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Psychedelic Medicine and Interventional Psychiatry

Includes 8 Pharmacotherapeutic/Pharmacology Hours

Audience
The course is designed for all members of the interprofessional team, including nurses, physicians, physician assistants, and mental health professionals, involved in caring for patients with mental disorders resistant to traditional treatment approaches.

Course Objective
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.

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

1. Outline factors that have contributed to the rise in interest in psychedelic and interventional psychiatry.
2. Define terms related to the discussion of psychedelic and interventional psychiatry.
3. Discuss the history of psychedelics in medical care.
4. Evaluate factors that may impact the provision of psychedelic or interventional psychiatry techniques, including stigma, setting, and culture.
5. Outline the role of psilocybin and ketamine in psychiatric care.
6. Describe how MDMA and ibogaine may impact mental health.
7. Review the clinical effects of kratom, LSD, and mescaline.
8. Discuss the potential clinical role of nitrous oxide, ayahuasca, and dimethyltryptamine (DMT).
9. Describe how psychedelics may be incorporated into the treatment of mental health disorders, including treatment-resistant depression, post-traumatic stress disorder, and substance use disorders.
10. Identify interventional approaches that may be used in the treatment of mental health disorders.

Faculty
Mark S. Gold, MD, DFASAM, DLFAPA, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work

helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. (A complete biography appears at the end of this course.)

Faculty Disclosure
Contributing faculty, Mark S. Gold, MD, DFASAM, DLFAPA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Sarah Campbell

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

INTRODUCTION

What are the categories of psychedelic drugs?

A new and intense interest in psychedelic drugs and interventional medicine is occurring now in the United States and worldwide, as scientists are exploring and discovering innovative ways to treat challenging psychiatric problems, including treatment-resistant depression, suicidal major depressive disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and substance use disorders, as well as multiple other psychiatric problems that have largely been impervious to traditional treatment. Psychedelic medicine refers to the use of drugs that are hallucinogenic and/or anesthetic and that have a unique action on the brain. These approaches may be used only in research situations or may be in current and active use as treatments. In contrast, interventional psychiatry refers to the use of brain-stimulating therapies to treat severe psychiatric disorders. These therapies include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). As with psychedelic medicine, interventional medicine may be used to provide relief for patients with multiple major and previously unremitting severe psychiatric disorders, although there is still much to learn about these therapies. This course will provide an overview of both of these forms of treatment, with an emphasis on psychedelic medicine.

Today, psychedelics like *N*, *N*-dimethyltryptamine (DMT), psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and lysergic acid diethylamide (LSD) are being explored to treat various psychiatric disorders. Trials of these drugs are in different stages, and the timeline for U.S. Food and Drug Administration (FDA) approval is not always obvious. While ketamine was approved in 2020, most experts believe the first psychedelic approval will come in 2024, likely for PTSD rather than treatment-resistant depression, even though treatment with psilocybin was found to relieve symptoms of major depressive disorder for at least one year for some patients in a 2022 Johns Hopkins study [1]. The safety and efficacy of MDMA-assisted therapy is currently under Phase 3 investigation, but concerns remain regarding efficacy and potential adverse effects. As of 2022, the Multidisciplinary Association of Psychedelic Studies (MAPS) is sponsoring MAPP2, the second of two Phase 3 trials to support FDA approval of MDMA as a breakthrough-designated therapy for the estimated 9 million adults in the United States who experience PTSD each year. In MAPS's first Phase 3 study, 88% of participants with severe PTSD experienced a clinically significant reduction in PTSD diagnostic scores two months after their third session of MDMA-assisted therapy, compared with 60% of placebo participants. Additionally, 67% of participants in the MDMA group no longer met the criteria for PTSD two months after the sessions, compared with 32% of participants in the placebo group [2].

When effective, psychedelic medicine is analogous to a "resetting" of the brain. It is somewhat like when a computer runs awry, and nothing of many actions that the user tries improves the situation. In frustration, the user shuts off the machine, but when the device is turned back on, everything works perfectly. The machine has reset itself. Similarly, psychedelic drugs, when effective, may aid the brain in a sort of resetting. Depending on the individual and the drug, the person may find they have marked improvements in symptoms of depression, PTSD, addiction, or other severe psychiatric problem.

As a result of today's research renaissance on psychedelic drugs, there is a new era of hope for people with major psychiatric disorders who have been largely unresponsive to traditional treatments.

One concern about psychedelic medicine is that many of the drugs may induce hallucinations, even in the low doses used for depression. Mental health professionals who prescribe or administer the drugs will need to ensure patients are monitored adequately. In some cases, the person receiving the drug is hospitalized, but in others, the drug is administered and changes observed in an office setting.

Ketamine's efficacy and protocols to ensure safety have resulted in thousands of patients being treated and reporting excellent responses for treatment-resistant depression. However, the ideal drug would provide the benefits without the hallucinatory side effects. In one unique experiment with mice, researchers effectively blocked 5-HT2A, the serotonin-detecting receptor, and this action appeared to stop mice being administered psilocybin from hallucinating ("tripping"). The antidepressant effects were unaltered in this study, as evidenced by the mice resuming consumption of sugar water, an act they had abandoned while depressed [5]. This is an area of great interest, with the potential that the hallucinations induced by psychedelic drugs could be blocked and increase the acceptability of these agents in the general treatment of depression.

Of course, there are many who believe that the psychedelic trip itself, hallucinations and all, is the crucial experience that allows people to experience psychic relief. These individuals believe that eliminating the crucial experience of hallucination would essentially block the full efficacy of the drug. This issue is likely to continue to be discussed and debated as the science advances.

Psychedelic drugs are often divided into two categories: classic and non-classic or dissociative. The classic psychedelics are usually derived from naturally occurring compounds and include such drugs as psilocybin, LSD, and DMT, an active component of ayahuasca, an increasingly popular sacramental drink originating from South America. The dissociative psychedelics are typically newer analogs and include ketamine, phencyclidine (PCP), MDMA, mescaline, *Salvia divinorum*, and dextromethorphan (DXM). While considered drugs of abuse, most agents being tested in psychedelic medicine clinical trials are not self-administered by laboratory animals, the usual test for abuse and dependence liability. If anything, hallucinogens tend to lose their ability to produce changes in the person over time and with regular use. These drugs are all variations on tryptamine, and while they may increase dopamine, they tend to do this through an indirect mechanism.

In their 1979 publication, Grinspoon, Grinspoon, and Bakalar define a classic psychedelic drug as [6]:

> A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis.

While the classic versus non-classic designation is of interest to researchers, it is likely not an important distinction for prescribers or patients.

THE IMPORTANCE OF PSYCHEDELIC AND INTERVENTIONAL MEDICINE

There are multiple reasons health and mental health professionals would benefit from education about both psychedelic and interventional medicine. Psychedelic medicine is a multibillion-dollar industry and is rapidly growing. It is likely that many healthcare professionals will become involved with these approaches as they enter more widespread use.

Many people in the United States suffer from severe depression, and suicide is a public health problem. In 2020, 21,570 people in the United States died from homicide, a significant increase from the number just one year earlier [7]. However, it did not come close to the suicide rate. In 2020, 45,855 people in the United States died from suicide. The annual U.S. suicide rate increased 30% between 2000 and 2020 [7]. As such, depression and suicide are major health problems in the United States today, and approaches to reverse depression rapidly and safely are greatly needed.

It is also important to consider the frustration of many patients with treatment-resistant depression and other disorders, many of whom have turned to cannabis to obtain relief. The majority of states have enacted laws approving medical marijuana, although its efficacy in the treatment of PTSD, depression, and other psychiatric disorders is often lacking [8]. Patients are clearly open to seeking help wherever it may be, whether evidence and healthcare professionals support the approaches. As such, it is vital that clinicians be aware of and knowledgeable regarding novel uses of psychedelic drugs and interventional psychiatry to best serve their patients.

Academic experts, universities, and medical groups continue to research psychedelic medicine, with exciting major breakthroughs in the treatment of depression/anxiety at the end of life and providing relief to patients with treatment-resistant depression, PTSD, and other disorders that most psychiatrists consider difficult to treat. This research will be detailed later in this course.

TREATMENT-RESISTANT DEPRESSION AND THE RISK OF SUICIDE

As noted, the suicide rate in the United States is more than twice as high as the homicide rate [7]. In 2019, suicide was the second leading cause of death for people 10 to 34 years of age and the tenth leading cause of death across all age groups (***Table 1***). Overall, suicide accounts for 1.7% of all deaths in the United States. Although official national statistics are not compiled on attempted suicide (i.e., nonfatal actions), it is estimated that 1.2 million adults (18 years of age and older) attempted suicide in 2020 [9]. Overall, there are roughly 25 attempts for every death by suicide; this ratio changes to 100 to 200:1 for the young and 4:1 for the elderly [9].

People with depression may experience suicidal ideation and behaviors, which can subsequently lead to suicide completions. As illustrated by ***Figure 1***, in 2020, adults 18 to 25 years of age had the highest risk for a major depressive episode, followed by those 25 to 49 years of age. In addition, individuals of two or more races had the highest risk for depression (15.9%), followed by White individuals (9.5%).

Suicidal behaviors are a major problem in the United States, as depicted in the converging circles shown in ***Figure 2***. This figure demonstrates that 12.2 million adults seriously considered suicide in 2020, represented by the outer circle, while 3.2 million adults made suicide plans, and 1.2 million adults attempted suicide. Of those adults who attempted suicide in 2020, 920,000 had made a suicide plan; 285,000 adults had made no such plan prior to the attempt [10; 12].

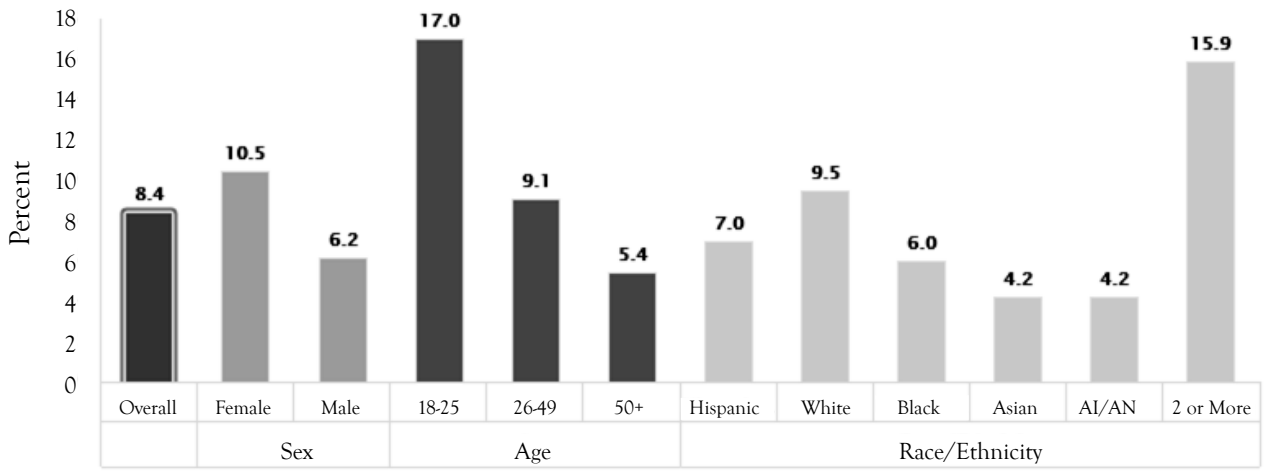
Clearly, action is needed to help address depression and suicide in the United States, and psychedelic and interventional medicine may have a role.

LEADING CAUSE OF DEATH IN THE UNITED STATES FOR SELECT AGE GROUPS, 2019							
Rank	Age (in Years)						
	10–14	15–24	25–34	35–44	45–54	55–64	All Ages
1	Unintentional injury (778)	Unintentional injury (11,755)	Unintentional injury (24,516)	Unintentional injury (24,070)	Malignant neoplasms (35,587)	Malignant neoplasms (111,765)	Heart disease (659,041)
2	Suicide (534)	Suicide (5,954)	Suicide (8,059)	Malignant neoplasms (10,695)	Heart disease (31,138)	Heart disease (80,837)	Malignant neoplasms (599,601)
3	Malignant neoplasms (404)	Homicide (4,774)	Homicide (5,341)	Heart disease (10,499)	Unintentional injury (23,359)	Unintentional injury (24,892)	Unintentional injury (173,040)
4	Homicide (191)	Malignant neoplasms (1,388)	Malignant neoplasms (3,577)	Suicide (7,525)	Liver disease (8,098)	CLRD (18,743)	CLRD (156,979)
5	Congenital anomalies (189)	Heart disease (872)	Heart disease (3,495)	Homicide (3,446)	Suicide (8,012)	Diabetes (15,508)	Stroke (150,005)
6	Heart disease (87)	Congenital anomalies (390)	Liver disease (1,112)	Liver disease (3,417)	Diabetes (6,348)	Liver disease (14,385)	Alzheimer disease (121,499)
7	CLRD (81)	Diabetes (248)	Diabetes (887)	Diabetes (2,228)	Stroke (5,153)	Stroke (12,931)	Diabetes (87,647)
8	Influenza/ pneumonia (71)	Influenza/ pneumonia (175)	Stroke (585)	Stroke (1,741)	CLRD (3,592)	Suicide (8,238)	Nephritis (51,565)
9	Stroke (48)	CLRD (168)	Complicated pregnancy (532)	Influenza/ pneumonia (951)	Nephritis (2,269)	Nephritis (5,857)	Influenza/ pneumonia (49,783)
10	Benign neoplasms (35)	Stroke (158)	HIV (486)	Septicemia (812)	Septicemia (2,176)	Septicemia (5,672)	Suicide (47,511)
CLRD = chronic lower respiratory disease, HIV = human immunodeficiency disease.							
Source: [10]							*Table 1*

POOR RESPONSE TO ANTIDEPRESSANTS

When they were first introduced, the monoamine oxide (MAO) inhibitors and tricyclic antidepressants were perceived as wonder drugs for depression. However, MAO inhibitors require strict dietary constraints, and both drug classes are associated with multiple troubling side effects. In contrast, when selective serotonin reuptake inhibitors (SSRIs) were introduced, they were much easier to prescribe and expanded treatment approaches to include primary care. Unfortunately, for many patients, SSRIs did not help as much as expected—or indeed at all, in some cases. Today, it is clear that non- or under-response to pharmacotherapy for major depression is far more common than was realized at the time. For example, researchers have found that antidepressants are ineffective for at least one-third of individuals who take them [2]. Suboptimal responses are also common. Many patients for whom the drugs do not work will recalibrate their expectations and accept the treatment response as the best they can hope to achieve. Treatment discontinuation is common among frustrated patients.

PAST YEAR PREVALENCE OF MAJOR DEPRESSIVE EPISODE AMONG U.S. ADULTS, 2020

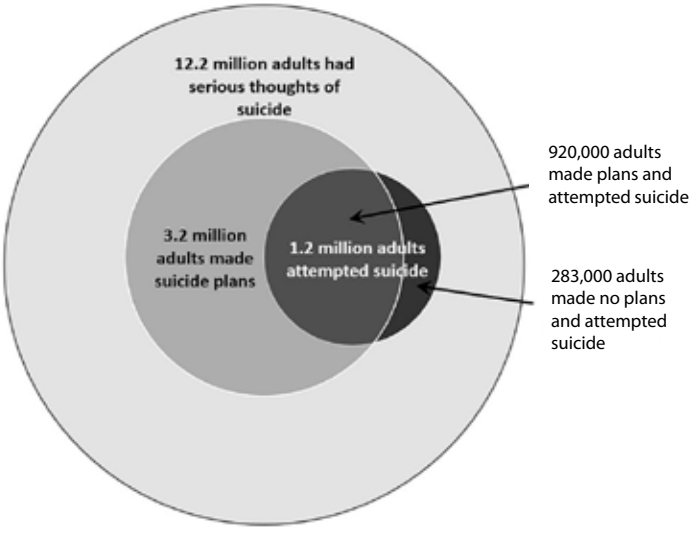


AI/AN = American Indian/Alaska Native

Source: [11]

Figure 1

SUICIDAL BEHAVIORS IN THE UNITED STATES, 2020



Source: [10; 12; 14]

Figure 2

It is also important to note that even when antidepressants actually are efficacious, it usually takes at least three or four weeks for the drug to begin to take effect. Tricyclic antidepressants, MAO inhibitors, SSRIs, and serotonin and norepinephrine reuptake inhibitors (SNRIs) all share this issue of a delayed onset of action. Psychiatrists and neuroscientists have been unable to develop faster-acting medications for depression to date. This means that many people with severe depression could take an antidepressant very faithfully for weeks without any relief. These patients may give up hope and halt treatment or try again with another antidepressant or medication combination.

As with any pharmacotherapy, antidepressants have many possible adverse effects, including weight gain, anorgasmia, sluggishness, anxiety, insomnia, and suicidal ideation. As such, a patient may experience no improvements in depression symptoms while also developing adverse drug effects. This is not the end of consequences; discontinuation symptoms are also a concern. Antidepressant discontinuation symptoms can be very challenging. For example, abruptly ending fluoxetine can cause nightmares, vomiting, and irritability. In most cases, patients who no longer wish to take an antidepressant should taper off the drug on a defined schedule [3].

To recap, patients may take antidepressants for months without significant improvements in depression symptoms while also experiencing side effects, and when they stop taking these ineffective drugs, they suffer more side effects unless they carefully taper off. In contrast, some psychedelic drugs have the potential to provide relief in a few sessions, with lasting efficacy over months or even years, although further research is needed. This contrast is the main reason that so many mental health professionals and patients are intrigued about the possibilities of psychedelic medicine, particularly for more difficult cases.

It is not clear why antidepressants work for some patients and not for others. Some have hypothesized it may be related to the size and shape of a person's neurons, which can vary considerably [3]. Another possible contributing factor is the similar mechanisms of action among the different classes of antidepressants. These agents increase blood levels of serotonin, dopamine, or norepinephrine. In contrast, some psychedelic drugs, such as ketamine, are *N*-methyl-D-aspartate (NMDA)/glutamate receptor antagonists. This represents a completely different target for antidepressant mechanism of action and also a novel approach to treating depression.

There is also some evidence that ketamine can reverse suicidality or depression after a single dose, which suggests that the drug reverses a neurochemical deficit that is close to the problem. Ketamine and psychedelic drugs are effective at promoting plasticity, reconnections, and healing within the brain, a feat beyond the capabilities of traditional antidepressants or most other drugs. Researchers have found that neuroplastic changes, specifically atrophy of neurons in the prefrontal cortex, are an underlying etiology of depression and other mood disorders. The extent to which these drugs, and ketamine in particular, are able to promote structural and functional plasticity in the prefrontal cortex is believed to underlie the fast-acting antidepressant properties [4]. Other drugs, such as LSD and DMT, may stimulate the formulation of synapses [4]. Psychedelic drugs may also create new connections within the brain, although much more research is needed to understand how and why these drugs may be effective in treating serious psychiatric disorders in some who have heretofore not proven responsive to traditionally effective treatments.

A GROWING MARKET

Certainly, psychedelic medicine is regarded as a major and burgeoning healthcare market. Data Bridge Market Research has estimated that the market for psychedelic drugs will more than triple, from about $2 billion in 2019 to nearly $7 billion by 2027 [13]. Other estimates are even more favorable; a report from Research and Markets anticipates a market of $10.75 billion in psychedelic drugs by 2027 [13]. In a post-COVID world in which the numbers of people with reported depression have increased by as much as three times, potentially effective treatment options should not be ignored.

It has been estimated that at least 50,000 therapists will be needed by 2031 to provide psychedelic-assisted therapy to patients, and as a result, some organizations have already begun to increase their hiring. The key types of therapies used will be cognitive-behavioral therapy (CBT), acceptance and commitment therapy (ACT), or other types of therapy adapted to psychedelic treatment [15].

The current high interest in psychedelic medicine may stimulate pharmaceutical companies to research and develop novel drug treatments for major psychiatric problems beyond the traditional classes of drugs that solely target serotonin, norepinephrine, and dopamine, which would be yet another positive consequence.

CONSUMER INTEREST

At the same time that the federal government has somewhat loosened its tight reins on psychedelic medicine and researchers and medical professionals have begun to explore the use of these agents, there has been a dramatic increase in interest among consumers in Schedule I drugs, particularly in cannabis, but also in psilocybin and other psychedelic drugs. As of 2022, 37 states as well as the District of Columbia and four U.S. territories allow the medical use of cannabis ("medical marijuana") [16]. (Note that medical use of cannabis is a bit of a misnomer, as prescribers generally have little or no involvement with patients who take the drug and it has not attained FDA approval for any condition.) In addition, the U.S. House of Representatives passed a bill to decriminalize cannabis use in 2022 [17]. In addition, 18 states, the District of Columbia, and 2 U.S. territories have legalized the recreational use of cannabis

for adults [18]. This followed several years of decriminalization at the local and state levels. While cannabis is not considered a psychedelic drug, its shift toward decriminalization and medicinal use is a sign that a similar path may be beginning for other Schedule I drugs with potential psychiatric benefit. Further, in states that allow medical or recreational use of cannabis for adults, the federal government has largely backed away from taking any punitive measures against individuals who use the drug, even though cannabis remains illegal at a federal level.

This movement may already be advancing with psychedelic drugs. This began with the decriminalization of psilocybin in Denver, Colorado, in 2019, followed by Oakland and Santa Cruz, California. In 2021, the city of Cambridge, Massachusetts, passed a law decriminalizing all "entheogenic plants," which includes the drugs ayahuasca, ibogaine, and psilocybin [19]. As of 2022, the largest city to decriminalize psilocybin is Seattle, Washington [19]. In 2020, the state of Oregon approved the use of psilocybin by consumers [20]. Also in 2020, the District of Columbia decriminalized the use of psilocybin mushrooms as well as other substances found in peyote and ayahuasca [20]. Other states are considering taking similar actions. In 2021, Health Canada, the premier health agency in Canada, approved trials of MDMA-assisted therapy for the treatment of PTSD [15]. It is important to note that it can be dangerous for psilocybin and other psychedelic drugs to be used by individuals who do not understand its risks. As popularity and interest in the medical use of these agents increases, clinicians have a responsibility to educate themselves and their patients about the safe and appropriate use of psychedelics.

A major factor in the popularity of psychedelic drugs is frustration resulting from unrelenting depression, anxiety, chronic pain, or other health and mental health conditions. Some patients may have already tried cannabis to address these conditions, with varying levels of success.

GROWING BODY OF RESEARCH FROM RESPECTED ACADEMIC AND PHYSICIAN LEADERS

Although researchers have historically chosen to avoid or been blocked from researching psychedelics because of bans by the federal government, this has changed in the past few decades. For example, in 2006, Johns Hopkins Medicine began their research on psychedelic medicine, subsequently producing more than 80 peer-reviewed clinical studies by 2020 [21]. A new home for the Center for Psychedelic and Consciousness Research was created in 2020, the first such establishment in the United States [21]. Private donors provided funding to launch the Center, and since its opening, the Center has also received federal funding for research. In addition, Yale, Massachusetts General Hospital/Harvard, and other psychiatric and research excellence centers are studying psychedelic medications as treatment options for serious psychiatric disorders.

PSYCHEDELIC PSYCHIATRY TRAINING PROGRAMS

Hopkins-Yale-NYU
https://medicine.yale.edu/news-article/grant-supports-development-of-training-for-psychiatrists-in-psychedelic-medicine

MAPS
https://mapspublicbenefit.com/training

Mount Sinai
https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research/training-education

Source: Compiled by Author *Table 2*

In addition, training programs focusing on psychedelic psychiatry are being established (***Table 2***). Johns Hopkins, New York University, and Yale are collaborating to create a psychedelics-psychiatrist program funded by a grant facilitated by Heffter Research Institute [22].

DEFINITIONS

What is set, in the context of psychedelic medicine?

Clear definitions of the concepts related to psychedelic drugs and interventional psychiatry are helpful. The following is a glossary of terms used throughout this course.

Classic psychedelic: Refers to older hallucinogenic drugs, such as psilocybin and LSD. These agents are often derived from natural sources.

Deep brain stimulation: With the use of implanted electrodes, the brain is stimulated to treat such psychiatric problems as treatment-resistant depression.

Electroconvulsive therapy (ECT): Stimulation of the brain causing a seizure. This therapy is administered under sedation and is used to help patients with severe psychiatric diagnoses.

Hallucinogen: Drug that may cause the user to experience visual, auditory, or other types of hallucinations.

Neuromodulation therapy: The use of noninvasive or invasive means to stimulate the brain in order to treat serious psychiatric problems.

Psychedelic medicine: The use of mind-altering (typically but not always hallucinogenic or dissociative) drugs by mental health professionals to improve or even provide remission from severe psychiatric problems, such as depression, PTSD, anxiety, and substance use disorders.

Set: Refers to the patient's mindset. For example, a person who is anxious and fearful is less likely to have a positive experience with psychedelic medicine than a person who has an open and positive outlook.

Setting: Refers to the overall ambiance in which psychedelic medicine is administered. A pleasant atmosphere that makes the individual feel safe is best.

Transcranial magnetic stimulation: A noninvasive form of therapy that uses large magnets external to the patient to stimulate the brain.

Vagus nerve stimulation: Invasive stimulation of the vagus nerve in order to treat serious, treatment-resistant psychiatric diagnoses.

PONDERING PSYCHEDELICS

More than 50 years have passed since the federal Controlled Substances Act first criminalized the use of psychedelics in the United States in 1970. The initial use (and misuse) of psychedelic drugs in that era was primarily associated with Timothy Leary, a Harvard professor who promoted the nonmedical use of LSD, a practice subsequently adopted by the amorphous "hippie" counterculture movement of the 1960s and 1970s. Dr. Leary was famously noted as advising his followers to "turn on, tune in, and drop out," scandalizing much of the conservative population of the time. Numerous events led to Leary's loss of reputation, academic standing, and position, but his impact during this period was indisputable. In response to this movement, drugs such as LSD, DMT, psilocybin, and mescaline were all placed in the Schedule I drugs category under the Controlled Substances Act 1970 (***Table 3***).

The categorization of psychedelics as Schedule I drugs immediately halted intense scientific research on psychedelics, which had begun in the 1950s. This prohibition on psychedelic drug research significantly delayed advances in medical knowledge on the therapeutic uses of these agents. While much of the focus at that time was on Timothy Leary and the counterculture's recreational LSD use, some researchers had demonstrated beneficial effects with psychedelic medicine in end-of-life care as well as in the treatment of addiction and other severe psychiatric problems [24].

This research did not restart in the United States in any meaningful way until the 21st century. In this new wave of research, researchers in Phase 2 and 3 clinical trials of psychedelic medications have found the possibility of remission in diverse psychiatric populations (including in patients with PTSD, depression, eating disorders, and substance use disorders) as well as reduction in end-of-life anxiety and despair in those with terminal diagnoses [25]. At the same time, researchers have explored the use of older drugs (e.g., nitrous oxide, ketamine) to treat unrelenting psychiatric disorders.

PSYCHEDELIC DRUG SCHEDULING

Drug	Schedule
Ayahuasca/DMT	I
Ibogaine	I
Ketamine	III
Kratom	Not scheduled
LSD	I
Mescaline	I
Nitrous oxide	Not scheduled
Psilocybin	I
MDMA ("Molly," "Ecstasy")	I

Source: [23] *Table 3*

Another interesting avenue of research has been in the field of addiction medicine. There is some evidence that certain psychedelic drugs, particularly psilocybin, may act as a sort of "anti-gateway drug." Years ago, there was a belief that some (or all) drugs were "gateway drugs," leading inevitably to taking other drugs; for example, this perspective holds that people who smoked marijuana would eventually progress to using "harder" drugs, injecting heroin or other opioids. This theory has largely been discredited and devalued. In fact, several studies have indicated that persons who use hallucinogens are less likely to progress to harder drugs. In one study, researchers used data from nearly 250,000 respondents from the National Survey on Drug Use and Health over the period 2015–2019. Respondents were asked about their past use of classic psychedelics, and these results were then compared to their later abuse (or non-use) of opioids. Individuals who had used psilocybin ("magic mushrooms") in the past had a significantly lower rate (30% lower than average) of opioid misuse and abuse later. This finding was not replicated with other psychedelic drugs [26]. An earlier study using National Survey on Drug Use and Health data for the period 2008–2013 found that past use of classic psychedelics decreased the risk for past-year opioid dependence by 27% and of opioid abuse by 40% [27].

Both of these studies relied on individuals reporting on their past use of psychedelic drugs, and there are multiple possible issues with this type of retrospective reporting. But the idea that past use of drugs such as psilocybin could be protective against opioid misuse and dependence in the future is promising, given the ongoing opioid epidemic in the United States.

A BRIEF HISTORY OF PSYCHEDELICS

It is unclear how long the various psychedelic substances have been used worldwide, but it is safe to say that some have been used for thousands of years in religious and tribal ceremonies. The earliest known written record of the use of psilocybin mushrooms appeared in the Florentine Codex, a manuscript of ethnographic research of Mesoamerica, particularly of Mexico and the Aztecs, compiled between 1529 and 1579. Psilocybin, mescaline, and ayahuasca (a concoction often brewed in a tea and that includes the psychedelic chemical DMT) have all been used in religious ceremonies in indigenous societies in South and Central America for centuries. The hallucinogenic effects of some plants and fungi also have been known by indigenous cultures and were deliberately exploited by humans for thousands of years. Fungi, particularly some types of mushrooms, are the principal source of naturally occurring psychedelics. Historically, the mushroom extract psilocybin has been used as a psychedelic agent for religious and spiritual ceremonies and as a therapeutic option for neuropsychiatric conditions [28].

Early Days of LSD

In the 1940s, LSD was marketed for the treatment of what conditions?

Modern pharmaceutical research on psychedelics started in earnest in 1930s Basel, Switzerland, with research chemist Albert Hofmann. Seeking to create a synthetic alkaloid to the ergot fungus, he developed LSD-25 in 1938. The uses of the drug were not immediately obvious, so it sat on a shelf for five years until Hofmann decided to repeat his synthesis of the chemical. Despite his care, Hofmann accidentally contaminated himself with the drug and thereafter experienced highly unusual sensations as well as dizziness. He described his experience as [29]:

> I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours, this condition faded away.

Hofmann decided to experiment on himself with what he believed to be a very low dose of LSD, but the dose was high enough for him to experience what he perceived to be demonic possession and other lurid sensations. His physician was called and only noted that Hofmann had extremely dilated pupils, with normal blood pressure and vital signs. When Hofmann related his experiences to his colleagues, they were dubious that he had measured correctly, but to be safe, they took even lower doses. Each experienced what were later referred to as psychedelic mind "trips" [29].

In 1947, Sandoz began marketing and distributing LSD, under the brand name Delysid, as a possible psychiatric drug to treat neurosis, alcoholism, criminal behavior, and schizophrenia. In addition, LSD-25 was also used to treat autism and verbal misbehavior [28; 30]. In his book, Hofmann described how LSD helped provide relief to people who were dying of cancer and in severe pain for whom major analgesics were ineffective. He hypothesized that the analgesic effect was not inherent to the drug but was a result of patients dissociating from their bodies such that physical pain no longer affected them [29].

However, early studies on LSD did not always inform patients about the potential risks. For example, in some cases, patients with schizophrenia were given LSD and not told about the possible risk for a psychotic break [31]. Patients at the Addiction Research Center in Lexington, Kentucky, were often given the drug without being told what it was or the possible effects. Researchers who believed in the importance of "set and setting" (the patient's mindset and the setting where the drug was administered) were more likely to inform patients about possible risks and benefits. The 1962 Kefauver-Harris Amendments required that all patients provide informed consent for therapeutic interventions and research participation. Despite this, the "informed consent" of the 1960s was not as comprehensive as informed consent today. Some have posited that the primary goal was to release researchers from legal responsibility rather than to provide ensure the safety of patients and prospective subjects of clinical trials [31].

For about a decade, Hofmann and Sandoz believed that LSD might provide breakthroughs in psychiatry. However, with the major social change of the 1960s, characterized by protests for social change and against the Vietnam War and increasingly liberal attitudes regarding drugs among young people, the focus shifted to recreational rather than medical use of LSD, and in 1965, Sandoz stopped manufacture and marketing of LSD. In 1966, Sandoz gave their remaining supplies to the National Institute of Mental Health [31].

Early Days of Psilocybin

In 1957, Hofmann received a sample of dried *Psilocybe mexicana* mushrooms from a mycologist in Huautla de Jiménez in Oaxaca, Mexico. The mycologist, R. Gordon Wasson, had received a sample of the mushrooms and information regarding the sacred rituals of the Mazatec people from a curandera to whom he promised secrecy; this promise was obviously not kept, and Wasson's actions resulted in retaliation against the indigenous woman who he betrayed [138]. Hofmann used paper chromatography to separate the various components of whole extracts of mushrooms and ingested each separated fraction. The active fraction was then chemically characterized, crystallized, and named psilocybin. In 1958, Hofmann and his colleagues subsequently elucidated the structure and synthesis

of psilocybin and psilocin, a minor component of the extract that is a dephosphorylated form of psilocybin. In the 1960s, Sandoz Pharmaceuticals began to distribute Indocybin, a psychotherapeutic drug in pill form, containing 2-mg psilocybin. This period also saw research focusing on psilocybin as a probe for brain function and recidivism and as an entheogen used by religious people (divinity students).

During this era, psilocybin, LSD, mescaline, and other psychedelics were used by some individuals with psychiatric diseases, and they were also used extensively by some psychiatrists to treat patients before the drugs were categorized as Schedule I of the U.N. Convention on Drugs in 1967, which preceded the Controlled Substances Act in the United States. Today, the medical value of hallucinogens is being tested in rigorous trials in settings such as Roland Griffith's Johns Hopkins research program. The experts from the psilocybin research group at Johns Hopkins University have described the importance of trained psychedelic therapists and other components of a psychedelic treatment session to optimize patient safety in hallucinogen research [32].

CONSIDERING PSYCHEDELIC-ASSISTED PSYCHOTHERAPY AS A TREATMENT OPTION

For most mental health professionals, the idea of psychedelic-assisted psychotherapy is a major paradigm shift and leap from current practices of providing pharmacotherapy or psychotherapy to individuals or groups. At the same time, it may represent a new opportunity to combine the talents and skills of therapists with the proven benefits of a psychedelic drug. Combined psychotherapy/pharmacotherapy is the treatment of choice for most patients with mental health disorders, so interprofessional collaboration is a typical (and vital) part of treatment. Psychedelic medicine requires that diverse disciplines collaborate closely and communicate to clearly ensure that the therapy is safely and effectively administered.

LEGAL AND REGULATORY BARRIERS

Today, the federal government has provided limited permission or even grants to study Schedule I drugs and their possible role in the treatment of patients. Outside of these limited cases, researchers find it difficult to obtain the needed drug for testing purposes. To avoid legal and regulatory issues, a good amount of research is performed outside of the United States.

"SET" AND "SETTING" IN PSYCHOTHERAPY-ASSISTED PSYCHEDELIC TREATMENT

Which aspects of a psychedelic medicine setting can enhance set?

Since the 1960s, therapists have noted that the response to psychedelic drugs is impacted by the patient's mindset as well as the setting where the psychedelic drug is administered. For example, if the person feels confident that the experience will be a positive one, then this "set" is considered more conducive to a good experience while under the influence of a psychedelic drug compared with when persons are extremely apprehensive and fearful beforehand. By extension, if patients are in an office setting with a therapist or other practitioner with whom they feel safe, the outcome is generally better than in those who feel unsafe. Research has shown a better outcome with patients receiving psychedelics in a therapeutic setting versus receiving the drug while undergoing a positron emission tomography (PET) scan [33]. These researchers stated [33]:

> The finding that the PET environment was strongly associated with anxious reactions could be partially explained by the perceived atmosphere. Whereas non-PET experiments were mostly conducted in laboratory rooms that were furnished in an aesthetically pleasing way, the environment at the PET center was much more clinical and "antiseptic" (i.e., lots of technical equipment, white walls, personnel in white lab coats). Our results are therefore in support of current safety guidelines, which recommend avoiding "cold" and overly clinical environments in human hallucinogen research in order to reduce the risk of anxious reactions.

Another element of setting, and one that is also used to enhance set, is the use of music while the patient undergoes therapy with psychedelic medicine. Johns Hopkins has developed a "psilocybin playlist" lasting nearly eight hours that is used for patients who are undergoing treatment with psilocybin [34].

In many cases, psychedelic therapy is administered after a therapeutic session. Psychotherapy is often also provided during the course of the drug's effects and at integration sessions that occur after the drug was given to help the patient to give meaning and context for the experience [35]. This provision of multiple hours of psychotherapy over a short period of time can translate to higher costs. This scenario might be less appealing to insurance carriers than traditional therapies (e.g., antidepressants or other drugs), but this is yet to be seen.

It should also be noted that in some areas, there are clear manualized approaches to treating patients that carefully consider both set and setting; this is particularly the case for MDMA in the treatment of PTSD. However, these approaches are yet to be developed for most other psychedelic drugs. Again, this field offers burgeoning opportunities for psychiatrists, psychologists, primary care providers, and other mental health practitioners.

ADVISING PATIENTS CONSIDERING PSYCHEDELIC MEDICINE

Some patients will approach their primary care providers to discuss the possibility of seeking care at a ketamine or MDMA (or other) clinic. It is important not to dismiss these treatment options out of hand. Instead, it may be best to ask the patients the following questions to help assess if the option would be helpful and if the facility is set up to provide optimal care:

- Who is the expert or experts running this clinic? What experience(s) make this person or team experts? What outcome data are provided?
- Does the patient have a severe and intractable diagnosis, such as treatment-resistant depression, substance use disorder, or PTSD? If not, then conventional medicine is still best.
- Does the clinic ensure professional observation after the drug is administered? This is always advisable in case the patient experiences adverse events.
- How soon after a drug is administered are patients discharged from the facility? Minimal times (e.g., 15 minutes) are not long enough to ensure safety.
- Does the facility offer psychotherapy before, during, and after the drug is administered? Combining psychotherapy with psychedelic medicine is the proven best practice.
- Is there a required follow-up?
- Are the costs for treatments clearly delineated? If not, patients should request, in writing, an estimate of total costs. Psychedelic medicine is likely not covered by health insurance and may be costly. Also, the cost may fluctuate significantly from one clinic to another.
- Has the patient experienced a psychotic break in the past or does the patient have first-degree relatives with a history of psychosis? Psychedelics have the potential to trigger an underlying predisposition for psychosis, although it can be temporary. Still, even a short-term psychotic break is a terrifying experience.

ADDRESSING STIGMA

For many people, including some clinicians, the phrase "psychedelic medicine" evokes images of free love, 1960s counterculture, and recreational intoxication. In reality, these therapies typically look much more pedestrian, consisting of a patient sitting or lying on a couch while a clinician guides the person through the experience in order to treat their severe psychiatric disorder. Although many of the drugs described in this course can and do induce hallucinations, subjects have reported that these experiences were integral and allowed them to resolve psychiatric issues that have been resistant to traditional treatments and that have significant impact on their lives. If further studies continue to bear these findings out, it would be unwise to ignore the benefits that may accrue.

EMERGING PSYCHEDELIC TREATMENTS

The key psychedelic drugs actively being researched and/or currently in use today include psilocybin, ketamine, MDMA, ibogaine, kratom, LSD, mescaline, and ayahuasca (***Table 4***). In addition, nitrous oxide, a gas used for many years by dentists as both an anesthesia and analgesic for patients undergoing painful procedures, has also been found effective as a treatment for some psychiatric disorders.

PSILOCYBIN

In studies using psilocybin, what were the most common adverse reactions?

Beginning in the 2010s, psilocybin has been undergoing an era of increased research attention, and this compound remains under active investigation. Psilocybin occurs in nature in hundreds of species of mushrooms as 4-phosphoryloxy-*N*,*N*-dimethyltryptamine. However, when used by researchers, the drug is nearly always a chemically synthesized compound to maintain a standard dosage as well as the purity of the drug. In 2020, COMPASS Pathways announced that it had gained a patent in the United States for COMP360, its form of synthetically derived psilocybin [15].

According to a 2022 report from the Associated Press, some states, even in conservative areas (e.g., Utah), have approved studying psilocybin as a treatment. This movement has largely been driven by increasing rates of treatment-resistant PTSD among military veterans [36].

Psilocybin was first studied during the 1960s to establish its psychopharmacologic profile; it was found to be active orally at around 10 mg, with more potent effects at higher doses, with a four- to six-hour duration. Psilocybin is rapidly metabolized to psilocin, a full agonist at serotonin 5-HT1A/2A/2C receptors, with 5-HT2A receptor activation directly correlated with human hallucinogenic activity. Time to onset of effect is usually within 20 to 30 minutes of ingestion. As a drug, it is about 20 times stronger than mescaline but much less potent than LSD [37].

MAJOR PSYCHEDELIC RESEARCH CENTERS IN THE UNITED STATES

Johns Hopkins Center for Psychedelic and Consciousness Research
https://hopkinspsychedelic.org

National Institutes of Health Funding
https://pubmed.ncbi.nlm.nih.gov/34624734

Yale University
https://medicine.yale.edu/psychiatry/education/residency/interest/psychedelic_science_group

Mount Sinai
https://www.mountsinai.org/about/newsroom/2021/mount-sinai-health-system-launches-center-for-psychedelic-research

Stanford University
https://med.stanford.edu/spsg.html

University of California, San Francisco
https://neuroscape.ucsf.edu/psychedelics

Duke University
https://dukepsychedelics.org

University of Texas at Austin
https://dellmed.utexas.edu/units/center-for-psychedelic-research-and-therapy

Washington University in St. Louis (WUSTL)
https://healthymind.wustl.edu/items/washington-universitys-program-in-psychedelic-research

Harvard/Massachusetts General Hospital
https://www.massgeneral.org/psychiatry/treatments-and-services/center-for-the-neuroscience-of-psychedelics

Source: Compiled by Author *Table 4*

In animal studies of the use of psilocybin, a link has been identified between reduced prefrontal mGluR2 function and both impaired executive function and alcohol craving. Psilocybin also restored healthy mGluR2 expression and reduced relapse behavior in mice [38]. Mice and humans do not always respond equivalently, but this finding may explain why psilocybin is effective in treating induced alcoholism in mice and provides an interesting research avenue in the investigation of psilocybin as a treatment for alcohol use disorder in humans, because relapse is a significant problem; even when a patient has abstained from alcohol for years, the underlying craving remains. If this craving could be reduced or altogether eliminated, this could revolutionize substance use disorder treatment.

In a study at King's College London, researchers studied the effects of psilocybin on the emotional and cognitive functions in healthy subjects in a Phase 1 randomized double-blind controlled study with 89 subjects (average age: 36.1 years). Subjects were randomized to receive placebo or 10 mg or 25 mg of psilocybin. Therapists were available to the subjects throughout the sessions. Six subjects at a time received the drug. The study showed that there were no short- or long-term adverse effects to the emotional processing or cognitive functioning of the subjects [39]. In this study, 70% of the subjects who received 25-mg psilocybin experienced visual hallucinations, compared with 60% of those who received 10-mg psilocybin and 6.9% of those who received placebo. The second most common treatment-emergent adverse event was illusion, which was experienced by 60% of subjects receiving 25-mg psilocybin and 63.3% of those receiving 10-mg psilocybin; 13.8% of those receiving placebo reported experiencing this effect. Other treatment-emergent adverse events reported more commonly among the treatment groups included mood alteration, headache, fatigue, and euphoric mood, all of which were lower or altogether non-existent in the placebo group. Also absent in the placebo group were auditory and tactile hallucinations [39]. The researchers concluded [39]:

> This study demonstrated the feasibility of one-to-one psychological support from specially trained therapists during [the] simultaneous administration of psilocybin in a supervised clinical setting in healthy volunteers. A single dose of psilocybin 10 mg or 25 mg elicited no serious adverse effects and did not appear to produce any clinically relevant detrimental short- or long-term effects, compared with placebo, in cognitive or social functioning or emotional regulation in this study in health volunteers.

In studies using psilocybin, the most common adverse reactions were found to be headache, nausea, and hypertension, and events were considered to be equivalent to those found with the use of SSRIs [40]. However, it should also be noted that the subjects in psilocybin clinical trials are usually screened for a family history of schizophrenia, major depression with psychotic features, high risk for suicide, and severe personality disorders before inclusion [40].

Another study at Johns Hopkins evaluated the efficacy and safety of psilocybin for the treatment of major depressive disorder. In this randomized study, 24 patients 21 to 75 years of age with moderate-to-severe unipolar depression were randomized to either immediate or delayed treatment. Subjects were administered two doses of psilocybin along with supportive psychotherapy. Researchers found a greater than 50% reduction in depressive symptoms, as measured by the GRID-Hamilton Depression Rating Scale (GRID-HAMD), in the treatment group. Before initiating psilocybin therapy, subjects first received six to eight hours of preparation with trained facilitators. The psilocybin was administered at doses of 20 mg/70 kg and 30 mg/70 kg, about two weeks apart, while subjects were in a comfortable room supervised by two facilitators. There were also follow-up counseling sessions [1]. The mean scores on the GRID-HAMD decreased from an average of 22.8 at the pretreatment level to 8.7 at 1 week, 8.9 at 4 weeks, 9.3 at 3 months, 7.0 at 6 months, and 7.7 at 12 months. These data indicate that the psilocybin provided persistent relief to many patients [1].

In a 2018 British study, 26 patients, 20 of whom were diagnosed with severe treatment-resistant depression, were administered separate doses of 10- and 25-mg psilocybin one week apart; administration took place in a supportive setting. Nineteen subjects completed the treatment process, including psychological support, and all of the completers reported improved symptoms based on Quick Inventory of Depressive Symptoms (QIDS-SR16) and HAM-D scores. Four patients experienced remission of their depression at week five. Many completers continued to benefit from treatment at three months and six months. Suicidality scores among the patients also significantly fell within the two weeks after treatment [41].

Not all researchers have offered a ringing endorsement of the use of psilocybin. A 2021 study studied 59 patients with moderate-to-severe major depressive disorder. The subjects were administered either two doses of 25-mg psilocybin three weeks apart plus placebo (30 patients) over six weeks, or they were given escitalopram (an SSRI) for six weeks (29 patients). All the patients also received psychological assistance. No significant differences were noted in depression symptoms between the two groups, and the researchers concluded that further studies with larger populations were needed. Even the adverse events in the two groups were somewhat similar; the most common adverse effect in both groups over the course of the study was headache, followed by nausea [42]. Even in this study, psilocybin was about as effective as antidepressant therapy. This is remarkable, in that this new treatment is about as effective as the established criterion standard treatment for major depressive disorder.

Although studies have supported the hypothesis that psilocybin provided under research conditions by physicians has a positive effect on depressive symptoms, until recently, the mechanism by which this improvement has occurred was largely unknown. However, in a study of 16 individuals with treatment-resistant depression, researchers used functional magnetic resonance imaging (fMRI) to assess functional brain changes both at baseline and one day after the study group received 25-mg psilocybin. The researchers found brain network modularity was reduced within just one day after the psilocybin was administered [43]. In a second study by the same researchers, 59 patients with major depressive disorder were randomized to either two doses of 25-mg psilocybin three weeks apart plus six weeks of daily placebo or to six weeks of 10- to 20-mg escitalopram per day plus 1-mg psilocybin (an ineffective dose). In this study, 29 subjects were in the escitalopram arm, although the group ultimately decreased to 21 subjects (28% dropout rate). The 30 patients in the psilocybin group decreased to 22 subjects (27% dropout rate) [43]. The researchers noted that [43]:

> It is plausible that this putative liberating effect of psilocybin on cortical activity occurs via its direct agonist action on cortical 5-HT2A receptors, dysregulating activity in regions rich in their expression. We surmise that chronic escitalopram does not have the effect on brain modularity due to its more generalized action on the serotonin system and predominant action on inhibitory postsynaptic 5-HT1A receptors, which are richly expressed in limbic circuity.

The researchers found that the antidepressant effect of the psilocybin was sustained and rapid and that it also corresponded with decreases in fMRI brain network modularity. This indicates that the antidepressant effect of psilocybin, when it works, is linked with a global increase in brain network integration. In contrast, the response to the escitalopram was mild and caused no changes to the brain network [43].

KETAMINE

Ketamine is a derivative of phencyclidine (PCP), which itself was originally developed as an anesthetic. However, the major adverse effects of PCP, such as aggression, psychosis, and dysphoria, made it an undesirable and unacceptable anesthetic choice [44]. In contrast, ketamine was effective as an anesthetic and had few adverse effects. PCP subsequently became a drug of abuse.

While ketamine has been used in operative analgesia for decades, it has also become a drug of abuse and misuse [45]. 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) [46]. As a result, ketamine developed a stigma, and this negative view may persist in many minds.

Ketamine is a Schedule III drug that is a combination of s-ketamine (esketamine) and r-ketamine (arketamine). In 2019, the use of esketamine as a nasal spray (brand name Spravato) was approved by the FDA for the treatment of treatment-resistant depression. Since then, it has also been approved to treat suicidal depression. However, it should be noted that this nasal spray formulation is not available at most pharmacies; instead, it is provided solely through a restricted distribution system. The FDA also requires that patients be overseen for a minimum of two hours after treatment, in order to allow sufficient time to identify and address and adverse reactions that develop in patients. (It is not clear if all ketamine clinics adhere to this provision.)

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with major depressive disorder who have not responded to several adequate pharmacologic trials, the Department of Veterans Affairs suggests ketamine or esketamine as an option for augmentation.

(https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFinal508.pdf. Last accessed July 8, 2022.)

Strength of Recommendation: Weak for

After treatment with ketamine, patients should not leave the facility until they are cleared to do so by a healthcare provider and they should also be cautioned to avoid driving or using heavy equipment until the following day. In addition, patients are not allowed to take the nasal spray home, because it may only be used in the medical office while under the supervision of qualified staff members [47].

Intravenous ketamine has been used off-label for treatment-resistant depression by some clinicians, and ketamine clinics are established in many parts of the United States, although their fees vary widely. The effects of intravenously administered ketamine may last for hours, days, or even weeks in some patients. Some believe that intravenous ketamine is significantly more effective than its intranasal form because it includes both the s and r forms of the drug.

Some researchers have found that the mental state of the patient (set) prior to receiving treatment with ketamine may affect the outcome of treatment. In a 2019 study, 31 patients with major depressive disorder were treated with ketamine infusions. Researchers used multiple instruments to measure the mental state of subjects prior to and after receiving treatment, including the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Hopelessness Scale. In this study, 17 subjects (55%) responded to the ketamine, while 14 (45%) had no response [48]. Non-responders had significantly higher rates on anxiety scales than responders. The researchers stated [48]:

> The present study showed for the first time that non-responders had more anxiety-related experiences induced by the first ketamine infusion than responders confirming our initial hypothesis of significantly different subjective experiences as a function of treatment response. Specifically, we found that it was the extent of ketamine-induced anxiety that was negatively predictive of a treatment response after a series of six infusions on average.

They also noted that providing a calm treatment environment to patients might be sufficient to reduce anxiety levels in patients to improve outcomes. This is the goal of treatment providers as well as researchers who emphasize the importance of set (mindset) and setting, as discussed. In this study, there was no follow-up after the last infusion, which may also have improved efficacy [48].

In another study of 30 individuals with PTSD of a median duration of 15 years, half of subjects were randomized to a ketamine group and half were assigned to a midazolam (a benzodiazepine) group. The subjects received six infusions over the course of two weeks of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). The subjects were evaluated with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) at baseline and also at the end of treatment [49].

The average CAPS-5 total scores following the infusions were 11.88 points lower among the subjects in the ketamine group compared with the midazolam group. About two-thirds of the ketamine subjects (67%) responded to the treatment, versus only 20% of treatment responders in the midazolam group. The median time to loss of treatment following the two-week ketamine treatment period was 27.5 days. However, in outlier cases, two subjects still had not lost their response; improve-

ments continued at 50 days and 102 days since the last infusion. The ketamine group experienced a major reduction in symptoms of depression as well as in clinical ratings of global psychiatric illness severity. The researchers concluded that the findings from this study support the assertion that "repeated ketamine infusions are safe and generally well tolerated among individuals with chronic PTSD, with only transient emergence of psychoactive and hemodynamic side effects" [49].

In a French study, ketamine was explored as a treatment for individuals with severe suicidal ideation in a double-blind randomized clinical trial. In this six-study report, published in 2022, 156 patients were given either a 40-minute infusion of ketamine or placebo (saline solution). The administration was repeated 24 hours later. The groups were also divided into subjects with bipolar disorder, depressive disorder, and other diagnoses. Of patients in the ketamine group, 93.1% had a past history of the commission of a suicidal act, as did 86.6% of the subjects in the placebo arm [50].

On day 3, nearly two-thirds (63%) of the patients in the ketamine group achieved full remission from suicidal thoughts. In contrast, 31.6% of the patients in the placebo group were in remission. In nearly 44% of the ketamine subjects, remission occurred within two hours after the first infusion, compared with 7.3% of the placebo group. Ketamine was particularly effective in the bipolar group, while its effect was not significant in the group with major depressive or other psychiatric disorders. The researchers speculated that ketamine might provide an analgesic kind of effect to mental pain [50].

MDMA

Researchers have demonstrated the efficacy of combination psychotherapy and MDMA in the treatment of what condition(s)?

In the past and even to date, MDMA (also referred to as "Ecstasy" or "Molly") has been largely a drug of abuse. According to the National Institute on Drug Abuse, about 2.6 million people in the United States 12 years of age and older reported past-year use of MDMA in 2020 [51]. The drug was originally developed by Merck in 1912, and in the 1970s, it was found to be useful in combination with psychotherapy [52]. However, because of considerable active abuse of the drug in the United States, in 1985, MDMA was categorized as a Schedule I drug under the Controlled Substances Act in an emergency ban, and consequently research on this drug largely halted until the 2010s [53].

Today, researchers have demonstrated the efficacy of combination psychotherapy and MDMA in treating PTSD. The FDA has granted "breakthrough therapy" permission for MDMA therapeutic treatment, largely as a result of the findings of several small studies. Clinicians who use MDMA-assisted psychotherapy to treat individuals with PTSD have access to a manual outlining best practices for this therapeutic use. In the 2017 revision of this manual, the following explanation is given [54]:

> The basic premise of this treatment approach is that the therapeutic effect is not due simply to the physiological effects of the medicine; rather, it is the result of an interaction between the effects of the medicine, the therapeutic setting, and the mindsets of the participant and the therapists. MDMA produces an experience that appears to temporarily reduce fear, increase the range of positive emotions toward self and others, and increase interpersonal trust without clouding the sensorium or inhibiting access to emotions. MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process with less likelihood of either feeling overwhelmed by these emotions or of avoiding them by dissociation or emotional numbing. In addition, MDMA can enable a heightened state of empathic rapport that facilitates the therapeutic process and allows for a corrective experience of secure attachment and collaboration with the therapists.

In six double-blind, randomized clinical studies conducted between 2004 and 2017, 72 subjects are administered 75–125 mg of MDMA in two or three sessions, comparing these results with 31 patients who received placebo; all the patients had diagnosed PTSD. The drug was administered following 90-minute sessions of psychotherapy and three to four therapy sessions were also provided during follow-up after MDMA therapy [55].

Members of the treatment group reported significantly reduced scores on the CAPS-5 compared with the control group. In addition, after two sessions, 54.2% of those who received MDMA no longer met the criteria for PTSD—they were in remission. In contrast, only 22.6% of the control group experienced remission. The researchers noted that "MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD" [55].

In another randomized, double-blind, placebo-controlled phase 3 clinical trial with 90 individuals with severe PTSD, the subjects received manualized therapy with either MDMA or placebo. Three preparatory sessions occurred before the administration of the drug, and there were nine integrative therapy sessions afterwards. Subjects in the MDMA treatment group experienced a significant decrease in CAPS-5 (-24.4) scores compared with placebo subjects (-13.9). Scores on the Sheehan Disability Scale (SDS) also significantly improved in the MDMA subjects compared with the placebo subjects [56]. The researchers noted [56]:

> Given that PTSD is a strong predictor of disability in both veterans and community populations, it is promising to note that the robust reduction in PTSD and depressive symptoms identified here is complemented by a significant improvement in SDS score (for example, work and/or school, social and family functioning). Approximately 4.7 million U.S. veterans report a service-related disability, costing the U.S. government approximately $73 billion per year. Identification of a PTSD treatment that could improve social and family functioning and ameliorate impairment across a broad range of environmental contexts could provide major medical cost savings, in addition to improving the quality of life for veterans and others affected by this disorder.

Because major problems with sleep quality are common among patients with PTSD, some researchers have studied the effects of MDMA-assisted psychotherapy to determine its effects on sleep disorder. In a series of four studies with 63 subjects at sites in the United States, Canada, and Israel, subjects were randomized to two or three sessions of MDMA-assisted psychotherapy or to a control group. PTSD symptoms were assessed with the CAPS-IV, and the Pittsburgh Sleep Quality Index (PSQI) was used to measure changes in sleep quality. At the conclusion of the study, the CAPS-IV severity scores had decreased by 34 points in the MDMA group, compared with a decrease of 12.4 points for the control group. In addition, sleep quality improved significantly in the experimental group compared with the control group. In the treatment group, 53.2% of subjects reported a PSQI score drop of 3 or more points, compared with 12.5% in the control group [57].

Although there appears to be a benefit for MDMA therapy in the management of PTSD, especially for patients who have failed other therapies, the durability of this affect has been questioned. One study indicated improvement may be persistent for a considerable period of time for some subjects. In a study involving 107 subjects with PTSD, individuals were administered either two or three doses of MDMA (75–125 mg) during blinded or open-label therapy sessions. The subject's PTSD symptoms were evaluated 1 to 2 months after the last MDMA session and again after 12 months. The researchers reported that at the 12-month follow-up time, nearly all (97.6%) of the subjects said they had benefited from the treatment, and 53.2% reported large benefits that had lasted or even increased. A minority of subjects reported unfavorable results; 8.4% reported harms. However, in 86% of these cases (six of seven subjects), the harms were rated as a 3 or less on a 5-point scale. There were no reports of severe harm, and all the subjects who reported harm also reported one or more benefits. The most common harm reported was worsened mood (3.6%) [58]. The researchers noted that, "Overall findings from the present analyses support MDMA-assisted psychotherapy as an efficacious treatment for PTSD with symptom improvements that were sustained at 1 to 3.8 years post-treatment. These findings corroborate and expand preliminary results from the first phase 2 trial of this treatment" [58].

IBOGAINE

Largely derived from the Western African shrub *Tabernanthe iboga,* ibogaine has been explored as a possible treatment for opioid use disorder, although there are many caveats to be considered, including the fact that ibogaine is a Schedule I drug. Given the current climate surrounding opioid misuse and use disorder in the United States, possible treatment options are a major focus. According to the Centers for Disease Control and Prevention, more than 70% of drug overdoses in the United States in 2019 were related to opioid use [59]. Ibogaine apparently acts to eliminate craving for opioids and rapidly detoxifies individuals with opioid dependence, although much further study with larger populations is needed. Most people who seek treatment with ibogaine have opioid use disorder, but some have been dependent on stimulants such as cocaine.

The anti-addictive capabilities of ibogaine were first noted by Howard Lotsof in 1962 as a result of his own experience with the drug as well as reports from others. Lotsof, a man in recovery from heroin use disorder from New York City who unexpectedly found relief and remission with ibogaine, subsequently actively and tirelessly lobbied researchers to study the drug. He eventually succeeded, and multiple researchers using both animal and human studies have demonstrated ibogaine's apparent ability to induce recovery in some persons struggling with substance use disorders [60; 61].

Metabolism of ibogaine is purportedly mediated by the p450 cytochrome enzyme CY2D6. Because of genetic differences, an estimated 10% of persons of European heritage (predominantly White Americans in the United States) lack the necessary gene to synthesize this enzyme. Among this group, including the many individuals who do not realize they lack this gene, administration of ibogaine can result in plasma levels as much as twice as high as those in persons with the gene. As a precaution, a test dose of the drug may be given to subjects to assess the response. Another option is genotype screening of subjects who seek treatment with ibogaine, to ensure safety and to aid in treatment decisions [62].

Although it provides insufficient data from which to draw major conclusions, a study of the use of ibogaine in two adults with opioid use disorder is interesting. The experiences of one of the patients are described here, although it should be noted that both patients have remained abstinent for several years [62]. The first patient developed an opioid use disorder secondary to pain from chronic pancreatitis. His physician was concerned about potential misuse and weaned the patient off opioids; however, the patient began taking large quantities of oxycodone tablets he purchased illegally. As the substance

use disorder progressed, this patient was actively resistant to conventional treatment despite clear physical and psychosocial consequences. Eventually, he agreed to experimental treatment with ibogaine.

The patient was screened with an electrocardiogram prior to treatment and administered a test dose of ibogaine. During the first four days of treatment, he was administered oxycodone (legally obtained via prescription). The opioid doses were steadily titrated down and on day 4, all opioid medications stopped. During this same period, the patient was given increasing doses of ibogaine. On day 4, the patient was given a "flood dose" of both iboga and ibogaine (variations of the same drug). Between treatments, diazepam was given to support sleep and assuage anxiety. Treatment lasted for six days, and the patient remained at the clinic for a total of eight days. At three-year follow-up, the patient had remained abstinent from opioids, as indicated by negative drug screens. Interestingly, after the flood dose of ibogaine, the client also reported that his chronic pain issues ended, and they have not recurred [62]. The reasons for this finding are unknown.

In a study of 14 individuals with opioid use disorder, subjects were given staggered doses of 200-mg ibogaine capsules at two different clinics. Because ibogaine is a stimulant, most patients were given benzodiazepines or sleep aids so they could attain sufficient hours of sleep. The first dose administered was a test dose given when the patient was in a withdrawal state from opioids; then, a larger dose of up to 600 mg of ibogaine was given one to four hours later. This was followed by smaller dosages of 200 mg given at 20-minute intervals until ended by the provider. The subjects were interviewed pretreatment, immediately post-treatment, and 12 months later. The outcome was that 12 of the 14 subjects (85.7%) had either a marked reduction in opioid use or ended use of the drug altogether [61].

In a larger study of 191 adults wishing to detoxify from opioids or cocaine, a single dose of ibogaine was administered during a medically supervised period of detoxification. According to the researchers, the goals of the study were to safely detoxify the subjects from opioids or cocaine, to provide motivational counseling, and to refer the patients to aftercare and 12-step programs [63]. All subjects received a physical examination, and a medical history was taken. Laboratory tests were administered, as were electrocardiograms. The subjects were drug tested at the beginning of the program, and all tested positive for either opioids or cocaine. A licensed therapist worked with the subjects during and after ibogaine was administered. The average age of subjects was 36 years, and all were habitual users. The subjects were given one dose oral (gel capsule) ibogaine 8–12 mg/kg. In this study, the most common adverse effect was headache, reported by 7% of the subjects; orthostatic hypotension occurred in 5% of the subjects. About 2% of adverse events were considered to be moderately severe.

After the ibogaine was administered, its effects began about 30 to 45 minutes later. According to the researchers [63]:

> Sensory and perceptual changes included reports of visual images, changes in the quality and rate of thinking, and heightened sensitivity to sound. Most subjects reported a dream-like experience lasting between four and eight hours, after which there was an abrupt change in the sensory experience to a more quiet period of deep introspection.

Approximately 92% of subjects reported benefits from the experience. They also reported that both drug craving and depression symptoms improved with doses of 500–1,000 mg. One shortcoming of this study, however, was a lack of follow-up. It would be especially helpful to know if these individuals remained abstinent 6 to 12 months later. Unfortunately, this was not among the goals of the researchers [63].

Ibogaine is difficult to obtain in the United States, and travel to other countries to obtain treatment has been reported, which can be very costly. Assuming that ibogaine were to be equal in efficacy to clonidine or lofexidine for detoxification from opioids or acute discontinuation, it is still unclear what long-term effects or level of continued abstinence can be expected. Naltrexone (Vivitrol) following detoxification might be facilitated. But, data supporting the use of suboxone and methadone in reducing overdoses, deaths, and emergency department visits are clear, including both short- and long-term outcomes. It is important to compare ibogaine to buprenorphine or methadone treatment, just as psilocybin was compared to SSRI therapy [64].

KRATOM

Kratom is a drug derived from *Mitragyna speciosa*, an evergreen tree native to Southeast Asia, where it has been used for generations, largely by locals who chew on the leaves or brew it into a tea and reportedly use the drug for an energizing purpose (e.g., to facilitate longer work periods), much as Americans use caffeine. Kratom is used by consumers in the United States as a drug of abuse and, less commonly, to manage depression. As of 2022, the drug is not scheduled by the U.S. Drug Enforcement Administration (DEA), although the DEA did consider categorizing kratom constituents mitragynine and 7-hydroxymitragynine under Schedule I in 2016. This effort was met with considerable resistance and was abandoned. As such, the product remains available locally in smoke and "head" shops, although many purchase the drug over the Internet. Kratom is banned in six states, including Arkansas, Indiana, Tennessee, Vermont, Wisconsin, and most recently in Alabama [65].

Experts exploring the potential psychiatric uses of kratom have expressed optimism. According to McCurdy, kratom "seems to have mood lifting and elevating properties in addition to its ability to seem to move people off of hardcore opiates" [66]. Although the drug is traditionally used as a stimulant, it has a sedative or opioid-like effects in very high doses. It has been hypothesized that kratom might have a role in the treatment of opioid use disorder, although much more study is needed.

It is important to note that kratom products available in the United States are very different from those that are used by people in their native environments. For example, the kratom used in Southeast Asia is almost always derived from fresh leaves, while in the United States, the products are freeze-dried leaves, concentrated extracts, or liquid "energy shots." As a result of these differences, concentrations and adulteration are concerns. Some individuals in the West who consume kratom products have displayed blood serum levels of mitragynine (the key alkaloid in kratom) 100 to 1,000 times higher than in those found in consumers in Southeast Asia [67].

Another issue is one of purity. In an analysis of eight samples of the drug, researchers found that all the samples tested positive for varying levels of *Mitragyna,* ranging from 3.9–62.1 mg/g, which is a wide range that could significantly alter efficacy and toxicity [68]. In addition, six of the samples tested positive for fungi and bacteria. Most (seven) of the samples were positive for significant levels of toxic heavy metals, including nickel, lead, and chromium. The presence of lead was particularly troubling, as lead has many potentially toxic effects, particularly in terms of potential problematic neurologic effects in children and young adults as well as a variety of cognitive, developmental, immunologic, renal, and cardiovascular effects [68]. Although this study did not find evidence of *Salmonella* contamination, in 2018, a *Salmonella* outbreak originating from kratom products was reported to affect 199 people spanning 41 states [69]. It is clear that the purity of kratom purchased in the United States is highly questionable, largely because there are no federal constraints on its production by the FDA or other federal agencies. Healthcare professionals who know or suspect that their patients are using kratom may wish to warn them about these findings.

LSD

As discussed, LSD is a compound synthesized from ergot. It is usually administered as an oral solution. LSD takes effect within 20 to 40 minutes after ingestion, and its effects may last for up to 12 hours. Flashbacks may also occur with this drug, defined as a feeling of re-experiencing an event or emotion that occurred during the course of the LSD "trip." LSD is about 2,000 times more potent than mescaline [37].

Prior to the Controlled Substances Act passage in 1970, there were numerous research studies on LSD as a treatment for depression, substance use disorder, and other psychiatric diagnoses, although some of these studies were not scientifically rigorous by today's standards. Fewer studies on LSD are published today, but several merit some attention. For example, a 2022 study assessed the impact of LSD on stressed mice [70]. Anxious mice were administered low doses of LSD for seven days, during which their anxiety levels decreased. In addition, researchers found that the mice given LSD showed signs of increased production of new dendritic spines, a sign of brain plasticity. The researchers also found that the LSD increased the production of serotonin in the treated mice, in a somewhat similar manner to SSRI antidepressants [70].

In an earlier study of the effects of LSD on humans with life-threatening diseases, 8 of the 12 subjects were given 200 mcg of LSD and a control group was given 20 mcg, an insufficient dose to generate significant response. After the initial blinded study was unmasked, the control group subjects were also given 200 mcg of LSD. All subjects had a score of higher than 40 on the state or trait scale of the Spielberger State-Trait Anxiety Inventory before the study. In addition, half the subjects had diagnosed generalized anxiety disorder. A therapist was present for two sessions conducted two to three weeks apart. The experimental sessions lasted eight hours, and patients left only to use the restroom [71]. Subjects who received the 200-mcg dose of LSD displayed a decrease in anxiety as measured by multiple instruments, and this decrease persisted at the 12-month follow-up evaluation. Overall, the subjects experienced a 78% drop in anxiety scores and a 67% increase in quality of life scores after one year. They also reported better access to and control of their own emotions [72].

While this research is interesting and points to areas for future research, it remains to be seen if LSD (or a similar compound) will ever be in clinical use for anxiety and depression. In addition to overcoming stigma and issues with adverse effects, significant additional research on efficacy is necessary.

MESCALINE

What are signs of mescaline toxicity?

3,4,5-trimethoxyphenethylamine, also known as mescaline, is a psychedelic drug that is mainly found in *Lophophora williamsii*, or the peyote cactus. Its effects upon ingestion are similar to the effects found with LSD or psilocybin, including hallucinations and euphoria [37]. The drug is known to have been used for thousands of years for these and perceived spiritual or medical effects; archaeologists have found evidence of this drug in Texas dating back 5,700 years [73]. Today, it is a Schedule I drug, but it may be used legally in religious ceremonies of the Native American Church. Mescaline has been suggested as a potentially effective treatment for a variety of mental health conditions, including depression, OCD, anxiety, and substance use disorder; however, research has yet to be conducted to support these claims.

The average dose of mescaline ranges from 20–500 mg, and the duration of action is about 10 to 12 hours. Individuals suffering from mescaline toxicity (typically seen with doses of 20 mg/kg or greater) may experience tachycardia, hypertension, seizures, hyperthermia, respiratory depression, and rarely death [73]. Concomitant use of mescaline with stimulant drugs (e.g., nicotine, cocaine, ephedrine, amphetamines) may increase the risk of adverse central nervous system effects.

In a survey of 452 individuals who reported using mescaline, researchers found that the drug was usually used once per year or less frequently, and only 9% of users reported a craving for mescaline. About 50% of users reported established psychiatric diagnoses, including anxiety and depression, and of this group, more than 65% reported that these problems improved after taking mescaline [74]. Clinical studies are necessary to confirm or refute these findings.

In another analysis of these data, nearly 50% of respondents reported their experience with mescaline was either the most meaningful experience of their lives or in the top five most meaningful experiences. Respondents who said they had experienced improvement in psychiatric problems were significantly more likely to also report experiencing mystical/spiritual experiences and psychological insight [75].

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. The origins of nitrous oxide are attributed to Joseph Priestley's discovery in 1772, who referred to it as "dephlogisticated nitrous air" [76]. Anesthetic use of nitrous oxide was discovered by a dentist in 1844, and it was used for this purpose almost solely until the 1980s. The first research into the use of nitrous oxide for neuropsychiatric purposes was published between 1920 and 1950, and in the early 1980s, low-dose titration of nitrous oxide was introduced into medical practice as a possible adjunct to the treatment of psychiatric disorders, including substance use disorders [77]. Before then, it was limited to use as an anesthetic or for analgesia during childbirth. In 1994, the term psychotropic analgesic nitrous oxide was introduced in order to better distinguish anesthetic and nonanesthetic preparations [77].

The anxiolytic action of nitrous oxide is believed to be due to binding at select gamma-aminobutyric acid (GABA) receptors, an action similar to the benzodiazepines [78]. The mild analgesic effect appears to be linked to the endogenous opioid receptor system, as experimental studies have shown that the introduction of opioid receptor antagonists to the brain decreases the analgesic efficacy of nitrous oxide [79].

The route of administration is inhalation via a mask secured to the patient's nose. In the dental setting, the concentration of nitrous oxide is 25% to 50% (usually 30% to 40%) nitrous oxide with oxygen. When utilized in obstetrics, a fixed 50% concentration with oxygen is used [77]. Onset of action can occur in as quickly as 30 seconds, with the peak effects seen in five minutes or less. Unlike the benzodiazepine medications, 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 [78]. Repeated doses could be problematic, as extended use of nitrous oxide has been linked to vitamin B12 deficiency [76]. As such, serum vitamin B12 level may need to be measured before and after treatment.

Nitrous oxide has been demonstrated to improve the condition of individuals with treatment-resistant depression. A study of 20 subjects with treatment-resistant depression were randomly placed in either a nitrous oxide treatment group (10 subjects) or placebo group (10 subjects). The nitrous oxide group inhaled 50% nitrous oxide/50% oxygen, and the placebo group received 50% nitrogen/50% oxygen. There were two sessions one week apart. At the end of the study, four patients (40%) had a decrease in symptoms of depression and three patients (30%) experienced full remission. In contrast, one patient improved after receiving the placebo (10%) and none of the placebo patients remitted from their depression. The improvements in the nitrous oxide group were rapid, occurring in some cases within as little as two hours of receiving the drug [80]. Adverse events were mild and included nausea and vomiting, headache, and dizziness/lightheadedness. At the time of the second session, some patients in the treatment group experienced a carryover effect from the first week's treatment, as evidenced by sustained improvements in their scores on the Hamilton Depression Rating Scale (HDRS-21).

A separate study was undertaken to determine whether a single solution of 25% nitrous oxide would be as beneficial as a 50% solution. This study included 24 subjects with treatment-resistant depression who were randomly placed in one of three groups. Each group received either 50% nitrous oxide therapy, 25% nitrous oxide therapy, or placebo each month; each patient had the opportunity to receive all three treatments. At the end of the study, 55% of the subjects reported improvement in at least half of their symptoms, while 40% reported full remission [81]. Of interest, the 25% nitrous oxide solution had about the same level of efficacy in reducing depression as the 50% solution; however, there were significantly lower levels of adverse events in the 25% group. For example, 21% of those who had received 50% nitrous oxide concentration reported nausea; this decreased to 5% in the group that received 25% concentration. Further, the incidences of headache and dizziness were 17% and 13%, respectively, in the 50% concentration group, while the rates were 10% and 0% in the 25% group [82].

The study made it clear that with nitrous oxide, a 25% solution administered over one hour could improve treatment-resistant depression. Most of the study patients had failed an average of 4.5 antidepressants before the study, so the results were significant for a group in need of additional treatment options.

AYAHUASCA/DIMETHYLTRYPTAMINE (DMT)

What is the most common adverse effect of ayahuasca?

Ayahuasca is a brew derived from the leaves of *Psychotria viridis*, a shrub found in Amazonian South America, and which contains DMT, a hallucinogenic alkaloid. The brew is also made with the *Banisteriopsis caapi* vine, the bark of which contains ingredients that act as MAO inhibitors.

In a Brazilian study involving 29 subjects with treatment-resistant depression, patients were randomized to receive a dose of either ayahuasca or placebo. Subjects were evaluated on the MADRS at the following points: baseline, day 1, day 2, and day 7 after dosing. They found MADRS scores were significantly lower in the ayahuasca group at all points and all individuals in this group experienced improvements. In contrast, 27% of patients in the placebo group developed worse depression symptoms. However, ayahuasca sickens many people, and most of the subjects who were given this substance felt nauseous and 57% vomited [83].

In another small Brazilian study, six subjects with recurrent major depressive disorder (without psychotic symptoms) were assessed for response to ayahuasca therapy. All individuals were inpatients at a psychiatric unit and were not taking any psychiatric or recreational drugs. The ayahuasca used by the volunteers was plant-based and refrigerated before the study, and each person drank 120–200 mg [84]. All subjects experienced decreases in depression symptoms on days 1 and day 7 of treatment. There were significant decreases in the Brief Psychiatric Rating Scale (BPRS), indicating improvements in both depression and anxiety. There were also statistically significant decreases in scores on the HAM-D and the MADRS. For example, on day 1, there was a 62% decrease on the HAM-D, and a 72% decrease by day 7. On day 14, however, depression symptoms increased. Similar changes were seen with the MADRS scores [84]. About half the volunteers did vomit; however, vomiting did not appear to impact the efficacy of the drug [84]. If ayahuasca is to be considered as a therapeutic option, a way to counteract the emetic effects and make the drug more tolerable to patients is necessary. To date, experts have hypothesized that antiemetic drugs might interfere with the action of ayahuasca.

Another problem with the scientific study of ayahuasca is that the effects of the drug depend on the concoction and there are no standardized dosages. If the drug could be provided in a synthesized form, it would become easier to evaluate and study in patients with depression and other disorders. In Barker's report on DMT, he states [85]:

> While ayahuasca obviously holds promise in many social, cultural, and therapeutic paradigms, including treatment of addiction, anxiety, and depression in psychiatry and many other possible applications, it is, nonetheless, a complex mixture of perhaps thousands of compounds.

DMT has been identified in additional substances. The Sonoran Desert toad (*Bufo alvarius*), native to Texas, California, and Mexico, excretes a venom when threatened that contains a naturally occurring form of DMT. This venom, which can be made into crystals and smoked, is popular for inducing psychedelic trips among recreational users. However, this venom is unsafe, and some have died after smoking it. Further, harvesting this venom has reduced the population of the toad in some areas. Overall, experts recommend that people not attempt to capture the toads or harvest the venom [86].

DIAGNOSES AND PSYCHEDELIC MEDICINE

This section will outline the possible role of psychedelics in the management of specific psychiatric diagnoses, including diagnoses not previously discussed. It is important to remember that most of these uses are investigational.

TREATMENT-RESISTANT DEPRESSION AND SUICIDE

Depression and suicidal depression are major problems in the United States. As noted, at least 30% of persons with depression do not respond to psychotherapy and/or medication. Psilocybin has proven effective at providing breakthroughs with treatment-resistant depression as well as in treating suicidal depression [41; 42]. Nasal spray esketamine (Spravato) is FDA-approved as an adjunct treatment in addition to a conventional antidepressant for treatment-resistant depression and/or major depressive disorder with suicidal ideation or behavior [87]. The nasal spray formulation of esketamine is administered in two sprays (28 mg) per device. The recommended dosage for adults with treatment-resistant depression is 56 mg on day 1, then 56 – 84 mg twice per week for four weeks, reducing to once per week for the next four weeks, and then once weekly or once every two weeks thereafter. This drug is only administered under medical supervision, and patients should remain under observation for at least two hours following administration.

There are concerns regarding misuse, excessive sedation, and diversion, and a Risk Evaluation and Mitigation Strategy (REMS) has been established. The full document is available online at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Spravato_2022_01_03_REMS_Document.pdf.

PTSD

MDMA and ketamine are well on their way to being proven safe and effective in the treatment of PTSD, and further studies on other psychedelics are likely to provide even more breakthrough information. According to the National Center for PTSD, an estimated 12 million adults in the United States have PTSD in a given year; 8% of women and 4% of men develop PTSD in their lifetime [88]. However, PTSD is very difficult to treat with medications and psychotherapy.

The usual dosage of ketamine for the treatment of persistent PTSD is 0.5 mg/kg given via a 40-minute IV infusion. The regimen typically consists of multiple sessions per week for two to four weeks [89].

In the research setting, MDMA for PTSD is typically given during or immediately preceding a psychotherapy session. The usual dose is 75–125 mg in a single dose [90]. As a Schedule I drug, MDMA is only used in clinical trials and research settings.

SUBSTANCE USE DISORDERS

To date, psychedelic drugs such as ibogaine have not been proven effective in treating opioid use disorder and may not compare well to existing and approved treatments. However, limited studies have shown decreased substance use after administration of psilocybin and ketamine. A 2014 open-label pilot study married a 15-week smoking cessation program with several doses of psilocybin. This study included 15 smokers who were considered psychiatrically healthy adults who had smoked an average of 19 cigarettes per day for an average of 31 years [91]. Psilocybin was administered during the 5th, 7th, and 13th week of the study. During the first four weekly meetings, cognitive-behavioral therapy was provided as was preparation for receiving psilocybin. A target quit date was set to occur with the first dosage of psilocybin during week five, when the subjects were given 20 mg/70 kg of psilocybin. Weekly meetings continued, and then on the seventh week, a higher dose of 30 mg/70 kg was given. During the 13th week, the higher dose of psilocybin was made optional for the subjects. Before the psilocybin was administered, subjects noted their motivational statement for smoking cessation. The subjects also participated in a guided imagery exercise at the end of the first psilocybin session [91]. At six-month follow-up, 80% of the former smokers (12 of 15) were abstinent from tobacco, as verified by breath and urine tests. This was a much higher abstinence rate than seen with traditional smoking cessation programs [91].

The researchers returned to their subjects later, reporting on smoking abstinence at 12 months and over the long term, with an average of 30 months after the study. They found that at the 12-month point, 67% were abstinent from smoking. At the long-term point, 60% were still smoking-abstinent, an excellent success rate [92].

In an older study of single versus repeated sessions of ketamine-assisted psychotherapy in 59 subjects who had detoxified from heroin, subjects were divided into two groups. The subjects in the first group received two addiction counseling sessions with ketamine, followed by two ketamine-assisted psychotherapy sessions, with sessions held at monthly intervals. The subjects in the second group received two addiction counseling sessions without ketamine and one ketamine therapy session. At the one-year follow-up point, 50% of subjects in the first group were still abstinent from heroin, versus 22.2% of subjects in the second group. The researchers concluded that three sessions in the ketamine-assisted psychotherapy program was more effective in promoting abstinence from heroin than one session followed by counseling [93]. There are also emerging data showing positive effects in alcohol use disorders and other substance use disorders.

It is important to keep in mind comparable efficacy. For opioid use disorder, it is vital to know both short- and long-term safety and efficacy comparisons to the standard of care (medication-assisted treatment plus therapy). Also consider that psychedelics will not be proved safe and effective by a professional consensus but rather by the FDA. It may be that psychoactive substances are legalized much in the same fashion cannabis has, but whether they are approved for clinical use will depend on the outcomes of Phase 2 and 3 FDA-qualifying clinical trials and safety and comparable efficacy trials. As of 2022, these trials are ongoing.

ANXIETY AND DEPRESSION RELATED TO LIFE-THREATENING DIAGNOSES

As discussed, research has demonstrated that psilocybin can be effective in improving mood and quality of life of patients with terminal cancer diagnoses. This aspect of cancer care has been largely overlooked and undertreated. Agrawal notes that, "Oncologists are well-equipped to fight the physical threats of cancer with powerful, yet sometimes imperfect tools including chemotherapy, radiation, and surgery, but they often feel helpless when it comes to treating the intense psychological agony many patients experience" [94]. A seminal study published in 2016 explored the use of a modest dose of psilocybin given to patients with terminal cancer under the supervision of trained therapists. The findings demonstrated that more than 80% of 51 patients who had received life-threatening cancer diagnoses and who subsequently developed depression or anxiety experienced significant and sustained improvements in mood and quality of life six months after taking psilocybin. In addition to feeling calmer and happier, the participants reported forging a closer connection with their friends and family [95]. This study demonstrated the careful and controlled use of psilocybin might be a safe and effective treatment for existential anxiety and despair that often accompany advanced-stage cancers. In addition, in limited studies, LSD has been found to significantly decrease anxiety levels in patients with life-threatening diseases.

Oncology and palliative care specialties have been associated with relatively high burnout rates, at least in part from seeing the psychological distress of patients with potentially terminal diagnoses. In this setting, any therapy that can improve patients' experiences and mood would be beneficial, and initial results of research incorporating psilocybin, LSD, and other psychedelics has been positive [94]. Agrawal further states [94]:

> I have never witnessed the sort of dramatic response to any medical intervention as I have with some patients through psychedelic-assisted therapy. It is not a magic bullet or cure for a cancer patient's suffering—and it won't change their prognosis or life expectancy. But it could be a spark that begins their healing journey, helping them come to terms with their most difficult fears.

The use of psychedelic medications in end-of-life care is logical and should be tested compared to the standard treatment (counseling) in randomized, blind clinical trials and other investigations to facilitate FDA approval.

OBSESSIVE-COMPULSIVE DISORDER

OCD can be an extremely debilitating disorder that is often difficult to treat. In a 2006 study of nine subjects with treatment-resistant OCD who were treated with psilocybin, the subjects experienced a significant decrease (range 23% to 100%) in OCD symptoms. One of the subjects experienced an issue with temporary hypertension. These are positive findings; however, it is obviously a very small study and additional research would be needed to replicate findings in a larger and more diverse group [96].

Other researchers have discussed the potential for the use of ketamine and esketamine in treating OCD [97]. In a 2013 randomized, double-blind, placebo-controlled, crossover study of drug-free adults with OCD, subjects were given two 40-minute intravenous infusions, one of saline and one of ketamine (0.5 mg/kg), spaced at least one week apart [98]. Individuals who received ketamine reported significant improvement in obsessions (measured by OCD visual analog scale) during the infusion compared with those given placebo. One-week post-infusion, 50% of those who had received ketamine met the criteria for treatment response (defined as a 35% or greater reduction in Yale-Brown Obsessive-Compulsive Scale scores); no subjects receiving placebo displayed treatment response after one week. The authors of this study concluded that "rapid anti-OCD effects from a single intravenous dose of ketamine can persist for at least one week in some patients with constant intrusive thoughts" [98]. However, other studies have found no effect on OCD symptoms [99]. Solid evidence is lacking and requires greater and more rigorous research.

SOCIAL ANXIETY IN PATIENTS WITH AUTISM

Which psychedelic has been studied for the treatment of social anxiety in persons with autism?

In a study of 12 adults with autism and issues with severe social anxiety, subjects were randomized to receive either MDMA (75 mg or 125 mg) or placebo during the course of two 8-hour psychotherapy sessions. The MDMA was administered after a guided progressive muscle relaxation exercise. The experimental sessions were held one month apart and separated by three nondrug sessions of psychotherapy. The patients were provided with as few sensory interruptions as possible, such as soft lights, noise abatement, and fidget objects to help them with self-regulation through repeated actions (i.e., "stimming") [100]. On the Leibowitz Social Anxiety Scale, the MDMA group experienced a significantly greater improvement in social anxiety scores compared with the placebo group. Improvements persisted at six-month follow-up. The researchers said of the follow-up, "social anxiety remained the same or continued to improve slightly for most participants in the MDMA group after completing the active treatment phase" [100].

Social anxiety disorder is relatively common among the general population; about 12% suffer from this disorder at some point in their lives [101]. If it is determined to be an effective treatment, MDMA-assisted psychotherapy could be an option for these patients who have not responded to traditional psychotherapy or pharmacotherapy.

ANOREXIA NERVOSA

Anorexia nervosa is a severe eating disorder characterized by restriction of energy intake relative to an individual's requirements, typically resulting in low body weight and malnutrition. It is notoriously difficult to treat and has a high mortality rate. Experts have continued to search for more effective treatment options for this population.

In one study, the authors treated 15 patients (23 to 42 years of age) with treatment-resistant anorexia nervosa with infusions of 20 mg/hour of ketamine over 10 hours. The subjects were also given 20 mg twice per day of nalmefene. The subjects showed a marked decreased in scores on compulsion. Before the ketamine was administered, the average scores were 44.0; after treatment, mean compulsion scores dropped to 27.0. Nine of the subjects (60%) showed remission after two to nine ketamine infusions over the course of five days to three weeks [102]. The authors reported the following details on three specific patients [102]:

> Patient 4 increased her weight after three treatments but agreed to more in the hope that her compulsion score would come down further. After a year in follow-up with a normal weight, she then started work and remained in a stable state while followed-up for nine months.

> Patient 5 was a married woman and reached a normal weight after five treatments. As an outpatient, her periods returned and she had a successful pregnancy. Patient 6 had a long history of alternating anorexia and bulimia. After four treatments and despite only a small fall in compulsion score, she became able to control her eating and her weight. She held a responsible job with no relapse during two years of follow-up.

In a 2020 study with only one subject, the researchers treated a patient, 29 years of age, who had developed anorexia nervosa at 14.5 years of age and had been unable to attain remission. The researchers prescribed a ketogenic diet along with intravenous ketamine infusions. (A ketogenic diet was chosen because it had proven in the past to prevent starvation, a real risk with anorexia.) The patient sustained complete recovery and continued her ketogenic diet while maintaining a normal weight [103]. After three months, the woman remained on the ketogenic diet and reported feeling significantly better but still suffered from anorexic compulsions. At that time, she was sent for ketamine infusions. The patient reported that within one hour of her first infusion the "anorexic voice" inside her was decreasing and she felt more like herself. The patient had three more infusions over the next 14 days. After the fourth infusion, the patient stated [103]:

> I know this sounds ridiculous, but I am no longer anorexic. I had so many rules I didn't even know them. But they are gone. I can exercise because it feels good. It isn't that I have to. I can stop when I want to.

Because this study had two potentially essential factors (ketamine and the ketogenic diet), it is unclear if either or both are responsible for the single patient's improvements. As is the case for many of these novel treatments, additional research is warranted.

CLUSTER HEADACHES

Cluster headaches, which affect less than 1% of adults, are considered to be the most painful of all headaches and can last for a week or longer, potentially becoming a chronic health issue [104]. Traditional treatment approaches include triptan medications and oxygen therapy. Understandably, most sufferers seek quick relief and would prefer to never experience another attack.

In one report, the authors interviewed 53 people with cluster headaches who had self-medicated with psilocybin or LSD. (This is not recommended or considered safe.) Of 26 patients who used psilocybin, 22 said the drug successfully aborted their headache attacks. Of five people who said they used LSD to treat their headaches, four reported experiencing remission [105]. Based on these findings, the authors recommend further study of psychedelics as a possible treatment for cluster headaches. It is important to remember that self-reports are no basis for concluding that psilocybin or LSD is effective at improving a cluster headache condition. There is a current clinical trial underway examining the role of LSD as a possible treatment for cluster headaches [106].

In another study of 77 patients with treatment-resistant migraines or new daily headaches, all of whom had failed aggressive outpatient and inpatient treatment, patients were infused with ketamine. According to the researchers, the mean headache pain rating at the start of the study was 7.1; this fell to 3.8 upon discharge. Most of the patients responded well to the ketamine. Researchers concluded [107]:

> Pending higher level evidence and given that ketamine is generally well-tolerated, ketamine may be considered a reasonable acute treatment for well-selected headache patients for whom standard therapies are either ineffective or medically contraindicated.

OTHER DISORDERS

Some psychiatric disorders, particularly those with psychotic features such as schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, and delusional disorder, should certainly not be treated with psychedelic drugs. It is unclear if other psychiatric conditions would be amenable to psychedelic treatment. This can only be determined by clinical trials that administer these drugs under scientific rigor and with a sufficiently high number of patients. Many of the studies published to date have included very small numbers of patients, though this is largely because of necessity. It may have been that few individuals with the disorder could be recruited into a trial consisting of experimental treatment with a psychedelic drug. As the knowledge base grows based on clinical trials, it is hoped that it will become increasingly more feasible to test psychedelics on patients with a multitude of psychiatric disorders, particularly for those individuals whose conditions have been challenging to treat.

INTERVENTIONAL PSYCHIATRY: BRAIN STIMULATION THERAPIES

Electroconvulsive therapy has been in use for nearly a century and continues to be used in psychiatric treatment today. Newer forms of brain stimulation are increasing popular options for patients—or likely will be soon at major medical centers, including rTMS, VNS, and DBS. New brain mapping techniques may help eliminate the need for more invasive procedures. Interventional psychiatry represents an opportunity to help patients who otherwise have found no relief from pharmacotherapy and standard treatments [108].

For health professionals interested in the latest techniques on neuromodulation to aid patients with refractory psychiatric disorders, interventional psychiatry may be the answer. In order for physicians to effectively enter this field, experts recommend an additional year of training with an emphasis on interventional psychiatry.

ELECTROCONVULSIVE THERAPY

What is the goal of electroconvulsive therapy (ECT)?

ECT has been used to treat depression, bipolar disorder, schizophrenia, and other psychiatric diagnoses for many years, starting in the first half of the 20th century. The goal of ECT is to induce a seizure through applied electric shocks. The procedure was initially introduced in the late 1930s in Italy, and in the 1940s through the 1960s, ECT became popular in the United States as a mainstream treatment [109]. However, early treatments did not provide anesthesia and sometimes led to physical and psychological trauma [110]. Physicians later learned that significantly milder shocks could achieve the same goals.

Today, the procedure is used rarely for treatment-resistant depression and major depression with suicidal ideation or behaviors, as well as for schizophrenia and schizoaffective disorder. A team of professionals are involved, including a psychiatrist, a neurologist, an anesthesiologist, and a nurse [110]. Some believe that ECT should be used before psychedelics or newer brain intervention therapies are attempted, although agreement on this subject is not universal. It should also be noted that there is some residual fear/concern of ECT itself that persists among many patients (and some healthcare professionals), largely because ECT was historically traumatic. However, ECT has proven highly effective at treating both major depressive disorder and suicidal depression. About 100,000 patients receive ECT each year, and most of them are residents in psychiatric hospitals or psychiatric units of hospitals [111].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Care Excellence recommends clinicians consider electroconvulsive therapy (ECT) for the treatment of severe depression if the person chooses ECT in preference to other treatments based on their past experience of ECT and what has previously worked for them OR a rapid response is needed (e.g., if the depression is life-threatening) OR other treatments have been unsuccessful.

(https://www.nice.org.uk/guidance/ng222. Last accessed July 8, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

The modern use of ECT consists of [112]:

> induction of brief general anesthesia (typically lasting less than 10 minutes), pharmacologic muscle relaxation, and continuous monitoring of oxygen saturation, blood pressure, and heart rate, and rhythm. An electrical charge is delivered to the brain through scalp electrodes, which results in a generalized seizure typically lasting for 20 to 60 seconds. Most patients receive between 6 and 12 treatments spaced over a period of 2 to 4 weeks as an initial course of treatment.

Patients who receive ECT may have mild-to-moderate cognitive side effects that generally resolve within days or weeks after the course of treatment has ended [112]. Improvement in depressive symptoms is apparent as soon as the third treatment, and remission rates may be as high as 60% among patients with treatment-resistant depression [113].

In a study of 31 patients with major depressive disorder who received ECT treatment, neurocognitive function was assessed with multiple tests, such as the MATRICS Consensus Cognitive Battery, the Everyday Memory Questionnaire, and the MADRS. These instruments were used before ECT, six weeks after ECT, and six months after the procedure. There was a significant decrease in depression scores six weeks and six months after ECT. Patients also exhibited significantly improved neurocognitive abilities six weeks subsequent to the ECT; these improvements were maintained at six months. The researchers concluded that improvements in depression and stability of subjectively reported memory function indicate that the antidepressant effects of ECT do not occur at the expense of cognitive function [114].

A Swedish analysis of 254,906 sessions of ECT conducted with 16,681 individuals between 2012 and 2019 found that fewer than 1% of individuals suffered broken teeth incurred as a result of their treatment. More specifically, the rate was 0.3% per individual, and there were no differences found between patients by age, gender, or diagnosis, although the dental fracture group had a greater number of treatments. Despite the low rate, bite guards and muscle relaxants are recommended to be used as a safety precaution during treatment with ECT [115].

In a 2021 survey of 192 ECT physician practitioners in the United States, 30% of the survey respondents had graduated from one of 12 residency programs in the United States. Several barriers to ECT programs were identified, stigma against ECT on the part of patients and problems with patient transportation, because patients cannot drive themselves home after treatment [116]. With regard to starting a new ECT program, barriers included lack of well-trained ECT practitioners, lack of institutional support or interest in leading the initiative, and insufficient physical space at the facility. The highest concentration of ECT providers were based in New England,

and the lowest concentration was in the southern central region of the United States. Overall, the researchers were able to identify a variety of institution-related barriers (e.g., finances, bureaucracy, stigma, lack of understanding) that prevent enthusiastic adoption of this intervention. As a result, although ECT potentially could provide relief to many patients with treatment-resistant depression and other disorders, it may not be an option for many patients who live remotely from centers that offer this service.

In a 2018 study, a MarketScan database of more than 47 million patients was analyzed to determine the incidence of ECT. Of about 1 million patients with a mood disorder, 2,471 (0.25%) had received ECT. Individuals who had received ECT were five times more likely to have additional comorbid psychiatric disorders and twice as likely to have comorbid substance use disorder [117]. Whether ECT should be used more frequently is beyond the scope of this course, but it is important to understand that is can be an effective treatment even though it remains rarely used.

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS, a noninvasive form of neural modulation, was initially developed in the 1980s. Later, it was discovered that repeated sessions of TMS (rTMS) were more effective than a single treatment. In 2008, the FDA approved rTMS to treat major depressive disorder; in 2018, it was approved to treat OCD [118]. Trials are also investigating the efficacy of rTMS in the treatment of substance use disorders with alcohol, opioids, cannabis, tobacco, methamphetamine, and cocaine [119]. The procedure is also used to treat patients with neurologic disorders, including Parkinson disease, multiple sclerosis, and stroke [120].

An increasingly popular procedure in the United States and other Western countries, rTMS is available at major medical centers throughout the country. This procedure uses large magnets to stimulate the neurons in the prefrontal cortex of the brain. An electromagnetic coil is placed on the patient's forehead at the site of the left prefrontal cortex, an area of the brain that often displays reduced activity in persons with severe and refractory depression. Nonpainful electromagnetic pulses pass through the skin and to the brain. There is no anesthesia needed or given with this procedure, and the only potential adverse effects are headache and minor discomfort in the scalp.

In a U.S. study involving 247 adults with severe treatment-resistant depression, the efficacy of rTMS in improving psychiatric symptoms was evaluated. The average age of the subjects was 43 years, and the average Patient Health Questionnaire-9 score was 21.7. The subjects received single 37-minute sessions over six weeks, up to a maximum of 30 total sessions [121]. Following rTMS therapy, there was a remission rate of 72% after three weeks, with no differences in response by sex of the subject, but age was a factor, with older individuals taking a longer time to achieve remission of their depression. In addition, remission correlated with past suicide attempts, previous psychiatric hospitalizations, and substance use disorder, illustrating that the procedure was highly effective for individuals with severe and/or comorbid disease. In this study, there was a higher efficacy with the MagVenture device compared with the NeuroStar device.

A Dutch study randomized 14 patients with alcohol use disorder to 10 days of rTMS therapy and 16 patients to sham rTMS. The patients were subsequently evaluated for alcohol craving and alcohol use. For a period of time, subjects in the rTMS treatment group reported lower levels of alcohol craving and use than those in the control group. Differences in alcohol craving in the study group were most prevalent 3 months after treatment; at the 12-month point, there were no differences between the two groups, indicating the beneficial effects of rTMS may fade over time [122].

Because rTMS is a safe and effective FDA-approved treatment for depression, some experts have recommended turning the treatment algorithm for depression upside down, putting TMS in a first-choice position. Rather than requiring patients to undergo months of potentially ineffective antidepressant trials, starting with TMS (with an artificial intelligence component to ensure the right dose and optimal targeting) may be a better option [123]. Additional studies are underway to examine TMS and expand evidence-based access to this treatment [123].

Another form of TMS, Stanford accelerated intelligent neuromodulation therapy (also known as Stanford neuromodulation therapy or SAINT), has been associated with an extremely high success rate in patients with treatment-resistant depression. In a 2022 study, nearly 80% of 29 subjects who had been depressed for a mean period of nine years experienced remission in just four weeks. This is a much quicker response time than traditional antidepressant therapy. The difference between SAINT and other TMS procedures lay with a greater number of treatments for a shorter time frame, such as 10-minute sessions 10 times per day. These treatments are also more targeted to the patient's brain circuitry [124].

VAGUS NERVE STIMULATION

VNS is an invasive form of neuromodulation consisting of implantation of a device that sends electrical pulses to the vagus nerve of the brain. The vagus nerve (also referred to as cranial nerve X) is very long and extends from the brain into the neck, chest, and abdomen. This nerve has many effects and impacts such diverse functions as mood, digestion, blood pressure, heart rate, immune function, saliva production, and taste [125].

The first VNS event occurred in the 1880s in New York, when James Corning applied an electrical current to a carotid compression fork, believing this approach would prevent or end seizures [126]. The procedure has evolved drastically to become the sophisticated procedure used today.

In 2005, the FDA approved VNS for the management of treatment-resistant depression [127]. Since then, a transcutaneous form of VNS has been developed, eliminating the need for surgery. However, this approach was not approved by the FDA as of 2022.

Some researchers have noted that cognitive dysfunction may accompany depression and be a factor in the associated reduced work productivity. A Canadian study analyzed the cognitive performance of individuals with treatment-resistant depression subsequent to their treatment with VNS. In 14 subjects, both the learning capabilities and memory of the subjects improved significantly after one month of receiving VNS. These cognitive improvements persisted for years subsequent to treatment with VNS. After VNS, 29% of the subjects experienced remission from treatment-resistant depression after 1 month, 50% after 3 months, 57% at 12 months, and 64% at 24 months. As such, at the end of the study, nearly two-thirds of patients had recovered with VNS therapy [128]. The researchers stated [128]:

> Improvements were observed in measures of psychomotor speed, verbal fluency, attention, and executive functioning, as well as verbal and visual memory. We observed clear differences in improvement rate between cognitive measure. Memory measures, such as recall of a complex figure, as well as learning and recall of a word list, show more than 25% improvement after two months of treatment.

DEEP BRAIN STIMULATION THERAPIES

An invasive form of therapy that is used infrequently, DBS has proven effective at treating severe depression and OCD. DBS is also approved to treat some patients with severe, refractory neurologic disorders, such as epilepsy and Parkinson disease. DBS is also under investigation for the treatment of schizophrenia, Alzheimer disease, substance use disorder, and other challenging psychiatric disorders [129].

The first documented use of DBS occurred in 1948, when neurosurgeon J. Lawrence Pool implanted an electrode into the brain of a women with anorexia and depression. Results were initially positive, until the wire broke several weeks later [130]. Today, DBS involves the permanent implantation of electrodes that send regular and continuous electrical impulses to stimulate a specific part of the brain. Some describe DBS as a sort of brain pacemaker to correct imbalances, comparable to a heart pacemaker that corrects cardiac abnormalities. It should be noted that DBS is an invasive and expensive procedure that is only available to very few individuals, and it is not approved for the treatment of depression by the FDA as of 2022.

The electrodes used in DBS are made of platinum-iridium wires and nickel alloy connectors, which are enclosed in a polyurethane sheath [129]. Some patients may worry about the potential for hacking into a DBS system in today's connected world and the possibility of control over individuals, referred to as "brainjacking." This does not appear to be a problem at this time of very limited use of DBS, but it is a subject worthy of consideration in the future.

In a nationwide database of 116,890 hospitalized patients in the United States with major depressive disorder, patients receiving DBS represented 0.03% [131]. The average age of participants was 49.1 years; all were White, and 88% were female. Patients stayed in the hospital for 1 to 1.6 days. The highest rate of DBS use occurred in the southern United States, followed by the northeast and west. Patients receiving DBS either had private insurance or they were self-pay patients [131].

In a study of five patients with severe OCD who received DBS over the period 2015–2019, not only did the patients experience improvement in their OCD symptoms after DBS, but they also experienced a 53% improvement in their levels of depression (on the MADRS scale) and a 34.9% improvement on the Hamilton Anxiety Rating scales. In addition, patients also improved on the Quality of Life Enjoyment and Satisfaction Questionnaire [132]. The researchers reported anecdotal evidence of improvement as well, such as this report from one of the five patients [132]:

> Despite persistent low body mass index [BMI] of 14, she has remained out of the hospital for 29 months, the longest time period since onset of OCD and anorexia. She is working part-time as a research assistant, is active in her church, and though she wishes for further reduction in symptoms, she notes her quality of life and mood is better than prior to DBS. In addition, she no longer engages in self-injurious behaviors and no longer experiences suicidal ideation.

In another study, DBS was used to treat seven patients with treatment-resistant depression [133]. Researchers specifically targeted the bilateral habenula, which is the seat of the anti-reward system [133]. After one month, depression and anxiety symptoms had decreased by 49%, and the patients reported a dramatic improvement in their quality of life.

In a one-person study of an individual treated with DBS for treatment-resistant depression, the patient experienced continuous improvement until depressive symptoms remitted by the 22nd week. At 37 weeks, the subject was randomized to continuous treatment or discontinuation. When treatment was stopped, the patient reported increasingly worse depression and anxiety until he met rescue criteria, resulting in the resumption of treatment. The depression symptoms rapidly abated when treatment restarted [134].

CAUTIONS

Although the news about both psychedelics and brain stimulation techniques is generally positive, caution is important, particularly in the case of psychedelic drugs. Patients should be actively discouraged from trying psychedelic drugs on their own, because these drugs can trigger an underlying psychosis in individuals who would otherwise likely have remained healthy, particularly because dosage and purity of the illicit drug is unpredictable. In addition, FDA-approval processes, regulated pharmaceutical drugs rather than street drugs, and comparable efficacy can help identify the safest and most effective medication or interventional treatment for a particular patient at a particular time. In essence, buying MDMA and taking it is not the same as being administered MDMA in a PTSD clinical trial at a research institution. Today, adulteration of street drugs is of great concern, particularly with potentially lethal doses of fentanyl [135].

Patients have no idea what dosage is in a street drug and could take a suboptimal dose (to no effect) or take an excessively high dose of the drug, which could cause inadvertent harm. Importantly, patients under the influence of such drugs require supervision, lest they take actions that might be potentially dangerous to themselves or others.

For patients considered for psychedelic or interventional psychiatric options who are not proficient in English, it is important that information regarding the risks associated with the use of psychedelics and/or interventional procedures and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

CONCLUSION

It is apparent that psychedelic medicine is now in a renaissance period, and this time could not have come too soon. Many people in the United States and around the world suffer from severe psychiatric disorders, including depression, PTSD, substance use disorders, anxiety disorders, OCD, anorexia nervosa, and multiple other psychiatric disorders that are not readily responsive to treatment with pharmacotherapy and/or psychotherapy [136]. In the aftermath of the COVID-19 pandemic, depressive disorders are more prevalent, and people are urgently and actively seeking effective treatments. Exploration of novel interventional and psychedelic therapies may be a path to recovery for patients with mental health disorders who have not improved on traditional approaches [137].

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

FACULTY BIOGRAPHY

Mark S. Gold, MD, DFASAM, DLFAPA, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. He continues on the Faculty of the University of Florida, Tulane, and Washington University in St Louis.

He is an author and inventor who has published more than 1,000 peer-reviewed scientific articles, 20 text books, popular-general audience books, and physician practice guidelines. Dr. Gold was co-inventor of the use of clonidine in opioid withdrawal and the dopamine hypothesis for cocaine addiction and anhedonia. Both revolutionized how neuroscientists and physicians thought about drugs of abuse, addiction, and the brain. He pioneered the use of clonidine and lofexidine, which became the first non-opioid medication-assisted therapies. His first academic appointment was at Yale University School of Medicine in 1978. Working with Dr. Herb Kleber, he advanced his noradrenergic hyperactivity theory of opioid withdrawal and the use of clonidine and lofexidine to ameliorate these signs and symptoms. During this time, Dr. Gold and Dr. Kleber also worked on rapid detoxification with naloxone and induction on to naltrexone.

Dr. Gold has been awarded many state and national awards for research and service over his long career. He has been awarded major national awards for his neuroscience research including the annual Foundations Fund Prize for the most important research in Psychiatry, the DEA 30 Years of Service Pin (2014), the American Foundation for Addiction Research's Lifetime Achievement Award (2014), the McGovern Award for Lifetime Achievement (2015) for the most important contributions to the understanding and treatment of addiction, the National Leadership Award (NAATP) from addiction treatment providers for helping understand that addiction is a disease of the brain, the DARE Lifetime Achievement Award for volunteer and prevention efforts, the Silver Anvil from the PR Society of America for anti-drug prevention ads, the PRIDE and DARE awards for his career in research and prevention (2015), and the PATH Foundation's Lifetime Achievement Award (2016) as one of the "fathers" of addiction medicine and MAT presented to him by President Obama's White House Drug Czar Michael Botticelli. He was awarded Distinguished Alumni Awards at Yale University, the University of Florida, and Washington University and the Wall of Fame at the University of Florida College of Medicine. Gold was appointed by the University President to two terms as the University's overall Distinguished Professor, allowing him to mentor students and faculty from every college and institute. The University of Florida College of Medicine's White Coat Ceremony for new medical students is named in his honor.

Since his retirement as a full-time academic in 2014, Dr. Gold has continued his teaching, mentoring, research, and writing as an Adjunct Professor in the Department of Psychiatry at Washington University and an active member of the Clinical Council at the Washington University School of Medicine's Public Health Institute. He regularly lectures at medical schools and grand rounds around the country and at international and national scientific meetings on his career and on bench-to-bedside science in eating disorders, psychiatry, obesity, and addictions. He continues on the Faculty at the University of Florida College of Medicine, Department of Psychiatry as an Emeritus Distinguished Professor. He has traveled extensively to help many states develop prevention, education, and treatment approaches to the opioid crisis.

Customer Information/Evaluation insert located between pages 36–37.

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
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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.

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].

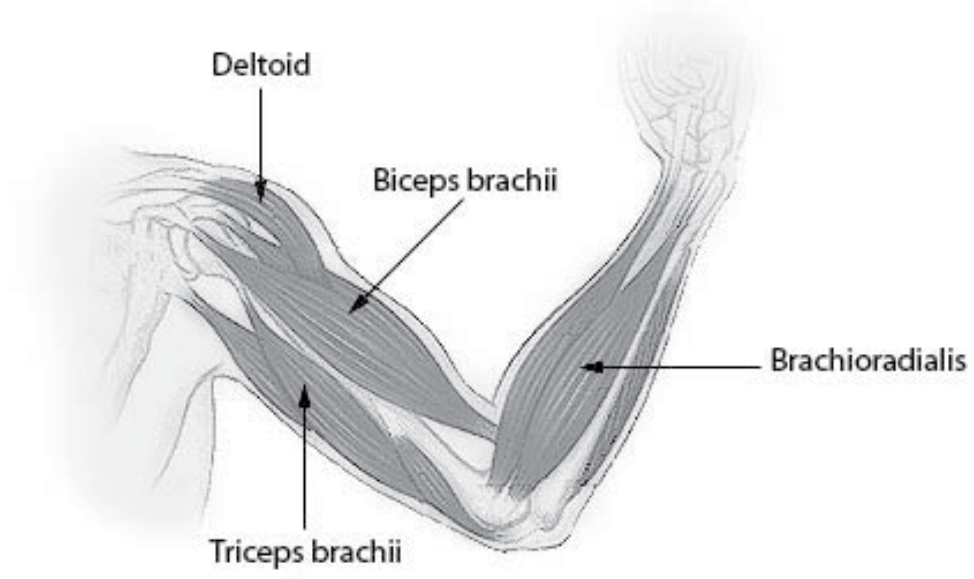
Most skeletal muscles work in groups. The prime mover is the muscle that contracts to produce the movement. Synergists are muscles that work with prime movers to assist in performing the movement. Antagonists are muscles that work opposite prime movers by relaxing during their contraction or by producing 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].

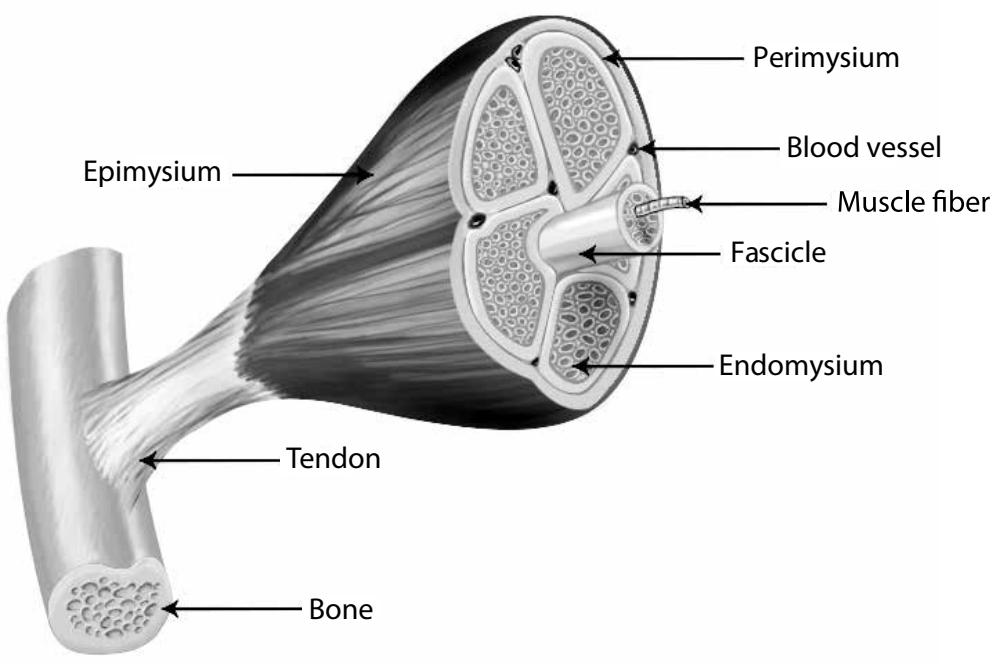
Muscle fibers are bound together by connective tissue into small bundles called fascicles, visible to the unaided eye. Fascicles are bound into larger bundles, which collectively form the muscle. The entire muscle is enclosed by a connective tissue covering called the epimysium, which is continuous with 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 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].

MUSCLES OF THE UPPER EXTREMITY



Source: National Cancer Institute *Figure 1*

STRUCTURE OF A SKELETAL MUSCLE



Source: National Cancer Institute *Figure 2*

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 facilitates 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 near 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 gait 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 ($5–25 \times 10^9$/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.

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].

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*

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 cyclooxygenase-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].

EVIDENCE-BASED PRACTICE RECOMMENDATION

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.

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*

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.

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

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*

- 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?
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.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Customer Information/Evaluation insert located between pages 36–37.

Course Availability List

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LUNG CANCER: DIAGNOSIS AND MANAGEMENT

#30723 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

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 / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

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

WOMEN AND CORONARY HEART DISEASE

UPDATE

#33224 • 15 ANCC / 5 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to identify the unique challenges that face women with heart disease, including prevention, diagnosis, and treatment.
Faculty: Margo A. Halm, RN, PhD, NEA-BC
Audience: This course is designed for all nurses in family practice or medical/surgical areas, especially critical care or cardiac units.
Additional Approval: AACN Synergy CERP Category A, CCMC

DIABETES AND STROKE: MAKING THE CONNECTION

#34943 • 2 ANCC / 1 Pharm Hour

Book By Mail – $23 • ONLINE – $15

Purpose: 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.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in all practice settings who care for patients with diabetes.
Additional Approval: AACN Synergy CERP Category A, CCMC

MULTIMODAL PHARMACOTHERAPY FOR PAIN MANAGEMENT

NEW!

#35270 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: 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.
Faculty: Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN
Audience: This course is designed for nurses involved in the care of patients with pain.
Additional Approval: AACN Synergy CERP Category A

HYPERLIPIDEMIAS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

UPDATE

#90844 • 10 ANCC / 7 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide a review of hyperlipidemia in the pathogenesis of cardiovascular disease, as well as the therapeutic benefits of pharmacologic and nonpharmacologic approaches to treatment. The objectives are to promote team-based care, foster patient awareness and shared provider-patient decision-making, and promote implementation of lifestyle changes and compliance with guideline-directed therapy for prevention of cardiovascular disease.
Faculty: A. José Lança, MD, PhD
Audience: This course is designed for physicians, physician assistants, nurses, and pharmacy professionals who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.
Additional Approval: AACN Synergy CERP Category A, CCMC

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Course Availability List *(Cont'd)*

PRESCRIBING OPIOIDS, PROVIDING NALOXONE, AND PREVENTING DRUG DIVERSION: THE WEST VIRGINIA REQUIREMENT

WV Mandate

#91603 • 3 ANCC / 3 Pharm Hours

Book By Mail – $26 • ONLINE – $18

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, physician assistants, nurses, and pharmacy professionals in West Virginia who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.
Additional Approval: AACN Synergy CERP Category A
Special Approvals: This course fulfills the West Virginia Board of Examiners for Registered Professional Nurses requirement for 3 hours of education related to Drug Diversion and Best Practice Prescribing of Controlled Substances.

This course fulfills the West Virginia State Board of Examiners for Licensed Professional Nurses requirement for 3 hours of education related to Chemical Dependency/Substance Abuse.

PROMOTING THE HEALTH OF GENDER AND SEXUAL MINORITIES

LGBTQ Competency

#91794 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: More individuals who identify as gender and sexual minorities and their families want culturally appropriate information as well as support and referral. The purpose of this course is to provide healthcare professionals with strategies that promote cultural competency when treating and caring for these patients, supporting the concept of patient-centered care.
Faculty: Leslie Bakker, RN, MSN
Audience: This course is designed for all members of the interdisciplinary team, including physicians and nurses, working in all practice settings.
Additional Approval: AACN Synergy CERP Category B
Special Approval: This course meets the District of Columbia requirement for 2 hours of LGBTQ education.

NECK PAIN IN ADULTS

UPDATE

#94131 • 10 ANCC / 3 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide primary care clinicians with the best available evidence on the clinical management of patients with acute or chronic neck pain.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all members of the interprofessional healthcare team involved in the care of patients with neck pain.
Additional Approval: AACN Synergy CERP Category A, CCMC

PNEUMONIA

New Guidelines

#94673 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

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

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

Federal MATE Act

#95300 • 8 ANCC / 8 Pharm Hours

Book By Mail – $56 • ONLINE – $48

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain 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 healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course is designed to meet the Federal MATE Act requirement for new or renewing DEA licensees to complete 8 hours of training on opioid or other substance use, disorders, and the appropriate treatment of pain.

OPIOID SAFETY: BALANCING BENEFITS AND RISKS

Opioid/ Controlled Substance

#95500 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

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 is designed to meet the requirements for opioid/controlled substance education.

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Course Availability List *(Cont'd)*

SUICIDE ASSESSMENT AND PREVENTION
#96442 • 6 ANCC Hours

WV Mandate

Book By Mail – $44 • ONLINE – $36

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approval: This course meets the West Virginia requirement for 2 hours of education on Veteran's Mental Health.

OBSESSIVE-COMPULSIVE DISORDER
#96473 • 4 ANCC / 2 Pharm Hours

UPDATE

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals with a basic understanding of obsessive-compulsive disorder (OCD), its clinical manifestations, and basic treatment approaches in order to facilitate optimum patient care and outcomes.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for healthcare professionals working with adults or adolescent patients who exhibit symptoms of obsessive-compulsive disorder.
Additional Approval: AACN Synergy CERP Category A

ALCOHOL AND ALCOHOL USE DISORDERS
#96563 • 10 ANCC / 1 Pharm Hour

Substance Use

Book By Mail – $68 • ONLINE – $60

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

ANXIETY DISORDERS IN OLDER ADULTS
#96690 • 3 ANCC / 1 Pharm Hour

Book By Mail – $26 • ONLINE – $18

Purpose: 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.
Faculty: Beyon Miloyan, PhD
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.
Additional Approval: AACN Synergy CERP Category A

IMPLICIT BIAS IN HEALTH CARE
#97000 • 3 ANCC Hours

Cultural Competence

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals an overview of the impact of implicit biases on clinical interactions and decision making.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for the interprofessional healthcare team and professions working in all practice settings.
Additional Approval: AACN Synergy CERP Category B
Special Approval: This course is designed to meet the requirements for implicit bias/cultural competence education.

GETTING TO THE POINT: ACUPUNCTURE AND ACUPOINT THERAPIES
#98030 • 4 ANCC Hours

NEW!

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to 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

NEW!

Book By Mail – $26 • ONLINE – $18

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

ANEMIA IN THE ELDERLY
#99083 • 5 ANCC / 2 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and tools necessary to identify anemia early and respond appropriately. Better health outcomes for the geriatric population will result from an increase in evidence-based clinical practices.
Faculty: Susan Waterbury, MSN, FNP-BC, ACHPN
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of elderly patients.
Additional Approval: AACN Synergy CERP Category A, CCMC

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☐	95300	Substance Use Disorders & Pain Management / 8	$56
☐	95500	Opioid Safety: Balancing Benefits and Risks / 5	$38
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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?
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10. Did study questions throughout the course promote recall of learning objectives?
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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?

#96790
Psychedelic Medicine
10 Contact Hours

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

#38950
Muscles, Joints, & 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

#96790 Psychedelic Medicine and Interventional Psychiatry — 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? _____
_____
_____
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