likely to be poorly adherent to the multidose oral regimen [87].

An inadequate response to therapy after escalation (<20% pain reduction within 24 hours or <50% pain reduction after ≥24 hours) should prompt reconsideration of the diagnosis. If gout is confirmed, switching to another form of monotherapy or adding a second agent may prove effective [83; 87].

Urate-lowering therapy should be initiated in all patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares [88]. Therapy should be started within 24 to 36 hours of the onset of an acute gout attack unless otherwise contraindicated. Urate-lowering therapy is not recommended for patients experiencing their first flare, or for patients with asymptomatic hyperuricemia (serum urate >6.8 mg/dL) with no prior gout flares or subcutaneous tophi [88]. Allopurinol (≤100 mg/day) is the preferred first-line agent. Febuxostat (≤40 mg/day) is an acceptable alternative [88]. Probenecid may be used as an alternative to allopurinol or febuxostat if there is contraindication or intolerance to these preferred agents. However, probenecid should be avoided in patients with a history of urolithiasis [83; 87; 88].

Clinicians may also consider screening for the HLA-B*5801 allele, which is associated with high risk of severe allopurinol hypersensitivity reaction. High-risk persons include Koreans with an estimated glomerular filtration rate <60 mL/min/1.73 m^2 or those with Han Chinese or Thai ancestry [89].

Anti-inflammatory prophylaxis (against precipitating an acute flare) is recommended when initiating urate-lowering therapy in asymptomatic patients [88]. Colchicine was once the treatment of choice but is now less commonly used than NSAIDs because of its narrow therapeutic window and risk of toxicity [90]. To be effective, colchicine therapy is ideally initiated within 36 hours of onset of the acute attack [78]. In the case of colchicine intolerance or contraindication, prednisolone may be used [88]. Prophylaxis should continue after achieving target serum urate level for three months in patients without tophi, for six months in patients with resolved tophi, and with any remaining signs of gout activity in all patients [88].

Patients with intermittent symptoms or chronic synovitis with tophi (chronic tophaceous gouty arthritis) should be treated with a single-agent XOI, such as allopurinol, at a dose to achieve and maintain the serum urate level within normal range [83; 87]. If the serum urate target is not achieved or disease activity persists, a uricosuric agent may be added to the XOI. Pegloticase therapy should be considered if the serum uric target is not achieved, disease activity persists, more than seven attacks occur per year and no tophi, two or more attacks per year and tophi, or chronic tophaceous gouty arthritis is present [88; 89].

Pseudogout

Calcium pyrophosphate deposition disease, or "pseudogout," is a similar crystalline arthritis that occurs in patients with underlying osteoarthritis and is identified by the presence in synovial fluid of calcium pyrophosphate dehydrate crystals [78; 80; 85]. X-ray findings of articular cartilage calcification usually accompany it. Many patients with pseudogout have other disorders, such as diabetes, hypothyroidism, and gout [37].

Clinical Manifestations

In pseudogout, arthritis occurs in a large joint, which is erythematous, swollen, warm, and painful. Like gout, pseudogout is usually monoarticular, but involvement of other joints can follow in succession. Attacks are often precipitated by trauma, surgery, or medical illness. Onset of symptoms is rapid, with a peak in 12 to 36 hours. Episodes are intermittent, usually involve the same joint, and typically last about one to two weeks. Joints are normal between attacks [37].

Therapeutic and Nursing Measures

The deposition of calcium pyrophosphate dihydrate crystals cannot be reversed. Acute attacks of pseudogout are treated with NSAIDs, colchicine, and/or oral corticosteroids; in more severe cases, drainage of the affected joint may be helpful [37].

Nursing measures for pseudogout include careful joint assessment, thermo- or cryotherapy, and monitoring for symptoms and signs of systemic illness and side effects of medications [18]. Patient education for home care includes instruction in the safe application of heat or ice, range of motion exercises, and the nature and side effects of prescribed medications. A weight-reduction diet can be helpful promote the long-term health of weight-bearing joints [18].

Low Back Pain

When it occurs, back pain is most often localized to the lower back, and chronic back pain is almost always chronic low back pain. Although acute-onset low back pain is a common problem that usually resolves within four to six weeks, many patients develop a persistent, disabling pain syndrome with a diminishing prognosis for return to normal function. When low back pain continues beyond 12 weeks, the prospect for subsequent remission is poor and progression to chronic low back pain is likely. Chronic low back pain imposes a great burden: for patients, pain and disability; for society and the healthcare system, an enormous expense in direct and indirect costs.

Risk factors for developing low back pain can be generally categorized as nonmodifiable, such as old age, female sex, poverty, and lower education level, and modifiable, including higher body mass index (BMI), smoking, lower perceived general health status, physical activity (e.g., bending, lifting, twisting), repetitive tasks, job dissatisfaction, and depression. The greatest contributors to low back pain episodes are single-event or repetitive exposures to mechanical stress and age-related degenerative spinal changes. With chronic low back pain, mechanical and biophysiologic factors play a minimal secondary role to the primary contribution from psychosocial factors [91].

Clinical Manifestations

The onset of low back pain is described as discomfort in the vicinity of the low back ranging from a dull ache to a sudden, sharp, shooting or stabbing pain and may include limited flexibility and/or range of motion or inability to stand straight [92]. Although the symptoms of back pain can originate anywhere from the thoracic spine to the sacrum and coccyx, most cases originate in the lumbar spine, as this is the site of support for upper body weight [92].

With low back pain, the clinical presentation varies according to etiology. In general, radicular pain suggests nerve root involvement, while axial pain suggests disk degeneration, facet arthropathy, sacroiliac (SI) joint arthropathy, or myofascial pathology of the spine.

Nonspecific Low Back Pain. Up to 85% of low back pain in patients presenting to the primary care setting is nonspecific, meaning that it lacks a clear origin and is not caused by specific local or systemic disease or spinal abnormality [93]. Nonspecific low back pain is a diagnosis of exclusion made after ruling out serious causes of the back pain. Although pain can originate from ligaments, facet joints, muscle, fascia, nerve roots, the vertebral periosteum, or outer portions of the disk, the effective management of nonspecific low back pain does not require a precise anatomic diagnosis [94]. The pain is usually unilateral and may radiate to the buttocks or posterior thigh but not past the knee. This can lead to incorrect diagnosis of radiculopathy or disk herniation. However, true radicular symptoms radiate below the knee in a dermatomal distribution and can involve sensory loss, weakness, or reflex changes. Painful spasm may be present, and pain may be worsened by movement, while lying flat decreases the pain. Complaints of numbness, weakness, or bowel or bladder dysfunction are absent [95]. Degenerative changes revealed by lumbar imaging should usually be considered nonspecific, because they poorly correlate with symptom severity [96].

Lumbosacral Radiculopathy. Lumbosacral radiculopathy is a clinical diagnosis of nerve root irritation and compression, resulting in a symptom distribution of the affected lumbar or sacral nerve root such as numbness, weakness, or paresthesia. Sciatica is the most common symptom of lumbar radiculopathy and refers to pain that radiates down the leg below the knee in the distribution of the sciatic nerve to indicate nerve root compromise from mechanical pressure or inflammation [96].

Causes of lumbar radiculopathy include disk herniation, arthritic degeneration, cord compression, spinal stenosis, tumor, and infection. With herniated disk, the pain is described as a deep, aching, axial midline pain concurrent with radicular pain. Discogenic pain results from a tear in the outer disk layer (annulus fibrosis) that causes the inner gelatinous material (nucleus pulposus) to prolapse, inflame, and compress a nerve root [95]. The resulting pain from pressure and nerve irritation improves with the resolution of local inflammation, and the disk protrusion may spontaneously remit with time. Although disk herniation and radiculopathy are often viewed as causally linked, herniation is often asymptomatic and only occasionally the cause of sciatica [95].

Lumbar Spinal Stenosis. Lumbar spinal stenosis refers to the frequently age-related narrowing of the spinal canal that may result in bony constriction of the cauda equina and the emerging nerve roots [96]. Spinal stenosis can produce pain in the low back that radiates down the back of both legs, often worsened with standing or walking. To make the pain more bearable, patients often walk a short distance with a hunched back, and then sit down for relief. The pain will then dissipate after several minutes. Congenital lumbar canal stenosis is a predisposing factor. Patients show less tenderness over the lumbar spine than those with acute lumbar disk herniation, and the straight leg-raising test may be normal [97].

Most persons 60 years of age and older exhibit varying degrees of spinal stenosis from disk herniation, osteophytes, or degenerative spondylolisthesis. Fortunately, clinical pain manifests in less than 30% and, just as with degenerative disk disease, there is poor correlation between symptom severity and extent of spinal canal stenosis revealed by MRI [95].

Myofascial Pain. Myofascial pain of the low back or neck is common, especially following trauma or repetitive motion injury. This is thought to result from strain or sprain to the muscles and ligaments. Myofascial pain is described as a deep, aching, poorly localized discomfort made worse by activity. It can be limited to discomfort in the paraspinal muscles or may extend to the buttocks and upper thigh areas [98].

Epidural Compression Syndrome. Epidural compression syndrome is an umbrella term that encompasses spinal cord compression, cauda equina syndrome, and conus medullaris syndrome. While these conditions differ in the level of neurologic deficit at presentation, they are otherwise similar in symptoms, evaluation, and management. Massive herniation of a midline disk, typically at the L4 to L5 disk level, is the most common cause of epidural compression syndrome. Tumor, epidural abscess, spinal canal hematoma, or lumbar spine spondylosis represent other causes [95].

In these patients, neurologic status at diagnosis is the greatest predictor of ultimate neurologic outcome and underscores the importance of early accurate diagnosis. The dominant symptom is back pain with accelerating pain severity. Pain from epidural spinal cord compression is made worse with recumbent positioning, and unilateral or bilateral radiculopathy may develop over time. For many patients, leg pain or neurologic symptoms are more dominant than back pain. Also common at diagnosis is symmetrical lower extremity weakness that may have progressed to gait disturbance or paralysis. Decreased lower extremity reflexes are associated with cauda equina syndrome [95].

Lumbar Facet Joint Syndrome. Lumbar facet joint syndrome is seen in as many as 35% of patients with low back pain and is frequently associated with arthritis or lumbar facet joint injury [97]. Dominant symptoms include unilateral low back pain that may radiate down the back or front of the thigh and morning stiffness with isolated facet arthropathy [99]. Tenderness is usually found over the lumbar paraspinal muscles and facet joints. Back pain is worsened with back extension and lateral rotation to the side of the pain, and the leg-raising test is negative. MRI and CT findings of facet joint arthropathy do not correlate with clinical findings [97].

Sacroiliac Joint Syndrome. SI joint syndrome typically manifests as localized pain in the lower back or upper buttock area that overlies the SI joint. Pain is intensified by attempts to walk up stairs, and while pain may be referred to the posterior thigh, extension below the knee is unusual [100]. Tenderness over the SI joint is often found in physical examination, and pain is aggravated by the Patrick test or single-leg standing [97]. The onset of SI joint pain is usually gradual (over months to years), and although etiology is often elusive, trauma, infection, and tumor represent infrequent yet known causes of SI joint pain [100].

Assessment and Diagnosis

What are considered "red flags" when assessing the patient with chronic low back pain?

Most patients with acute low back pain have ligamentous or muscle strain syndrome, follow a benign course, and show significant improvement within two to three weeks. The challenge for clinicians is to recognize early the possibility of serious disease, such as spinal metastatic cancer or vertebral and epidural space infection, and then to identify those with herniated disk, radiculopathy, or spinal stenosis.

The proper assessment of the patient with back pain requires vigilance and careful attention for factors and warning signs suggestive of serious or life-threatening disorders. A thorough history and physical examination should be performed on all patients, during which the patient is assessed for the presence of warning signs or "red flags." Red flags represent alarm symptoms or signs that warrant prompt, specific diagnostic testing, urgent treatment, or referral to a specialist. Among these are weight loss, prior history of cancer, nocturnal or rest pain, age older than 50 years, recent trauma, fever and chills, history of injection drug use, chronic corticosteroid therapy, difficulty urinating, bowel or bladder incontinence, and neurologic deficits such as saddle anesthesia, perianal or perineal sensory loss, or motor weakness in the extremities [93; 95; 101]. As an example, there is a common association between spontaneous vertebral fracture and any combination of age older than 70 years, female gender, recent trauma, and prolonged corticosteroid use. There is also a moderate to highly significant predictive value for age older than 50 years, history of prior cancer, unexplained weight loss, and failure of conservative therapy in identifying spinal malignancy [101].

Patients should also be assessed for "yellow flags," or risk factors for poor prognosis and chronicity [94; 101]. Areas to explore include maladaptive beliefs, attitudes, and behaviors regarding the back pain and recovery, such as passivity or reluctance to self-manage, dependency on the provider to "cure," fear avoidance beliefs, and beliefs that harm will come from activity and discomfort. Other areas include depression, anxiety, maladaptive coping response to stress, social withdrawal or isolation, and lack of social support. Adverse economic and work environment circumstances, such as job dissatisfaction, excessive and inflexible physical workplace demands, high levels of work-related stress, poor workplace social support, and adversarial or dysfunctional workplace relationships should also be noted [94]. Early detection and intervention (if indicated) for problematic motivational, emotional, or social dysfunction are important because these factors influence the selection and effectiveness of therapeutic interventions.

In the absence of red flags, use of imaging and diagnostic tests for acute low back pain is discouraged, as imaging findings rarely change clinical management. Overuse of lumbar imaging in low back pain correlates with, and likely contributes to, the two- to threefold increase in surgical rates for low back pain over the last 10 years [93]. Assigning significance to imaging anomalies requires skill at the specialist level to integrate historical, clinical, and imaging findings. Imaging abnormalities are essentially normative by 40 years of age; for instance, 80% of persons 60 years of age and older exhibit a protruding disk, which is symptomatic for only a fraction of patients. Incorrect communication of imaging findings to the patient may lead to patient fixation, contribute to fear-avoidance behaviors, and increase the risk of iatrogenic aggravation of chronic low back pain. Guidelines suggest that physicians without advanced training defer imaging tests to qualified specialists [93; 102].

However, imaging and other testing should be performed in patients with new-onset or progressive neurologic deficits and those with suspicion of serious underlying conditions. In patients with persistent pain and symptoms consistent with radiculopathy or spinal stenosis, MRI should be performed only when such patients are candidates for surgery or epidural steroid injection. CT scanning is an alternative option to first-line MRI [93].

Therapeutic Measures

Although acute low back pain improves in most patients within three to six weeks using conservative therapy, up to 33% of patients with low back pain report pain of moderate or greater severity at one-year follow-up and 20% report ongoing pain severe enough to limit activity [96]. With chronicity, low back pain may become disabling and impose a severe emotional and functional burden. The management goals for chronic low back pain are to minimize pain and disability, improve functional status, and facilitate restoration of normal activity, while limiting the use of marginally effective or inappropriate medication [93].

Many pharmacologic therapies and minimally invasive or invasive procedures have been utilized in a strategy designed simply to relieve pain—with variable results. However, there is little evidence these focused pain approaches are comparable or superior to interventions that focus primarily on restoration of function instead of pain relief. This contradicts the biomedical model in medicine that emphasizes escalation of costly and invasive therapies to achieve "pain cure" in patients lacking response to lower-intensity approaches [102; 103]. It is now recognized that treatment for conditions such as chronic low back pain persisting in the absence of a unique underlying pathologic lesion must address potential contributory factors such as affective disorders, maladaptive beliefs and coping skills, and interpersonal and occupational dysfunction. Dysregulated cortical, pre-frontal, and higher neural level mechanisms associated with chronic low back pain are being identified and may represent therapeutic targets in functional restoration-based approaches. As with other chronic pain syndromes, greater understanding of pain pathway alterations will better inform therapy selection.

Virtually universal among practice guidelines for chronic low back pain is the emphasis on a multidisciplinary, multi-modal approach that includes exercise and activity, cognitive restructuring of maladaptive attitudes and coping skills, a behavioral component addressing fear avoidance, physiotherapy and manual therapy, and analgesics as indicated [93; 96; 102; 104; 105; 106; 107]. This is often best accomplished by consultation or referral to an established pain treatment center. Multidisciplinary functional restoration programs, which are intensive (more than 100 hours) biopsychosocial interventions whereby physical rehabilitation is combined with cognitive-behavioral therapy and delivered by an interdisciplinary team, embody this recommendation. Moderate-to-strong evidence supports their efficacy in chronic low back pain. They have been found effective in reducing pain and improving physical function, work readiness, and return to work. Weaker outcomes are found in programs that are less intensive or lacking a behavioral component. Patients who do not improve with less intensive therapy options and have high levels of pain, distress, and disability should be considered for multidisciplinary functional restoration programs [94].

According to the Institute for Clinical Systems Improvement, clinicians should advise patients with acute and subacute low back pain to stay active and continue activities of daily living within the limits permitted by their symptoms.

(https://www.icsi.org/guideline/low-back-pain. Last accessed September 26, 2022.)

Strength of Recommendation/Level of Evidence: Strong Recommendation/Moderate Quality Evidence

Scoliosis

Scoliosis is a lateral curvature of the spine, most commonly in the thoracic area with convexity to the right and compensatory convex curve to the left in the cervical and lumbar areas. Scoliosis can be functional (a result of poor posture or leg-length discrepancy) or structural (a result of deformity of the vertebral bodies, paralysis, congenital malformations, or idiopathic causes). Idiopathic causes are the most common and appear with increased growth during adolescence. It disproportionately affects girls, who are 10 times more likely to be diagnosed than boys at 10 years of age or older [108].

Clinical Manifestations

Symptoms of backache, fatigue, and dyspnea occur only after scoliosis is well established. Untreated scoliosis can result in pulmonary insufficiency from decreased lung capacity, back pain, degenerative arthritis of the spine, intervertebral disease, and sciatica [108]. While screening for idiopathic scoliosis has typically occurred between 10 and 18 years of age, the current evidence is insufficient to assess the balance of benefits and harms [109].

Older patients may exhibit kyphosis, a postural curvature of the spine that is due to aging, disc degeneration, atrophy of spinal muscles, osteoporosis, or vertebral collapse. Adults with kyphosis have a rounded back and possible weakness and generalized fatigue. Kyphosis rarely produces local tenderness except in severe osteoporosis with compression fractures [108].

Therapeutic Measures

Early treatment of scoliosis consists of a combination of physical therapy, bracing, and/or surgery. If the condition is untreated in adolescence, problems that develop can only be treated symptomatically. Any upper respiratory tract infections are treated aggressively to prevent pneumonia and atelectasis [108].

Specific Nursing Measures

Patients with scoliosis often have body image issues and difficulty finding clothes that fit properly. When patients with scoliosis are hospitalized for any problem, careful attention to positioning is essential; improper positioning is not only extremely uncomfortable for the patient, but it can precipitate a vertebral fracture, especially in those with osteoporosis [108].

Carpal Tunnel Syndrome

Carpal tunnel syndrome is generally associated with such umbrella terms as repetitive stress injuries, work-related upper extremity disorders, musculoskeletal disorders, entrapment neuropathies, and cumulative trauma disorders [110; 111]. Specifically, carpal tunnel syndrome is a painful disorder of the wrist and hand that occurs when the median nerve (which runs from the hand to the forearm) becomes compressed [112; 113].

The carpal tunnel is a narrow passageway on the palm side of the wrist. Surrounded by bones and ligaments, the carpal tunnel houses and protects the tendons of the hand and the median nerve, which controls sensations to the thumb and fingers. When the median nerve becomes pinched or compressed (due to swelling or irritation in adjacent tissues or tendons), the result can be pain, numbness, hand weakness, and in extreme cases, loss of hand function. Cases of bilateral carpal tunnel syndrome have been reported, but typically only one hand is affected [112; 114; 115]. Carpal tunnel syndrome is rare in children; it usually occurs only in adults [116].

Clinical Manifestations

The symptoms of carpal tunnel syndrome typically appear gradually and may include [114; 116]:

- Numbness, burning, or tingling in the fingers and palm of the hand
- Pain in the wrist, palm, or forearm, especially during use
- Decreased grip strength
- Weakness in the thumb
- Sensation of swollen fingers, whether or not swelling is apparent
- Difficulty distinguishing between hot and cold

Symptoms may cause waking during the night with the urge to "shake out" the hand or wrist. Symptoms may occur with activities that require prolonged grasping and/or flexing of the wrist (e.g., driving, holding a book). Left untreated, carpal tunnel syndrome can progress to persistent numbness and permanent loss of hand function. In severe and chronic cases, irreversible muscle damage or atrophy may occur [112; 116; 117]. Complete sensory loss in the hand has also been reported.

Assessment and Diagnosis

Early diagnosis of carpal tunnel syndrome is important to prevent muscle atrophy or damage to the median nerve that cannot be reversed by treatment [112; 116]. Early diagnosis, including a physical examination, medical history, routine laboratory tests, and imaging, can also help to identify or rule out other health conditions that may present with similar signs and symptoms and require specialized treatment [118; 119]. The physical examination should include specific testing, such as Phalen's maneuver or Tinel's sign, that can produce the symptoms of carpal tunnel syndrome [114; 116]. In elderly patients, particular attention should be given to the objective evidence of carpal tunnel syndrome rather than subjective complaints [120].

Therapeutic and Nursing Measures

Surgery, corticosteroids, NSAIDs, diuretics, wrist splints, exercise, ultrasound therapy, laser therapy, and yoga are among the methods that have been recommended for the treatment of carpal tunnel syndrome [121; 122; 123; 124; 125]. Although no single treatment method has been universally accepted, there is agreement that the treatment of carpal tunnel syndrome should begin as early as possible and should include attention to underlying causes, such as diabetes or rheumatoid arthritis. There is also agreement that successful treatment depends on patient compliance with the treatment program [116; 126].

Corticosteroid injection has been found to improve patient satisfaction, symptoms, and function when measured at intervals of 2, 4, 8, and 12 weeks. As noted, it demonstrates a more significant overall improvement in the symptoms of carpal tunnel syndrome than oral corticosteroids but does not appear to provide a better long-term outcome (greater than six

months) than splinting or NSAIDs. Two treatment injections do not appear to provide any added benefit when compared to one treatment injection [124; 127].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Academy of Orthopaedic Surgeons, strong evidence supports that the use of steroid (methylprednisolone) injection should improve patient-reported outcomes in those with carpal tunnel syndrome. (https://www.aaos.org/globalassets/quality-and-practice-resources/carpal-tunnel/cts_cpg_4-25-19.pdf. Last accessed September 26, 2022.)

Strength of Recommendation: Strong (Evidence from two or more "high" strength studies with consistent findings for recommending for or against the intervention)

Splinting has been found to improve patient satisfaction, symptoms, and function when measured at intervals of 2, 4, and 12 weeks. The American Academy of Orthopaedic Surgeons suggests that splinting be considered before surgery. This may be particularly helpful when weighing the risks of surgery versus the benefits. Splinting is not recommended for use after routine carpal tunnel release surgery. The benefit of splinting for postoperative rehabilitation is undetermined [126; 127; 128].

NSAIDs are used to treat a variety of acute and chronic pain conditions, including carpal tunnel syndrome, but opinion varies as to their effectiveness and safety for long-term use [129; 130; 131]. Specifically, NSAIDs have been associated with gastrointestinal and cardiovascular risks and toxicity with long-term use [132].

Diuretics and vitamin B6 (pyridoxine) may also help with temporary relief of symptomatic carpal tunnel syndrome, but their long-term benefits are unproven [127; 131; 133]. Acupuncture, yoga, exercise, laser therapy, activity modification, and ergonomic workplace modifications also have been mentioned as non-surgical treatment alternatives, but most experts agree that further research is needed to determine the viability and efficacy of these methods [116; 124; 126; 127; 131; 134; 135].

Carpal tunnel release is the preferred treatment for patients with chronic or severe carpal tunnel syndrome. It is achieved by either an open or endoscopic procedure [116; 122; 126; 128]. Both types of surgery are generally performed on an outpatient basis under local anesthesia. Open release surgery involves making an incision of up to 2 inches at the base of the palm of the hand and cutting the transverse carpal ligament, which releases pressure on the median nerve [116; 136]. Endoscopic surgery involves making a small, one-half inch incision at the wrist and introducing an arthroscope beneath the transverse carpal ligament. Using the scope as a guide, the ligament is cut, relieving pressure on the median nerve [116; 134; 136].

DEGENERATIVE DISORDERS

Osteoarthritis

Osteoarthritis is the most common form of arthritis and is characterized by degeneration of cartilage and its underlying bone within a joint, with resultant bony overgrowth. This process of tissue breakdown eventually leads to pain and joint stiffness [137]. Osteoarthritis develops most frequently in the knee, hip, and hand. Although pain in the lower back and the neck are the most frequently occurring musculoskeletal conditions and are the leading cause of functional limitation and work absences, the etiology of back and neck pain is often unclear, with many cases involving muscles and ligaments rather than osteoarthritic changes [138; 139; 140].

Osteoarthritis is classified as primary or secondary. The cause of primary osteoarthritis is idiopathic; no abnormality is the cause of changes in the joint [141]. Secondary osteoarthritis is the result of a known cause, most often trauma/injury or systemic diseases. Secondary osteoarthritis is most often found in the shoulder, elbow, and ankle and is more likely to become clinically apparent at a younger age than primary osteoarthritis [141; 142; 143; 144]. A population-based study showed that secondary osteoarthritis related to trauma accounts for approximately 12% of the overall prevalence of symptomatic osteoarthritis of the knee, hip, or ankle [145]. Injuries sustained in sports activities comprise a large portion of post-traumatic osteoarthritis [146]. A wide variety of systemic diseases have been identified as frequent causes of secondary osteoarthritis; these conditions include metabolic diseases, endocrine disorders, bone dysplasias, and crystal deposition diseases [141; 147].

Clinical Manifestations

What is the primary symptom of osteoarthritis of the knee?

The diagnosis of osteoarthritis at most joints is made primarily on the basis of clinical findings, with imaging studies and laboratory tests more useful for ruling out other diagnoses rather than for confirming the diagnosis of osteoarthritis [148; 149; 150]. Although radiographic findings are considered to be diagnostic criteria for osteoarthritis, radiographs are not usually part of the initial diagnostic evaluation for several reasons. The primary reasons are the lack of evidence of early osteoarthritic changes on radiographs and the poor correlation between symptoms and radiographic evidence of osteoarthritis [148; 151; 152; 153]. Thus, the absence of radiographic evidence of osteoarthritis in the presence of joint-related symptoms should not exclude the diagnosis of osteoarthritis.

When obtaining a history, questions should focus on the nature of joint-related symptoms, patients' self-reports of limitations in function or activities, and information related to established risk factors for osteoarthritis. The following questions can help elicit important information needed for a diagnosis:

- Do you have any joints that hurt? If so, how long have they been bothering you?
- When does the pain occur? After certain physical activities? At rest?
- Do you have relief of pain if you rest?
- Does the pain bother you at night? Does pain wake you up at night?
- Are your joints stiff when you wake up in the morning? If so, how long does the stiffness last?
- Do the joints that hurt ever lock up or give out on you?
- Do you have a family history of osteoarthritis or rheumatoid arthritis?
- What types of recreational activities or sports do you participate in? If you play sports, do you do so for leisure or competitively?
- What is your occupation? Are there tasks or activities that are part of your job that bother any joints?
- Have you ever had an injury to a joint?
- Are there daily activities or other tasks that you cannot do because of pain or other symptoms in any joint?

The primary symptom of osteoarthritis of the knee is pain, especially with weight-bearing exercise or activity, that improves with rest. Stiffness in the joint occurs in the morning, lasting 30 minutes or less, and may occur after periods of inactivity [154]. The clinical presentation of hip osteoarthritis is similar to that of knee osteoarthritis, with pain being the most common symptom driving individuals to seek medical care [155]. Pain related to hip osteoarthritis is an ache—most often diffuse—that is usually felt during use of the joint and relieved by rest. Pain is typically gradual, variable, or intermittent; the joint may feel stiff after a period of inactivity [155]. The loss of function or mobility is usually related to the degree of pain.

Osteoarthritis of the hand is characterized by pain with use, which affects one or a few joints at any one time, and mild stiffness in the morning and/or after a period of inactivity [158]. The severity of osteoarthritis-related pain varies, and the pain may be intermittent. The joints most often affected are the distal and proximal interphalangeal joints and the base of the thumb [156; 157; 158]. Individuals who have evidence of osteoarthritis at several joints in the hand are at increased risk for generalized osteoarthritis, and clinicians should evaluate such patients as appropriate [158].

Pain related to osteoarthritis of the shoulder is typically progressive, related to activity, deep in the joint, and often localized posteriorly [142]. Pain is usually present at rest and interferes with sleep, with nocturnal pain becoming more common as the disease progresses. More advanced disease is also associated with stiffness that limits function.

Individuals with osteoarthritis of the elbow typically have pain, stiffness, and weakness in the joint [143]. Later stage disease is associated with pain when carrying a heavy object at the side of the body with the elbow in extension. The history is important when evaluating symptoms related to the elbow because of the strong relationship between trauma or occupation with osteoarthritis, especially in individuals who are younger than 40 years of age [159].

A history of ankle fracture or ligamentous injury is a hallmark feature of osteoarthritis of the ankle [144]. Diagnostic evaluation includes radiographs of the ankles made with the patient standing. MRI is also recommended, as it can provide evidence of osteonecrosis as well as indicate the amount of involvement, the extent of bone loss, and the size of subchondral cysts [144].

Therapeutic Measures

There is currently no curative therapy for osteoarthritis, and treatments to alter or arrest the disease process are few and mostly ineffective [151]. As clinicians on the frontline of care, primary care providers and nurses are typically the first to see individuals with symptoms indicative of osteoarthritis. Primary care providers can coordinate the management of osteoarthritis, and a multidisciplinary approach is best. The ACR and the Association of Rheumatology Health Professionals (a division of the ACR) support such an approach, noting that the healthcare team may include a rheumatologist, primary physician, nurse, nurse practitioner, physician assistant, physical therapist, occupational therapist, physiatrist, psychiatrist, psychologist, orthopedic surgeon, social worker, registered dietician, vocational counselor, and others [160].

The optimal management of osteoarthritis encompasses both nonpharmacologic and pharmacologic measures, beginning with basic modalities and following a so-called pyramid approach as the disease progresses or symptoms do not respond [161]. Several factors should be considered when selecting treatment modalities, including risk factors (e.g., age, comorbidity, overweight/obesity), the level of pain and functional limitations, signs of inflammation, and degree of structural damage [162].

According to the American Academy of Orthopaedic Surgeons, oral acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

(https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Last accessed September 26, 2022.)

Strength of Recommendation: Strong (Evidence from two or more "high" quality studies with consistent findings for recommending for or against the intervention.)

Many treatment options are associated with benefits and risks, and the clinician should discuss the benefits and risks with patients and support their participation in the decision-making process [163; 164]. Patient preferences are an important consideration when choosing treatment options and establishing treatment goals, and the ACR advocates care that addresses treatment goals that are meaningful to the individual patient [160]. Decision aids can help enhance patients' knowledge of treatment options, improve patients' participation in their care, and produce realistic expectations of outcomes [164]. Decision aids for osteoarthritis have been developed in a variety of media (e.g., print, online, video) and are available online (https://decisionaid.ohri.ca) [164].

The pain and disability associated with osteoarthritis often has a substantial psychologic and social effect. It is important to discuss these aspects with patients and to address psychologic issues, especially depression, in order for treatment measures to be effective [165].

Specific Nursing Measures

Education and self-management, through lifestyle modifications are universally recognized as the core of treatment in clinical guidelines [166]. This recommendation is based on research showing that education helps patients become more involved in their care, leading to improved outcomes [163]. The Agency for Healthcare Research and Quality notes that an effective partnership is the key to the effective management of osteoarthritis; the healthcare professional's role in this partnership is to [163]:

- Encourage patients to change their behavior to improve symptoms or slow disease progression
- Promote the proper use of medications
- Instruct patients on how to interpret and report symptoms accurately
- Support patients' efforts to maintain normal activities
- Help patients adjust to new social and economic circumstances and cope with emotional consequences

Nurses should emphasize to patients that adhering to the management program will alleviate their symptoms, improve their function, and enhance their quality of life. Education should be tailored to address individual needs. For example, patients who participate in sports should be advised to avoid sports with direct contact and high impact and to wear protective equipment to prevent injury [167]. Similarly, for patients in occupations with high risk for osteoarthritis, clinicians should discuss the importance of avoiding high-risk tasks. It is also essential to encourage patients with osteoarthritis of the glenohumeral joint or the elbow to modify activities that led to the development of the disease [143; 159]. Periodic contact during follow-up can help promote self-management [166].

IMMUNOLOGIC DISORDERS

Rheumatoid Arthritis

Rheumatoid arthritis is defined as a chronic inflammatory disease characterized by uncontrolled proliferation of synovial tissue and a wide array of multisystem comorbidities [24]. In its most common presentation, rheumatoid arthritis affects the joints, causing inflammation of the synovium and cartilage and bone loss. The precise etiology of rheumatoid arthritis is presently unknown [26]. Most likely it has an autoimmune origin (whereby an individual's immune system confuses healthy synovial tissue for foreign substances, thereby attacking the synovial joint surfaces) given that autoantibodies (e.g., rheumatoid factor, ACPA) are present and often precede the clinical manifestation of rheumatoid arthritis by many years [22; 25; 168].

The course and severity of the illness can vary considerably, and infection, genetic factors, and hormones may contribute to the disease. Rheumatoid arthritis appears to require the complex interaction of genetic and environmental factors with the immune system and ultimately in the synovial tissues throughout the body. Triggers for rheumatoid arthritis have long been the target of active research. Purported triggers have included bacteria (*Mycobacterium*, *Streptococcus*, *Mycoplasma*, *Escherichia coli*, *Helicobacter pylori*), viruses (rubella, Epstein-Barr virus, parvovirus), and superantigens [25; 26; 27].

Although rheumatoid arthritis has a clear genetic component, only about 1 in 25 White individuals with the so-called shared epitope develop rheumatoid arthritis [27]. Even if one monozygotic twin has rheumatoid arthritis, there is only approximately a one in six chance that the other twin will develop the same disease. Thus, other factors in addition to genetics are active as precipitators or triggers of rheumatoid arthritis [27].

Clinical Manifestations

Findings on general physical examination are normal except for an occasional low-grade fever (38°C) and a slightly elevated pulse rate. The characteristic patient with rheumatoid arthritis initially presents with complaints of pain and stiffness in multiple joints. There is prominent and prolonged morning stiffness (lasting more than one hour) that usually begins gradually with fatigue, loss of appetite, widespread muscle aches, and weakness [23; 25; 27].

After this initial presentation, joint pain appears. When the joint is not used for some time, it can become warm, tender, and stiff. After inflammation of the joint, increased synovial fluid is produced and the joint becomes swollen. There is accompanying soft tissue swelling, and joint pain is often felt bilaterally, affecting the fingers, wrists, elbows, shoulders, hips, knees, ankles, toes, and neck [25]. Though the joints are tender, the small joints of the hands and feet are not usually painful when the patient is at rest. Palmar erythema and prominent veins on the dorsum of the hand and wrist indicate increased blood flow. Distal interphalangeal joints are rarely involved.

The temperature over the involved joints (except the hip) can be elevated, but there is usually no accompanying erythema. There are limitations in the range of motion, muscle strength, and function around inflamed joints.

In addition, soft, poorly delineated subcutaneous nodules (rheumatoid nodules) are often found in the extensor surface of the forearm. Soft, small lymph nodes are found occasionally in epitrochlear, axillary, and cervical areas [24]. Other symptoms that may present include anemia due to deficits in bone marrow production; eye burning, itching, and discharge; or lung inflammation (pleurisy) [23; 24; 25; 27]. Joint destruction may occur within one to two years after the appearance of the disease.

Rheumatoid arthritis is not solely a disease of joint destruction; it can involve almost all organs. Approximately 18% to 41% of patients with rheumatoid arthritis develop extra-articular manifestations [169; 170]. Rheumatoid arthritis may cause inflammation of the outer cardiac lining (pericarditis) and cardiac muscle (myocarditis), leading to congestive heart failure. In a population-based cohort study, patients with rheumatoid arthritis had a significantly higher risk of cardiovascular disease than those without rheumatoid arthritis [171]. More than half of the patients 50 to 59 years of age and all of those older than 60 years of age with a new diagnosis of rheumatoid arthritis had a more than 10% increased risk of cardiovascular disease within 10 years of rheumatoid arthritis onset.

Pulmonary manifestations are also seen in patients with rheumatoid arthritis, occurring in approximately 30% to 40% of patients. In approximately 10% to 20% of these patients, involvement of the respiratory system is the first manifestation of rheumatoid arthritis [170]. There are several types of potential pulmonary manifestations of rheumatoid arthritis: pleural disease, interstitial pneumonitis, and fibrosis. Pleural effusions and pulmonary rheumatoid nodules are the most common manifestations, along with high rheumatoid factor titers [172; 173; 174]. Pleuritis is more often found in autopsies of patients with rheumatoid arthritis than in living patients. In about 20% of patients, pleuritis develops concurrently with rheumatoid arthritis onset [174]. Although pleuritic pain is not usually a major complaint, the effusions may be large enough to cause dyspnea. Pulmonary fibrosis can either be slowly progressive or result from pulmonary inflammatory disease; on physical exam of the lungs, they present with fine, diffuse, dry rales.

Ocular involvement is another major manifestation of rheumatoid arthritis, usually manifesting as scleritis, development of anterior uveitis, and peripheral ulcerative keratitis (corneal melt) [175; 176]. These disorders are associated with inflammatory cytokines produced by ocular mononuclear cell infiltrates [176; 177].

Osteopenia and osteoporosis are very common extra-articular complications in patients with rheumatoid arthritis [178]. The development of osteopenia in patients with rheumatoid arthritis appears to occur independent of corticosteroid use and is directly linked to elevated levels of the RANK ligand expressed by T cells, which promotes osteoclastic bone resorption [178; 179; 180].

Diagnosis

Which conditions should be included in the differential diagnosis of rheumatoid arthritis?

Rheumatoid arthritis is a clinical diagnosis [181]. As discussed, several laboratory tests are recommended for the diagnosis of rheumatoid arthritis, including rheumatoid factor, ESR, CRP, and anti-CCP antibody [22]. While the results of these tests are relatively sensitive and specific, false positives are possible. In 2010, a multi-biomarker disease activity test, Vectra DA, was introduced. This test uses a unique algorithm to derive a composite score (1 to 100) based on the results of 12 blood protein biomarkers, including vascular cell adhesion molecule-1, epidermal growth factor, vascular endothelial growth factor A, interleukin-6 (IL-6), TNF receptor type 1, matrix metalloproteinase-1 or collagenase-1, matrix metalloproteinase-3 or stromelysin-1, YKL-40, leptin, resistin, serum amyloid, and CRP [182; 183]. Vectra DA has been independently verified and found to correlate well to disease activity measured with rheumatoid arthritis assessment tools (e.g., Disease Activity Score in 28 joints using the CRP level). The test is validated for use in adults already diagnosed with rheumatoid arthritis but is not intended to diagnose rheumatoid arthritis [184].

There are several other laboratory tests used in the differential diagnosis of rheumatoid arthritis. Complete blood count may reveal mild normochromic and either normocytic or microcytic anemia (hemoglobin 10 g/dL); white blood cell count and differential may reveal thrombocytosis [24; 29]. Although baseline evaluation of renal and hepatic function is not sensitive or specific for rheumatoid arthritis, it is recommended because the findings will guide medication choices.

Popular imaging tests for rheumatoid arthritis include joint ultrasound, MRI, and joint x-rays. Imaging studies may show normal findings or osteopenia and erosions near joint spaces in early disease; wrist and ankle films are useful as baselines for comparison with future studies [24; 185]. Implementing the modern treatment strategy in rheumatoid arthritis (i.e., early initiation and optimal adjustments of aggressive therapies) requires methods for early diagnosis and sensitive monitoring of the disease process.

A number of different medical conditions may be considered in the differential diagnosis of rheumatoid arthritis [181; 186; 187; 188]. These include:

- Connective tissue diseases (e.g., lupus, scleroderma, polymyositis)
- Fibromyalgia
- Hemochromatosis
- Infectious endocarditis
- Lyme arthritis
- Osteoarthritis
- Polyarticular sepsis
- Sarcoidosis
- Thyroid disease
- Viral arthritis

Therapeutic Measures

Rheumatoid arthritis has no known prevention or cure. Lifelong treatment is usually required, including medication, physical therapy, exercise, and possibly surgery. In order to provide the best outcomes, patients should be educated regarding the most appropriate treatment regimens for their disease manifestations, as earlier rheumatoid arthritis diagnosis can assist in aggressive early treatment for rheumatoid arthritis (when indicated), thereby delaying joint destruction. The 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis is now a well-established diagnostic and prognostic tool; as such, guidelines (e.g., the 2016 update of the EULAR Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs) recommend that patients start treatment with a disease-modifying antirheumatic drug (DMARD) immediately following a rheumatoid arthritis diagnosis [189]. Therapeutic goals include preservation of function and quality of life, minimization of pain and inflammation, joint protection, and control of systemic complications, with the ultimate aim being low disease activity or remission [23; 24; 27; 189; 190].

Today, the recommended standard of treatment is a tightly controlled, aggressive strategy tailored to each patient, with modifications to the individual medication regimen to achieve a particular target (remission, or alternatively, low disease activity) in a specific period of time (usually six months) [189; 191]. The "treat-to-target" approach for a patient with early high disease activity and poor prognostic features typically involves initiation of methotrexate and/or another DMARD(s) immediately upon diagnosis [189; 190; 191]. Initial combination therapies with DMARDs, particularly those including a biologic anti-TNF agent, appear to provide earlier clinical improvement and less joint damage progression in patients with early moderate or highly active disease; they can be withdrawn successfully, and fewer treatment adjustments are needed than with initial monotherapies [189; 191; 192; 193; 194]. Patients with active disease are monitored closely (every one to three months), and it is recommended that treatment adjustments be made if there is no improvement at three months (or if the six-month target has not been reached) [189; 191]. Patients with low-to-moderate disease activity or high disease activity without poor prognostic features are typically started on DMARD monotherapy. NSAIDs, glucocorticoids, or COX-2 inhibitors are often used concurrently to treat rheumatoid arthritis-associated joint pain and inflammation. However, they do not alter the disease course and should not be used as single therapy.

Occasionally, surgery is needed to correct severely affected joints. Surgeries serve to relieve joint pain, correct deformities, and modestly improve joint function [23; 24; 27]. The most successful locations of surgery are those performed on the knees and hips [23; 24; 27]. The first surgical treatment performed is a synovectomy, which removes part or all of the joint lining (synovium). This procedure may only provide temporary relief, but it can be effective for patients for whom pharmacologic treatment has not resulted in improvements. Surgeries performed in later-onset disease include total joint replacement with a joint prosthesis. In extreme cases, total knee or hip replacement can have enhanced importance, making the difference between a dependent or independent lifestyle for a patient.

Range-of-motion exercises and individualized exercise programs prescribed by a physical therapist can also delay the loss of joint function. Joint protection techniques, heat and cold treatments, and splints or orthotic devices to support and align joints may be of assistance [23; 24; 27]. Some therapists will use specialized devices to apply deep heat or electrical stimulation to reduce pain and improve joint mobility [23; 24; 27]. Occupational therapists can construct splints for the hand and wrist and teach patients with rheumatoid arthritis how to protect and use their joints most effectively. In addition to physiotherapy, occupational therapists can also show patients with rheumatoid arthritis how to better cope with limitations that can affect their daily tasks at work and at home. For example, many clinicians have recommended frequent rest periods between activities and proper sleeping habits (e.g., 8 to 10 hours of sleep per night) [195].

In addition to the medical management of rheumatoid arthritis, several lifestyle changes may improve symptom severity and decrease the number of flare-ups. The National Institute of Arthritis and Musculoskeletal and Skin Disorders recommends advising patients regarding rest and exercise, use of orthotic devices, stress reduction, and healthful diet [23].

INFECTIOUS DISORDERS

Infectious Arthritis

Infectious arthritis (also known as septic arthritis) is the inflammation of a joint resulting from an invading organism that attacks the synovium and synovial fluid. Viral, bacterial, and fungal infections all predispose susceptible people to arthritis involvement. Pathogens present in the host circulate freely in the bloodstream and become trapped in the richly perfused

synovial membrane, leading to inflammation and subsequent degenerative changes. Infectious arthritis is an opportunistic disease that primarily occurs in patients with immunocompromise or who already have joint destruction from another disorder (e.g., rheumatoid arthritis). Early diagnosis and treatment can prevent serious degenerative changes [76; 196].

Patients with infectious arthritis undergo repeated arthrocentesis, which can be stressful. Additional treatment will depend on the underlying pathogen, with antibiotics, antiviral, or antifungals prescribed as appropriate [76; 196].

The nurse should be available to both the patient and family for psychological support, physical care, health education, and monitoring the patient's response to therapy. The control of pain and protection of the involved joint or joints are priorities of nursing management [76; 196].

Therapeutic and Nursing Measures

What is the most common causative pathogen of infectious arthritis in young, sexually active patients?

The patient history is key to diagnosis, and nurses should be careful to obtain a complete and accurate history. This should include any recent viral (e.g., parvovirus, alphavirus, hepatitis, Epstein-Barr virus) and bacterial (e.g., *Streptococcus pneumoniae*) infection. In young, sexually active patients, the most common causative pathogen is *Neisseria gonorrhea*. For patients who develop infectious arthritis following trauma, puncture wounds, or injection drug use, *Pseudomonas aeruginosa* is the most likely cause [18; 197].

It is important that the pathogen responsible for the infectious arthritis be identified and treatment begun as quickly as possible to prevent joint destruction. Isolating the organism will guide in the selection of intravenous antimicrobial therapy and the level of aggressiveness needed to control the infection. Pathogens are identified through the aspiration of synovial fluid, synovial fluid cultures, and synovial biopsy. Empiric therapy is started after joint aspiration is complete and cultures are obtained [76]. Other therapeutic measures for infectious arthritis include surgical excision of the affected synovium in instances where destruction of the joint cartilage, tendons, or both appears imminent [76].

To protect the intra- and extra-articular structure from future damage and reduce the patient's discomfort, the involved joint should be immobilized during the acute stage. However, after two to three days, aggressive physical therapy is recommended to prevent long-term damage and disability [18].

The involved joint should be assessed frequently for drainage and any change in condition. Sterile technique should be maintained with any dressing changes [18]. For patients receiving parenteral fluids, intake and output should be measured and documented accurately. Laboratory test results will be monitored daily, especially the results of culture and sensitivity tests [18].

Patient education should include instruction about range-of-motion exercises to maintain joint mobility; dressing change techniques and wound care, if appropriate; and adherence to prescribed medications. The patient should be advised of symptoms and signs of repeated infection (e.g., increased pain, fever, swelling, redness, drainage) and to avoid any trauma to the joint [18].

NEOPLASTIC DISORDERS

In this section, the discussion of masses and tumors of the joints and surrounding structures will be limited to the benign and malignant lesions generally included in a differential diagnosis for arthritis.

Masses and Benign Tumors of the Joint

Patients with a benign lesion of the joint may experience years of intermittent minor problems with the involved joint, with a history of discomfort and joint instability. Because the symptoms of a benign tumor can remain innocuous for long periods, joint damage may result prior to diagnosis. No matter the extent of damage, joint surgery is required to resolve the issue and prevent further deterioration [37].

Lipoma

A lipoma of a joint is a lobulated fatty mass. Lipomas develop frequently in the elbow or knee joint of patients with osteoarthritis [37]. In many cases, patients seek medical attention when the involved joint begins locking or when pain, decreased motion, or an effusion occurs. Effusion aspirate is clear, and x-rays are non-diagnostic [37].

Hemangioma

What are hemangiomas?

Hemangiomas are rare vascular tumors often associated with arteriovenous malformations of skin vascular disease. They tend to affect younger individuals, often teenage girls who have been symptomatic since childhood. The knee is the most commonly involved joint [37].

In patients with joint hemangioma, there is a history of episodic, unilateral "doughy" joint swelling; pain; limitation of motion; and locking, buckling, or both. Aspiration of the joint repeatedly produces serosanguineous fluid in the absence of trauma. X-rays early in the course of the hemangioma may appear normal; ultrasound is often more helpful. With more advanced disease, enlarged epiphyses, joint narrowing, and enlargement of the intercondylar notch layer may be visualized [37].

Surgical removal yields good results in the treatment of a localized hemangioma. If accessible, therapeutic embolization of a major feeder vessel may be effective as well. Because of the vascular nature of this tumor, a diffuse form may involve the entire joint capsule and make resection impossible. For these patients, radiation therapy is the usual treatment [37].

Synovial Chondromatosis

Synovial chondromatosis is a condition of unknown etiology in which numerous cartilaginous nodules form. These nodules involve the joint, bursae, and in some cases the tendon sheaths of a knee, hip, elbow, shoulder, or ankle. It is a self-limiting disease that most frequently affects young and middle-aged men [37].

Synovial chondromatosis has an insidious onset, and many years often pass before the patient seeks evaluation for the problem. Presenting symptoms usually consist of swelling, pain, stiffness, limitation of motion, and joint locking. Particularly with synovial chondromatosis, the patient experiences joint crepitation or a grating sensation from the multiple intrasynovial nodules. X-ray findings may demonstrate calcified, free-floating bodies in the synovium [37].

Excision of the involved synovium and removal of all loose bodies is the treatment of choice. Surgical therapy has a good prognosis, although the condition may recur if removal is incomplete [37].

Pigmented Villonodular Synovitis

Pigmented villonodular synovitis is a condition in which the synovial lining cells have a marked proliferation that results in the appearance of numerous villi and folds. The formation of the finger-like projections can affect not only the synovial lining but also the tendon sheath, bursa, and bone. Unilateral involvement of the knee, hip, ankle, or elbow joint of young adults is most common [37].

There are two forms of pigmented villonodular synovitis: localized and diffuse. The diffuse type causes pain and mild, episodic joint swelling over a period of months to years. Occasionally, the patient may note an acutely painful, warm, swollen joint with limited motion. Repeated aspirations of joint fluid yield dark serosanguineous fluid in the absence of trauma [37].

The localized type of pigmented villonodular synovitis occurs in either the medial or lateral knee compartment as a solitary nodule. It, too, may begin with episodic pain and mild swelling and can be misdiagnosed as torn meniscus. Serosanguineous fluid is rarely aspirated with this type of lesion [37]. Imaging studies may show soft tissue density, but angiographies are more useful because the vascularity of these enable the condition to be diagnosed [37].

Surgical resection is the treatment for both types of pigmented villonodular synovitis. The localized form is usually cured with simple excision. With the diffuse type, lesions may recur if synovectomy is incomplete [37].

Specific Nursing Measures

During the diagnostic phase, the health history is important. The nurse should concentrate on any significant joint trauma and inquire regarding any past history of arthritis. The patient should be asked for a detailed description of swelling, pain, limitation of motion, and/or joint instability [7].

In cases of significant joint instability, a cane or crutches may be necessary. Patients should also receive education on appropriate pain management measures, including thermotherapy, over-the-counter medications, and biofeedback. In most cases, the patient will also require education to prepare for surgery and postoperative recovery [7].

Postoperative care includes monitoring for wound drainage or other signs of infection, dressing changes (as necessary), and splinting. Discharge planning includes instruction in the care of the surgical site, activity restrictions, and follow-up appointments [7].

Malignant Tumors of the Joint

Malignant tumors of the joint are rare. However, if a patient has a slow-growing monoarticular mass, malignancy should be suspected [198].

Synovial Sarcoma

Though it is the most common primary tumor of the joint, synovial sarcoma is rare. This malignancy can appear at any age, although it seems to predominate in young adults. The growth generally appears on a lower extremity, but synovial sarcomas can also develop in an upper extremity, the neck, or the chest [198].

Patients with synovial sarcoma often present with a slow-growing mass that may have been present for months to years, depending on how deeply seated it is in tissue. Pain may be present, or the patient may have a vague sensation of discomfort over the involved area. There may also be localized swelling. In cases involving the neck, tumor invasion may produce hoarseness, dysphagia, or dyspnea [198].

As with most cancer, survival time is dependent on the size of the tumor, site in the body, and age at diagnosis. The five-year survival rate is approximately 60%; this increases to 75% in patients 30 years of age or younger. If the tumor is in an extremity, five-year survival is about 65%; if the tumor is present in the trunk, the rate decreases to 40% [199].

The goals of treatment for synovial sarcoma are to eliminate the tumor, preserve a functional limb, and minimize mortality and morbidity. Preoperative chemotherapy and radiation therapy may be undertaken to decrease the size of the tumor [198]. Wide surgical resection is typically undertaken, followed by continued radiation therapy.

Clear Cell Sarcoma

Clear cell sarcoma is a rare tumor that involves tendons rather than joint spaces. It can occur in any age group and usually is found in an extremity, particularly the foot. However, it can develop in the trunk, head, genitals, stomach, and intestines. Because of this lesion's location and its predisposition to metastasis, it can be difficult to remove entirely, making treatment complicated and prognosis poor [198]. The average age at diagnosis is 25 years [200].

The primary treatment of clear cell sarcoma is radical resection of the tumor. In some cases, an extremity may be amputated. Preoperative and postoperative radiation therapy are employed. In some cases, chemotherapy may be used, but it is not particularly effective [200].

TRAUMATIC DISORDERS OF THE JOINT

Permanent structural changes may occur in a joint as a result of cartilage and capsular tears, detachment of menisci, hemorrhagic effusions, articular fractures, or repetitive trauma. Because of the realignment of involved bone, bursa, and tendons, a mechanical deterioration of articular cartilage results in osteoarthritis [201; 202].

Traumatic arthritis may result from unexpected force (e.g., sports, motor vehicle accidents) or from repetitive trauma—a chronic injury resulting from repeated smaller stresses to a joint through vibrations, blows, abnormal strain, or position. Injury resulting from repetitive stress is often related to occupation and lifestyle, for example, the stress placed on the metatarsophalangeal joints of a ballet dancer or the knees of a jogger. Over time, repetitive trauma may realign the joint and lead to the same result as an acute injury [201; 202].

The patient with traumatic arthritis must make lifestyle changes. In order to continue participating in chosen sports or occupations, patients may require braces, splints, or special equipment; in some cases, they may need to halt participation or seek accommodations in their workplace. Although these options are effective in halting the progression of traumatic arthritis, they are often undesired or impossible for patients. The responsibility of the nurse is to provide accurate information about the alternatives available [201; 202].

Nurses also play an important role in the therapeutic and preventive care of traumatic disorders. If they are the first person on the scene of an accident, nurses may be able to prevent any residual damage by splinting, elevating the area, and not allowing weight on the area to protect the joint. It may be possible to identify tasks that expose employees to repetitive trauma; employees then can rotate through the jobs rather than be assigned permanently to potentially harmful tasks [201; 202].

Joint Effusions

What is the clinical sign of joint effusion?

Joint effusions can occur as a result of simple trauma or secondary to fractures, internal derangements, or severe sprains. Within 24 hours after a blow to the joint, synovial fluid accumulates. If blood vessels in the synovium are broken, hemarthrosis also occurs. The knee is most commonly affected by this injury, although it can occur in other joints as well [75].

Clinical Manifestations

In simple cases of traumatic synovitis, joint swelling with mild pain occurs. Aspiration of the joint produces clear fluid with elevated protein content and decreased viscosity. Hemarthrosis, which usually develops within 15 minutes to 2 hours after the trauma, is usually more painful than clear effusion and is accompanied by low-grade fever. Diagnosis of traumatic synovitis is primarily by physical examination, but x-ray examination is done to rule out fracture [75].

Therapeutic Measures

Immediately following injury, patients should be advised to apply cryotherapy (e.g., ice) for 30 minutes; this can be repeated up to four times per day to reduce swelling and relieve pain. After the first 24 hours, patients should switch to moist heat to relax surrounding muscles and reduce pain. If fluid accumulates in the joint, repeated joint aspirations may be necessary. Compression dressings applied to the joint, along with limited weight bearing, may be used, depending on the severity of the injury [75].

Dislocation and Subluxation

Dislocation is the complete displacement of a joint's articulating surfaces following trauma. Partial displacement of the articulating surfaces results in subluxation. Both subluxations and dislocations can damage soft tissues, nerves, or blood vessels if not attended to promptly. The joints most often affected are shoulders, wrists, elbows, fingers, hips, knees, and toes [75].

Clinical Manifestations

After injury, the joint appears deformed; it is tender, and motion is limited. The involved extremity may be visibly shortened. Joint pain may be intense, especially if articular surface fractures are present. With immediate treatment, there is a good prognosis. However, bone necrosis can result if reduction of the subluxation or dislocation is delayed [75]. Diagnosis is made through physical examination and patient history, with x-rays taken to evaluate joint displacement and to determine whether fractures are present [75].

Therapeutic Measures

The longer the delay in correcting a joint displacement, the more difficult the procedure becomes because of edema and muscle spasms. Two types of procedures can correct this injury. Closed reduction is manual traction done under local or general anesthesia. The pain associated with this procedure can be intense, and pain management techniques (including strong analgesics) are necessary. If muscle spasms are an issue, tranquilizers and/or muscle relaxants may be administered. Open reduction is done when wire fixations of the joint or repair of torn ligaments is also necessary [75].

If present at the site of injury, the joint should be splinted—even if crooked—to prevent further damage. Cold compresses can be applied to decrease pain and swelling [35]. The area distal to the injury should be observed for evidence of vascular damage (e.g., pallor, absent pulse, abnormal coolness) and nerve damage (e.g., paresthesia, paralysis) [35].

If analgesics, muscle relaxants, or tranquilizers are administered, it is important to monitor the patient's respiratory status. Any dressings or casts should be checked for pressure that may impair blood flow. Patients should receive education on gradual mobilization and return to activities [7].

CASE STUDIES

SYSTEMIC LUPUS ERYTHEMATOSUS

Patient A is a woman, 29 years of age, with two small children. She presents to her primary care provider with complaints of rashes developing on her arms and legs whenever she spends time in the sun. She also reports several small patches of hair loss on her head that she attributes to the stress of new motherhood and to a recent trip and her fear of flying. She reports a lack of energy, being easily fatigued, and always needing to nap during the day. Patient A also reports mild pain in her fingers and elbows but attributes the joint discomfort to caring for the children. She states that these problems have been ongoing for approximately four months.

Medical History

Patient A has no known allergies and takes no prescription or over-the-counter medication aside from occasional naproxen for joint pain and antacid for heartburn. She neither smokes nor drinks alcohol. Her youngest child is 2 years of age, and she reports unremarkable childbirths and postpartum periods. Aside from the current complaints, the patient's medical history is unremarkable.

She has four brothers and three sisters. The family history indicates an older sister with rheumatoid arthritis, an aunt with pernicious anemia, and mother with hyperthyroidism.

Assessment and Diagnosis

The primary care provider conducts a full physical assessment (***Table 2***). Several laboratory tests are ordered, with the following results:

- Hematocrit (HCT): 23%
- Red blood cell (RBC) count: 3.5 million cells/mcL
- White blood cell (WBC) count: 5,500 cells/mcL
- Platelets: 350,000 cells/mcL
- ESR: 25 mm/hour
- Urinalysis: Normal
- ANA: 1:640
- Anti-DNA antibody test: Elevated
- Complement assay: Decreased C3 level at 43 mg/dL and decreased C4 level at 14 mg/dL

Further, a tissue biopsy of one of the lesions is taken and reveals vasculitis (i.e., white blood cells within the walls of blood vessels).

Based on the results of the assessment and laboratory studies, Patient A is diagnosed with SLE.

Management

A one-month course of prednisone with tapered doses is prescribed. Nabumetone, an anti-inflammatory, is added to the regimen prior to the prednisone being weaned off. After one month of treatment, all signs and symptoms of lupus have resolved.

However, 13 years later, Patient A again presents to her primary care provider, this time with complaints of a productive cough and transient stiffness and pain in her hands and feet (migratory polyarthritis). She is afraid that she is developing rheumatoid arthritis like her sister. The provider conducts a physical examination (***Table 3***) and is concerned that the patient may be showing signs of pneumonia. A chest x-ray revealed mild pulmonary edema but no white blood cell infiltrates in the terminal airways. Laboratory tests reveal:

- HCT: 43%
- Platelet: 330,000 cells/mcL
- WBC count: 1,200 cells/mcL
- Urinalysis: Within normal limits

Patient A is diagnosed as experiencing a lupus flare and is prescribed a one-month course of prednisone along with a 10-day course of antibiotics to prevent pneumonia. Within three months, all signs and symptoms have resolved.

Five years later, Patient A returns to her primary care provider complaining of fatigue, anorexia, weight loss (25 pounds in the last four months), and significant swelling in her abdomen, face, and ankles. The nurse practitioner notes a "butterfly-shaped" rash present across the bridge of the patient's nose and cheeks. Blood tests reveal an HCT of 24% and a WBC count of 2,400 cells/mcL. A dipstick examination of the urine reveals an abnormal protein concentration, and microscopy indicates the presence of significant numbers of red and white blood cells. A 24-hour urine protein collection reveals excretion of 2.5 g protein in 24 hours.

PATIENT A'S FIRST PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Significantly underweight, with a decrease in weight of 23 pounds since last exam one year prior Height: 5 feet 5 inches (165.5 cm) Weight: 108 pounds (49 kg)
Skin and nails	Multiple rash-like lesions on sun-exposed areas of the body, primarily on the arms and legs Slightly jaundiced
Head and nose	Nares clear Oropharynx benign and without obvious lesions Mucous membranes moist
Eyes	Some yellowing within the sclera Pupils equal, round, reactive to light and accommodation Conjunctiva normal No retinal exudates
Ears	Tympanic membranes intact
Neck	Supple No signs of lymphadenopathy, jugular vein distension, or thyromegaly
Chest	Clear to auscultation throughout Equal air entry bilaterally No wheezing or crackles Chest resonant on percussion
Abdomen	Soft and nontender Active bowel sounds No masses or organ enlargement
Extremities	No cyanosis, clubbing, or edema Rash-like lesions present
Genitourinary system	Normal female
Neurologic status	Alert and oriented Deep tendon reflexes 2+ with symmetrical flexor plantar responses No focal deficits noted
Cardiovascular system	Regular rate and rhythm Prominent S_1 and S_2
Vital Signs	
Blood pressure	110/70 mm Hg
Temperature	99.8° F
Heart rate	70 beats per minute with regular rhythm
Respiratory rate	15 breaths per minute
Source: Author	*Table 2*

PATIENT A'S SECOND PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Healthy and calm White woman Height: 5 feet 5 inches (165.5 cm) Weight: 131 pounds (59.5 kg)
Skin and nails	No lesions or abnormalities noted
Head and nose	Nares clear Oropharynx irritated but without obvious lesions Mucous membranes moist
Eyes	Pupils equal, round, reactive to light and accommodation Conjunctiva normal
Ears	Tympanic membranes intact
Neck	Supple Lymph nodes slightly enlarged
Chest	Auscultation reveals abnormal lung sounds (bronchitis) No wheezing, but some crackles
Abdomen	Soft and nontender Active bowel sounds No masses or organ enlargement
Extremities	No cyanosis, clubbing, or edema Axillary lymph nodes swollen
Genitourinary system	Normal female Inguinal lymph nodes slightly enlarged
Neurologic status	Alert and oriented Deep tendon reflexes 2+ with symmetrical flexor plantar responses No focal deficits noted
Cardiovascular system	Regular rate and rhythm Prominent S_1 and S_2
Vital Signs	
Blood pressure	140/90 mm Hg
Temperature	100.0° F
Heart rate	105 beats per minute with regular rhythm
Respiratory rate	15 breaths per minute
Source: Author	*Table 3*

Study Questions

1. What is the significance of the patient's family history?
2. Is this patient underweight, normal weight, overweight, or obese?
3. What underlying pathologic process is responsible for Patient A's hair loss? What is the relevance of the abnormal ESR?
4. Vasculitis in lupus results from the trapping of antigen antibody complexes in blood vessel walls followed by an intense inflammatory response to the immune complexes. Why is prednisone effective in relieving vasculitis?
5. What is the most likely cause of jaundice in this patent?
6. What pathophysiology underlies lymph node enlargement in this patient?

7. The patient's WBC differential was: 75% neutrophils, 15% lymphocytes, 5% monocytes/macrophages, 4% eosinophils, and 1% basophils. Which one of these white blood cell types has been specifically targeted by the patient's immune system?
8. Why was Patient A experiencing swelling throughout her body?

LOW BACK PAIN

Patient B is a woman, 35 years of age, who has worked as a housekeeper for the past 10 years. She is 5 foot 3 inches in height with a weight of 178 pounds. She presents to her primary care provider with complaints of low back pain. She reports having had this pain intermittently for several years; however, for the past two days, it has been worse than ever. The recent exacerbation started after vacuuming a rug (i.e., pulling and twisting at the waist). Patient B reports that the pain is primarily on the right lower side and radiates down her posterior right thigh to her knee; it is not associated with any numbness or tingling. The pain can be relieved by lying flat on her back with her legs slightly elevated and is lessened somewhat when she takes ibuprofen 400 mg. Except for moderate obesity and difficulty maneuvering onto the examination table because of pain, the patient's examination is fairly normal. The only abnormalities noted are a positive straight leg raise test, with raising the right leg eliciting more pain than the left. Her strength, sensation, and deep tendon reflexes in all extremities are normal.

Study Questions

1. What is the patient's likely diagnosis?
2. How will the patient be treated?

RHEUMATOID ARTHRITIS

Patient C is a woman, 50 years of age, who presents to her primary care provider for her annual exam. She reports having been very tired for the past month and also experiencing stiffness, pain, and swelling in multiple joints. She states, "I ache all over, and I have pain in different places all the time. One day it is in my right shoulder, the next day in my right wrist, and the following day my left wrist. I'm stiff everywhere when I get up in the morning or if I sit for any length of time. And I feel so tired, like I have a case of the flu that won't go away."

The patient has been diagnosed with hypothyroidism in the past, for which she is taking levothyroxine. She is also prescribed venlafaxine to treat major depressive disorder, and she indicates that her mood has been good, despite the fatigue. She is also taking an over-the-counter multivitamin and calcium supplement. Patient C reports rarely using alcohol and never smoking. There is no family history of autoimmune disorders.

Assessment and Diagnosis

The primary care provider does a complete physical exam (***Table 4***) and orders laboratory tests. The laboratory blood test results are:

- Sodium: 140 meq/L
- ANA: Negative
- HCT: 43%
- Uric acid: 2.9 mg/dL
- Potassium: 3.7 meq/L
- ESR: 38 mm/hour
- WBC count: 15,100 cells/mcL
- Cholesterol: 189 mg/dL
- Chloride: 104 meq/L
- Creatinine: 1.0 mg/dL
- Platelets: 270,000 cells/mcL
- Albumin: 4.0 g/dL
- Bicarbonate: 23 meq/L
- Blood glucose: 94 mg/dL
- RBC count: 4.7 million cells/mcL
- Thyroid stimulating hormone (TSH): 1.7 mcU/mL
- Blood urea nitrogen: 18 meq/L
- Hemoglobin: 14.9 g/dL
- Calcium: 8.8 mg/dL
- Rheumatoid factor: Positive

A urinalysis is performed and is normal, with no RBCs, WBCs, or protein. A chest x-ray finds no fluid, masses, infection, or cardiomegaly. An x-ray of the hand shows soft tissue swelling and bone demineralization but no erosions. Synovial fluid removed from the left knee (7.4 mL) is cloudy and pale yellow in appearance; analysis indicates 14,000 white blood cells/mcL (primarily neutrophils) and a glucose level of 60 mg/dL.

Based on these findings, Patient C is diagnosed with rheumatoid arthritis and referred to a rheumatologist for follow-up.

Study Questions

1. Which of Patient C's vital signs is consistent with a diagnosis of rheumatoid arthritis and why?
2. Are there any other abnormal findings from the patient's physical exam that are consistent with a diagnosis of rheumatoid arthritis?
3. What is the association between the fixed nodules at pressure points on the left wrist/right elbow and a diagnosis of rheumatoid arthritis?
4. Why is it reasonable that this patient has no stiffness, pain, or swelling in the DIP joints of the fingers?

PATIENT C'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Pleasant and alert, but appears very tired and is in moderate acute distress from joint pain Height: 5 feet 4 inches (162.5 cm) Weight: 140 pounds (63.5 kg)
Skin and nails	Intact, warm, pink, and dry No rashes Normal turgor
Head and nose	Head atraumatic
Eyes	Pupils equal, round, reactive to light and accommodation Normal funduscopic examination
Ears	Tympanic membranes intact
Neck	Supple with no jugular vein distention or thyromegaly No bruits Mild lymphadenopathy bilaterally
Chest	Clear to auscultation and percussion No lumps, dimpling, discharge, or discoloration noted in breast exam
Abdomen	Soft, non-tender, and non-distended Positive bowel sounds throughout No superficial veins or organomegaly
Extremities	No clubbing or ankle edema Hands: Swelling of the 3rd, 4th, and 5th proximal interphalangeal joints bilaterally. Pain in the 4th and 5th metacarpophalangeal joints bilaterally. Poor grip strength bilaterally. Wrists: Good range of motion. Fixed nodule at pressure point on left side. Elbows: Good range of motion. Fixed nodule at pressure point in right side. Shoulders: Pain and decreased range of motion bilaterally. Hips: Good range of motion. Knees: Pain, significant edema, and decreased range of motion bilaterally. Feet: No edema. Full plantar flexion and dorsiflexion and full pedal pulse bilaterally.
Genitourinary system	Last menstrual period 16 months ago Normal pelvic exam
Neurologic status	Alert and oriented Cranial nerves II–XII intact Muscle strength 5/5 in upper extremities and 4/5 lower extremities Deep tendon reflexes 2+ in biceps, triceps, and patella
Cardiovascular system	Regular rate and rhythm Normal S_1, S_2, no S_3 or S_4 No murmurs, rubs, or gallops
Vital Signs	
Blood pressure	125/80 mm Hg
Temperature	100.0° F
Heart rate	80 beats per minute with regular rhythm
Respiratory rate	15 breaths per minute
Source: Author	*Table 4*

5. Which of these patient's laboratory test results are consistent with a diagnosis of rheumatoid arthritis?
6. In terms of the progression of the disease, what do the results of the hand x-ray suggest?
7. Which findings in the examination of the synovial fluid are consistent with a diagnosis of rheumatoid arthritis?
8. What causes limitation of joint motion that occurs early in the clinical course of rheumatoid arthritis? What causes limitation of joint motion that occurs late in the clinical course of rheumatoid arthritis?

CONCLUSION

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

Customer Information/Evaluation insert located between pages 44–45.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 44–45.
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 starting at only $79!** Additional titles are also available.

www.NetCE.com

Like us at NetCE4Nurses

BREAST CANCER

UPDATE

#30613 • 15 ANCC Hours

Book By Mail – $83 • ONLINE – $75

Purpose: The purpose of this course is to provide nurses and allied health professionals with the information necessary to accurately diagnose and effectively treat patients with breast cancer according to established guidelines, with the ultimate goal of improving patient care and quality of life.

Faculty: Jacqueline Houtman, RN, MA, CDP

Audience: This course is designed for nurses and allied healthcare professionals invested in the care, delivery of treatment, and relevant education of patients with breast cancer.

Additional Approval: AACN Synergy CERP Category A, CCMC

LUNG CANCER: DIAGNOSIS AND MANAGEMENT

#30723 • 10 ANCC Hours

Book By Mail – $58 • ONLINE – $50

Purpose: The purpose of this course is to address the various aspects of diagnosis, treatment, disease management and appropriate patient care for healthcare professionals caring for patients with lung cancer.

Faculty: Marilyn Fuller Delong, MA, BSN, RN

Audience: This course is designed for all nurses, especially those involved in the care of patients with lung cancer.

Additional Approval: AACN Synergy CERP Category A, CCMC

CHILDHOOD OBESITY: IMPACT ON HEALTH CARE

#32013 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

Purpose: The impact of childhood obesity on an already stressed healthcare system is high and is estimated to rise as the diagnoses of comorbid conditions continue to occur at a younger age. The purpose of this course is to provide nurses with the information necessary to improve the care of children and adolescents who are overweight or obese.

Faculty: Diane Thompson, RN, MSN, CDE, CLNC

Audience: This course is designed for nurses in all practice settings with a desire to better understand the issues facing obese children and their families and the impact of childhood obesity on national and global health care.

Additional Approval: AACN Synergy CERP Category A, CCMC

PRESSURE INJURIES AND SKIN CARE

UPDATE

#34344 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

Purpose: The purpose of this course is to provide nurses with the information necessary to accurately identify, treat, and manage skin breakdown (pressure ulcers), thereby improving patient outcomes and quality of life.

Faculty: Maryam Mamou, BSN, RN, CRRN, CWOCN

Audience: This course is designed for nurses in all practice settings, particularly those caring for patients at high risk for developing pressure injuries.

Additional Approval: AACN Synergy CERP Category A, CCMC

THYROID DYSFUNCTION

#38503 • 4 ANCC Hours

Book By Mail – $28 • ONLINE – $20

Purpose: As a result of the high prevalence of thyroid conditions, nurses and other healthcare providers encounter thyroid dysfunctional patients every day. The purpose of this course is to provide the most current information regarding thyroid disease diagnosis, treatment, and management to facilitate early diagnosis and treatment and optimum patient outcomes.

Faculty: Marilyn Fuller Delong, MA, BSN, RN

Audience: This course is designed for nurses, allied surgical professionals, and other healthcare workers in all practice settings who may care for patients with thyroid dysfunction.

Additional Approval: AACN Synergy CERP Category A, CCMC

HIPAA PRIVACY AND SECURITY

NEW!

#91140 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

Purpose: The purpose of this course is to provide information that will allow health and mental health professionals to more easily comply with the Privacy and Security Rules defined by HIPAA.

Faculty: Carol Shenold, RN, ICP

Audience: This course is designed for all members of the interprofessional healthcare team.

Additional Approval: AACN Synergy CERP Category B

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.

Course Availability List *(Cont'd)*

MONKEYPOX: THE 2022 GLOBAL OUTBREAK

NEW!

#94040 • 3 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to address these knowledge gaps to enable timely diagnosis, treatment, and prevention of monkeypox, thereby promoting public health strategies to limit spread of the outbreak.
Faculty: John M. Leonard, MD
Audience: This course is designed for physicians, physician assistants, nurses, pharmacy professionals, and other healthcare professionals who may identify and care for patients with suspected or confirmed human monkeypox infection.
Additional Approval: AACN Synergy CERP Category A

PNEUMONIA

New Guidelines

#94673 • 10 ANCC Hours

Book By Mail – $58 • ONLINE – $50

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals who manage the care of patients with pneumonia a foundation for effective management strategies in order to improve outcomes and foster an interprofessional collaborative practice consistent with published guidelines.
Faculty: Carol Whelan, APRN; Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for all physicians, physician assistants, and nurses, especially those working in the emergency department, outpatient settings, pediatrics, nursing homes, and intensive care units.
Additional Approval: AACN Synergy CERP Category A, CCMC, CCMC

MEDICAL MARIJUANA AND OTHER CANNABINOIDS

#95172 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

Purpose: 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.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, nurses, physician assistants, pharmacists, social workers, therapists, and counselors in the primary care setting involved in the care of patients who use or who are candidates for the therapeutic use of marijuana or other cannabinoids.
Additional Approval: AACN Synergy CERP Category A, CCMC

DIABETES PHARMACOLOGY

UPDATE

#95324 • 10 ANCC Hours

Book By Mail – $58 • ONLINE – $50

Purpose: The purpose of this course is to meet the needs of healthcare professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for pharmacy professionals and nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.
Additional Approval: AACN Synergy CERP Category A, CCMC

OPIOID SAFETY: BALANCING BENEFITS AND RISKS

NEW! MI Mandate

#95500 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

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, LP
Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing and/or dispensing practices to ensure safe opioid use.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course meets the Michigan APRN requirement for opioids and controlled substance awareness education.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

UPDATE

#96213 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

Purpose: Attention deficit hyperactivity disorder (ADHD) has a significant effect on day-to-day functioning and quality of life; however, it often goes unrecognized. The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ADHD.
Faculty: John J. Whyte, MD, MPH; Paul Ballas, DO
Audience: This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients with attention deficit hyperactivity disorder.
Additional Approval: AACN Synergy CERP Category A, CCMC

HUMAN TRAFFICKING AND EXPLOITATION

MI Mandate

#96313 • 5 ANCC Hours

Book By Mail – $33 • ONLINE – $25

Purpose: As human trafficking becomes an increasingly more common problem in the United States, healthcare and mental health professionals will require knowledge of human trafficking patterns, the health and mental health needs of human trafficking victims, and successful interventions for victims. The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.
Additional Approval: AACN Synergy CERP Category B, CCMC
Special Approval: This course fulfills the Michigan requirement for training in identifying victims of human trafficking.

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

Course Availability List *(Cont'd)*

DEPRESSION AND SUICIDE
#96403 • 15 ANCC Hours

Book By Mail – $83 • ONLINE – $75

Purpose: Although contact with the primary care setting represents a potential opportunity for timely identification and intervention, abundant evidence indicates that many patients with depression are inadequately diagnosed and treated in these settings. The purpose of this course is to provide the information and encouragement necessary to allow primary care providers to properly diagnose, treat, and follow-up with patients with depression.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting who may identify and treat patients who are depressed and/or suicidal.
Additional Approval: AACN Synergy CERP Category A, CCMC

ALCOHOL AND ALCOHOL USE DISORDERS
#96563 • 10 ANCC Hours

Book By Mail – $58 • ONLINE – $50

Purpose: The purpose of this course is to address the ongoing alcohol competency educational needs of practicing physicians, nurses, and other healthcare providers. The material will include core competencies as well as knowledge, assessment, and treatment-based competencies.
Faculty: Mark S. Gold, MD, DFASAM, DLFAPA; William S. Jacobs, MD
Audience: This course is designed for physicians, nurses, and allied health professionals involved in the treatment or care of patients who consume alcohol.
Additional Approval: AACN Synergy CERP Category A, CCMC

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY


#96790 • 10 ANCC Hours

Book By Mail – $58 • ONLINE – $50

Purpose: The purpose of this course is to provide medical and mental health professionals with the knowledge and skills necessary to effectively treat mental disorders using emerging psychedelic and interventional techniques.
Faculty: Mark S. Gold, MD, DFASAM, DLFAPA
Audience: The course is designed for all members of the interprofessional team, including physicians, physician assistants, nurses, and mental health professionals, involved in caring for patients with mental disorders resistant to traditional treatment approaches.
Additional Approval: AACN Synergy CERP Category A

GETTING TO THE POINT: ACUPUNCTURE AND ACUPOINT THERAPIES


#98030 • 4 ANCC Hours

Book By Mail – $28 • ONLINE – $20

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of acupoint and acupressure therapies.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are using or an interested in using acupoint and/or acupressure therapies.
Additional Approval: AACN Synergy CERP Category A

TOP-SELLING HERBAL SUPPLEMENTS


#98080 • 3 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the most popular herbal supplements and to better counsel patients regarding their use.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking herbal supplements.
Additional Approval: AACN Synergy CERP Category A

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

NetCE
A TRC Healthcare Company

Customer Information

(Incomplete information may delay processing.)

For office use only:

MI23 _____

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/MI23

Last Name _____ First Name _____ MI _____

State _____ License # _____ Exp. _____

State _____ Additional License # _____ Exp. _____

License Type (circle one): RN / LPN / NP / CNS / 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

Complete before December 31, 2023, pay $41

Complete after December 31, 2023, pay $62

ENCLOSED SPECIAL OFFER: 25 HOURS

You may complete ALL four of these courses for a maximum payment of $41 (or pay the individual course price).

✓	Course #	Course Title / Contact Hours	Price
	34943	Diabetes and Stroke: Making the Connection / 2 Contact Hours	$15
	96690	Anxiety Disorders in Older Adults / 3 Contact Hours	$15
	35270	Multimodal Pharmacotherapy for Pain Management / 5 Contact Hours	$25
	38950	Pathophysiology: Muscles, Joints, and Connective Tissues / 15 Contact Hours	$75

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
☐	30613	Breast Cancer / 15	$83
☐	30723	Lung Cancer: Diagnosis and Management / 10	$58
☐	32013	Childhood Obesity: Impact on Health Care / 5	$33
☐	34344	Pressure Injuries and Skin Care / 5	$33
☐	38503	Thyroid Dysfunction / 4	$28
☐	91140	HIPAA Privacy and Security / 5	$33
☐	94040	Monkeypox: The 2022 Global Outbreak / 3	$23
☐	94673	Pneumonia / 10	$58
☐	95172	Medical Marijuana and Other Cannabinoids / 5	$33
☐	95324	Diabetes Pharmacology / 10	$58
☐	95500	Opioid Safety: Balancing Benefits and Risks / 5	$33
☐	96213	Attention Deficit Hyperactivity Disorder / 5	$33
☐	96313	Human Trafficking and Exploitation / 5	$33
☐	96403	Depression and Suicide / 15	$83
☐	96563	Alcohol and Alcohol Use Disorders / 10	$58
☐	96790	Psychedelic Medicine & Interventional Psychiatry / 10	$58
☐	98030	Getting to the Point: Acupuncture & Acupoint Therapies / 4	$28
☐	98080	Top-Selling Herbal Supplements / 3	$23

☐ 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 (before December 31, 2023) $41

$62 (after December 31, 2023) _____

I would like my certificates mailed for an additional $6 _____

Additional Courses _____

Subtotal _____

Expedited Delivery _____

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.

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

NetCE
A TRC Healthcare Company

Evaluation

(Completion of this form is mandatory)

MI23

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. Do you plan to make changes in your nursing practice as a result of this course content?

#34943
Diabetes and Stroke: Making the Connection
2 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

#96690
Anxiety Disorders in Older Adults
3 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

#35270
Multimodal Pharmacotherapy
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

#38950
Muscles, Joints, and Connective Tissues
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

#34943 Diabetes and Stroke: Making the Connection — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

#96690 Anxiety Disorders in Older Adults — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

#35270 Multimodal Pharmacotherapy for Pain Management — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

#38950 Pathophysiology: Muscles, Joints, and Connective Tissues — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

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

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.

Want More CE Choices?

NetCE
A TRC Healthcare Company

Get One Year of Unlimited Online CE starting at ONLY $79*!
Includes access to our entire course library of more than 1,500 hours as well as special offers and state-required courses!

The following Online Specials are included with your Unlimited Subscription, or may be purchased individually.

NURSES:

NATURAL MEDICINE SPECIAL OFFER
Cannabinoids • Top-Selling Supplements • Commonly Abused Supplements • Acupuncture • Microbiome Medley • Glucosamine and Chondroitin • The Scoop on Collagen
17.5 Hours $49

WOUND MANAGEMENT SPECIAL OFFER
Pressure Injuries and Skin Care • Hyperglycemia and Wound Management • Treating Pressure Injuries and Chronic Wounds
15 Hours $41

TRAUMA SPECIAL OFFER
Postoperative Complications • Transport Methods for the Critically Ill Patient
30 Hours $62

ADVANCED PRACTICE NURSES:

DESIGN A DEAL SPECIAL OFFER
Choose from our entire library of courses to create your own unique Special Offer.
$52 to $73 (Based on number of hours selected)
NetCE.com/Design

ADVANCED PRACTICE SPECIAL OFFER
Bacterial Sexually Transmitted Infections • Diagnosing and Managing Headaches • Autoimmune Diseases
30 Hours (includes 22 Pharm Hours) $62

PHARMACOLOGY SPECIAL OFFER
Epidural Analgesia Update • Diabetes Pharmacology • Moderate Sedation/Analgesia
30 Hours (includes 28 Pharm Hours) $73

***APRNs, get One Year of Unlimited Online CE for $110. Includes over 500 Pharmacology Hours.**

NetCE.com/NurseUnlimited for more details.

BUSINESS HOURS: Monday through Friday, 8am-5pm Pacific Time. We are closed on weekends and holidays.

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 Development and 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
A TRC Healthcare Company

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

NetCE
A TRC Healthcare Company

P.O. Box 997571
Sacramento, CA 95899

PRESORTED
STANDARD
U.S. POSTAGE PAID
PERMIT NO. 182
SACRAMENTO, CA

Vol. 148
No. 12
MI23

Complete online at NetCE.com/MI23

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/MI23.