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Alternative Therapies for Depression and Anxiety

Includes 5 Advanced Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for healthcare professionals whose patients are taking or are interested in using complementary therapies to manage symptoms of depression and/or anxiety.

Course Objective
The purpose of this course is to help healthcare professionals in all practice settings increase their understanding of nutrients, lifestyle changes, complementary modalities, and herbal products that are often used by patients experiencing depression or anxiety.

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

1. Discuss the prevalence and severity of depression and anxiety in the U.S. adult population.
2. Provide counseling points for the safe and effective use of alternative modalities for anxiety and depression.
3. Review the evidence for herbal supplements commonly used for depression and anxiety.
4. Compare the evidence for vitamins and minerals in the management of mental health.
5. Consider the evidence for safe and appropriate use of alternative therapies during pregnancy and breastfeeding.

Faculty
Chelsey McIntyre, PharmD, is a clinical pharmacist who specializes in drug information, literature analysis, and medical writing. She earned her Bachelor of Science degree in Genetics from the University of California, Davis. She then went on to complete her PharmD at Creighton University, followed by a clinical residency at the Children's Hospital of Philadelphia (CHOP). Dr. McIntyre held the position of Drug Information and Policy Development Pharmacist at CHOP until her move to Washington state in 2017, after which she spent the next six years as a clinical editor for Natural Medicines, a clinical reference database focused on natural products and alternative therapies. She continues to create rigorous professional analysis and patient education materials for various publications while also practicing as a hospital pharmacist. Her professional interests include provider and patient education, as well as the application of evidence-based research to patient care.

Faculty Disclosure
Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

INTRODUCTION

Mental health, which includes emotional, psychological and social well-being, affects the way that a person acts, thinks and feels. Although mental health has traditionally been considered separate from physical health, there has been a large and relatively successful movement toward recognizing mental health as equally important to physical health, and a core component of a person's overall well-being.

In fact, it is now well-established that mental health issues can increase a person's risk of physical health problems, such as diabetes, heart disease and stroke. Conversely, chronic physical health conditions can increase the risk for mental health concerns [1].

PREVALENCE AND IMPACT

What percentage of U.S. adults lived with a mental illness in 2021?

In the United States, it is estimated that more than one in five adults (20%) live with a mental illness. This statistic covers what is referred to as "any mental illness," defined as a mental, behavioral or emotional disorder that can vary in its impact from mild to severe. In the United States, women are more likely to have a mental illness than men (27.2% vs. 18.1%) and younger adults are more likely to have a mental illness than older adults. In 2021, 34% of all adults 18 to 25 years of age had a mental illness, compared to 28% of adults 26 to 49 years of age and 15% of all adults 50 years of age and older [2]. The prevalence of mental illness in adolescents (12 to 17 years of age) is also increasing [3].

The majority of mental illnesses are classified as mild to moderate, meaning that they cause mild-to-moderate functional impairment. According to the National Institute of Mental Health, a mental illness is considered serious (or severe) if it "substantially interferes with or limits one or more major life activities" [2]. In 2021, it was estimated that 14 million adults (5.5%) had a serious mental illness. This suggests that about 75% of all mental illnesses in U.S. adults are classified as mild to moderate at any given time [2].

Even mental illness that is not considered severe can have serious long-term impacts if not addressed. Mental illness is known to cause significant disability and can even contribute to premature mortality. The Global Burden of Disease study attributes nearly 15% of years of life lost to mental disorders, making mental illnesses one of the largest causes of disability worldwide [4].

Mental illness is also known to increase the number of "deaths of despair." These deaths from drugs, alcohol, and suicide—which tend to be caused by mental health difficulties, as well as pain and economic distress—more than doubled between the 1960s and 2017 and have continued to rise [5]. Adolescents and younger adults have not been immune to this increase. In the decade prior to 2018, suicide death rates among individuals 10 to 24 years of age increased by 47% [6].

AN OVERVIEW OF COMMON MENTAL HEALTH DISORDERS

DEPRESSION

Depression is one of the most common mental illnesses reported in the United States. In 2021, 21 million U.S. adults (8.3%) had at least one major depressive episode. This rate was highest in those 18 to 25 years of age (18.6%). Major depressive episodes resulting in severe impairment affected 5.7% of all U.S. adults in 2021. That same year, 5 million adolescents—representing about 20% of those 12 to 17 years of age—reported major depressive episodes. This rate was much higher in girls than boys, at 29% and 11.5%, respectively [2].

Major depressive disorder (MDD) is defined in the revised fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) as a period of at least two weeks when a person experienced a depressed mood or loss of interest or pleasure in daily activities, and had a majority of specified symptoms, such as problems with sleep, eating, energy, concentration, or self-worth [7].

The prevalence of depression in the general population increased significantly during the COVID-19 pandemic. According to a scientific brief published by the World Health Organization (WHO) in early 2022, the global prevalence of depression increased by 27.6% in the preceding year. Women were more affected than men, and younger adults (especially those 20 to 24 years of age) were most affected [8].

Seasonal Depression

Some forms of depression manifest only at certain times. One such form that affects many adults in the United States, but with a more intermittent impact, is seasonal affective disorder (SAD), also known as seasonal depression or winter depression. This mental illness is identified in the DSM-5-TR as a type of depression (Major Depressive Disorder with a Seasonal Pattern) [9].

People with seasonal depression experience mood changes and symptoms similar to other forms of depression. The symptoms usually occur during the fall and winter months—comprising about 40% of the calendar year—when there is less sunlight. In the United States, the most difficult months tend to be January and February, with the majority of people experiencing improvement with the arrival of spring. This form of depression is estimated to affect 5% of all U.S. adults. As with other forms of depression, it is more common women than in men [9].

Postpartum Depression

Postpartum depression is another important form of depression that manifests only at certain times, in this case, after giving birth. This should not be confused with what is sometimes referred to as the "baby blues," which often resolves within a few days of delivery. Rather, postpartum depression is more intense, lasts much longer, and mirrors the symptoms of MDD. For some patients, this manifests as crying more often, feelings of anger, withdrawing from loved ones, feeling numb or disconnected from the newborn, and feelings of guilt [10].

Some adults are at a higher risk of postpartum depression, including those who have recently experienced stressful life events, experienced pregnancy complications, have low social support, have a previous history (or family history) of depression, delivered preterm, and/or gave birth to multiple newborns at once. However, it can also affect otherwise healthy adults with no apparent risk factors [10].

This form of depression seems to occur in about one of eight adults (13%) who have recently given birth in the United States. This rate is higher (greater than 20%) in those who were 19 years of age or younger at the time of delivery. Due to this high prevalence, experts recommend that all pregnant adults be screened for depression [11].

ANXIETY

Anxiety is another common mental illness in the United States, although it can take many forms. When referred to under the general umbrella of anxiety, this can include generalized anxiety disorder (GAD), panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, and separation anxiety disorder, among others.

Most adults diagnosed with anxiety are considered to have GAD. This is characterized by excessive worry that is difficult to control and is accompanied by physical symptoms like restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and/or sleep disturbance. In 2019, approximately 15% of adults had experienced symptoms of anxiety of some level in the past two weeks, with 9.5%, 3.4%, and 2.7% of adults experiencing mild, moderate, or severe symptoms of anxiety, respectively [12].

Anxiety symptoms were most common in those 18 to 29 years of age. In this age group, about 20% experienced any symptoms, with 12% experiencing mild symptoms, 5% moderate, and 3% severe. More than 19% of women reported symptoms of anxiety in the past two weeks, compared with 12% of men [12].

Symptoms of anxiety are often assessed using the GAD-7 scale, which is a validated brief self-report screening that can assess the severity of symptoms. Adults with GAD-7 scores of 0–4 are considered to have no or minimal symptoms; those with scores of 5–9, 10–14, or 15–21 are considered to have mild, moderate, or severe symptoms, respectively [13].

As with depression, the COVID-19 pandemic led to a notable global increase in the prevalence of anxiety. The same WHO report that identified an increase in symptoms of depression also identified a 25.6% increase in the prevalence of anxiety disorders during the first year of the pandemic. As with depression, women and adults 20 to 24 years of age were most affected [8].

In the United States, as many as 40% of all adults reported symptoms consistent with anxiety and depression during the first year of the pandemic. This declined to about 30% of all adults as the pandemic continued into 2022 and 2023. A full 50% of young adults (18 to 24 years of age) reported anxiety and depression symptoms in 2023, with women reporting symptoms of anxiety and/or depression at a rate of 36% (compared with 28% of men) [14].

OTHER MENTAL ILLNESSES

Many other conditions fall under the umbrella of "mental illness" and affect adults and adolescents in the United States. Some examples of these conditions include attention deficit hyperactivity disorder (ADHD), psychotic disorders, post-traumatic stress disorder (PTSD), bipolar disorder, eating disorders, and more.

Due to the severity and specificity of these conditions, these mental illnesses will not be covered in this course. Similarly, severe depression and anxiety are also not within the scope of this course. The research discussed will instead focus on adults with mild-to-moderate depression and anxiety.

AN IMPORTANT NOTE ABOUT TREATMENT AND DIAGNOSIS

Mental illnesses should always be taken seriously, even in patients who report only mild or moderate impairment. Screening for these conditions should occur consistently, in alignment with national recommendations. Any patients identified as having a mental illness should be provided with referrals for appropriate and evidence-based treatment options.

Unfortunately, due to an ongoing shortage of behavioral health workers, patients may experience difficulties accessing standard treatments, such as counseling and support groups. For patients who are experiencing more modest impairment from a mental health condition, or for those who are waitlisted with a specialized provider, alternative therapies may be considered as a stopgap measure. Additionally, for patients who are currently receiving recommended treatment, alternative therapies may be considered as supplemental treatment options.

Alternative treatment options should never be considered or relied upon as a replacement for evidence-based care in a patient with a serious mental health disorder or in a patient experiencing symptoms of suicidality.

EXERCISE-BASED THERAPIES

Over the years, exercise has become a well-accepted tool for the management of depression and anxiety. In fact, the American Psychiatric Association (APA)'s guideline on the treatment of depression acknowledges exercise as a relevant and beneficial treatment modality for all severities of depression. For mild depression, the guideline indicates that a patient may elect to try exercise as a sole treatment for their symptoms for the first several weeks. As for patients with more severe depression and/or those who are using other treatments, exercise is considered a reasonable addition to any treatment plan [15].

A 2023 meta-analysis pooled together more than 90 studies to assess the overarching benefits of exercise for the management of depression, anxiety, and stress. The analysis found that physical activity had medium benefits for all three conditions when compared with usual care. Some of the largest benefits were seen in people with depression, certain chronic conditions, and pregnant and postpartum females. Higher intensity interventions were associated with greater improvements, although the benefits of physical activity appeared to wane over time [16].

A separate, large meta-analysis pooled data from more than 200 studies in people with depression. That analysis determined that certain forms of exercise, including walking or jogging, strength training, mixed aerobic exercises, yoga, and tai chi or qi gong, offered the greatest benefits. Here, we will review the evidence for these last three forms of physical activity, all of which contain a meditative component.

YOGA

How long should yoga be practiced to improve symptoms of mild or new-onset depression?

Yoga is a form of meditative physical activity that originated from a traditional system of medicine in India: Ayurveda. Yoga generally involves controlled breathing, meditation, and body posturing, although there are many subtypes of yoga which involve differing levels of physical activity.

The evidence to date indicates that practicing yoga for one to two months can improve symptoms of depression in people with mild or new-onset depression. Additionally, it appears to be beneficial as an adjunct therapy in people who are taking conventional antidepressants. Importantly, most of these studies evaluated the use of "Western yoga," which tends to entail a greater focus on physical yoga poses [17].

Research on the use of yoga for anxiety is limited to smaller clinical studies. However, that research does suggest that practicing differing styles of yoga can modestly improve symptoms of anxiety when compared with a control or other active treatment [17].

Yoga is generally considered safe, with temporary musculoskeletal pain as the most common adverse effect. For adults with limited prior exercise, mobility concerns, or other serious health issues, encourage a consultation with a trained practitioner prior to participation in yoga.

Pregnancy and Breastfeeding

A number of studies have evaluated the benefits of yoga during pregnancy. Most of these studies suggest that practicing yoga during pregnancy reduces the rate of depression. However, some studies have yielded conflicting findings, which may be associated with whether or not the person already had depression at the start of the study. Some studies have also evaluated yoga for the management of anxiety during pregnancy, finding modest benefits when compared with either baseline or a control group [18; 19; 20; 21].

Importantly, these studies all indicate that yoga is generally safe during pregnancy and does not adversely affect the child's outcomes. However, aggressive or more extreme forms of yoga, such as hot yoga, should likely be avoided during pregnancy.

QI GONG AND TAI CHI

Qi gong is a martial art-like exercise with a focus on meditation and breathing that originated in China. It is intended to regulate the body's qi (vital energy or life force). There are several varieties of qi gong, with some that involve slow movements and exercise and others that involve bodywork conducted by a trained practitioner [22].

Tai chi is one specific form of qi gong that has become relatively popular in North America. This form of exercise involves controlled breathing and slow, rhythmic body movements which are intended to facilitate the flow of qi [23].

Small clinical studies suggest that practicing qi gong for 90 to 350 minutes each week for up to four months can reduce symptoms of depression when compared with various control groups [22]. Tai chi has also been evaluated in people with depression, although these studies have been relatively small. While one study suggests that practicing tai chi for two hours weekly for 10 weeks can improve symptoms when compared with simple health education, a follow-up study in this same group of patients did not ultimately identify additional benefit with tai chi [23; 24].

A meta-analysis of 10 clinical studies in healthy adults, some of which were low-quality and not randomized, shows that practicing tai chi five times weekly for a year can modestly improve anxiety symptoms when compared with a waitlist or control group. However, it did not seem to improve depressive symptoms or stress [25].

Qi gong and tai chi are generally considered safe; temporary musculoskeletal pain is the most common adverse effect of qi gong. However, for adults with limited prior exercise, mobility concerns, or other serious health issues, encourage a consultation with a trained practitioner prior to participation.

Pregnancy and Breastfeeding

There is little to no research evaluating the benefits or safety of qi gong or tai chi while pregnant or breastfeeding. Advise patients to consult with a trained professional before initiating tai chi or any other exercise program when pregnant or breastfeeding.

ALTERNATIVE MODALITIES

For patients who are interested in pursuing alternative treatment options that do not involve the use of an oral supplement, a variety of other modalities have been evaluated for both anxiety and depression. However, it is important to note that many of these modalities have been studied in conjunction with the use of conventional treatment options, including antidepressants and therapy.

ACUPUNCTURE

Acupoint therapies, which utilize concepts based in traditional Chinese medicine, have grown in popularity over recent years. These include acupuncture, acupressure, moxibustion, and acustimulation.

Although there is general interest in the use of these therapies for the management of depression and anxiety, the best evidence is for acupuncture. Most clinical studies suggest that acupuncture can reduce symptoms of depression when used as an adjunct to conventional therapy. These studies suggest that acupuncture can improve the rate of treatment response with conventional antidepressants and may also reduce remission rates [26; 27]. Importantly, most of these studies were of low quality and conducted in a single country (outside of the United States); their relevance to the typical patient with depression in North America remains unclear.

Acupuncture is considered generally safe, so long as it is performed in a hygienic environment with sterilized needles by a licensed practitioner using appropriate techniques. The most common adverse effects include bruising, pain, and swelling at the site of needle entry.

Pregnancy and Breastfeeding

Small clinical studies have evaluated acupuncture for postpartum depression, suggesting that there may be a small benefit when acupuncture is added to conventional antidepressants [28]. Generally, research with traditional acupuncture during pregnancy has not identified any safety concerns for the unborn baby. However, there is one specific acupoint (SP6) which may be unsafe to stimulate during pregnancy, as it has been associated with an increased risk for early contractions and miscarriage [29].

It is unclear if laser acupuncture or electroacupuncture are safe during pregnancy. Additionally, there is little to no research evaluating the safety of acupuncture while breastfeeding. Counsel patients to consult with a licensed practitioner prior to undergoing any form of acupuncture while pregnant or breastfeeding.

ANIMAL-ASSISTED THERAPY

Animal-assisted therapy, as the name implies, involves using a trained animal to help with either recovery from or coping with various health conditions. This form of therapy has been used for the management of both physical and mental illness.

Clinical research has found that single sessions of various types of animal-assisted therapy can improve short-lived situational symptoms of anxiety (often self-reported). These studies mostly involved a dog as part of individual or group therapy and the sessions lasted for 8 to 30 minutes [30; 31]. The benefit is similar to that seen with therapeutic recreation sessions or interactions with social workers, suggesting that animal-assisted therapy may be a reasonable adjunct to various other anxiety treatments. Research on the use of animal-assisted therapy for depression, however, is limited and inconclusive.

Animal-assisted therapy is generally safe for most people, although people who are at increased risk of infection should take appropriate precautions. Additionally, allergies may be an important consideration for some individuals.

EXPRESSIVE THERAPIES (MUSIC AND ART)

Expressive therapies combine some form of artistic expression with some form of therapy. This artistic expression can include art, music, dance, drama, poetry, or creative writing. Two specific forms of expressive therapy—art and music—have shown benefit for symptoms of anxiety and depression.

The best evidence for both forms of expressive therapy is in the management of depression. Various forms of art therapy can improve symptoms of depression, from adolescents to the elderly. Research has shown that art therapy, in the form of regular sessions over 10 to 20 weeks, can offer modest benefit as an adjunct to conventional antidepressants or as monotherapy [32; 33]. Similarly, music therapy has shown benefit for symptoms of depression across various age groups. This therapy may include listening to and/or making music, with or without the presence of a therapist. In most cases, the patients in these studies were already taking a conventional antidepressant [34; 35].

There is also a large body of evidence showing that music therapy can benefit people with symptoms of anxiety. In these studies, music therapy had a small to medium benefit in a variety of patients, including postpartum adults, people with a variety of underlying health conditions, and adolescents. These benefits appear to be short-term, however, and do not

seem to continue after the therapy has ended [36]. Some small clinical studies have also shown modest benefit with art therapy, particularly in the elderly or in women with various anxiety disorders. In most of these studies, 10 to 12 art therapy sessions occurred over about three months [37; 38].

Particularly for patients who already enjoy music and/or art, these expressive therapies could be considered as safe adjunctive modalities for managing symptoms of depression and anxiety.

Pregnancy and Breastfeeding

Some small clinical studies suggest that music therapy may be beneficial for postpartum depression, although those same studies did not find benefit for postpartum anxiety [39]. Art therapy has not been adequately evaluated for the management of perinatal or postpartum depression or anxiety.

Although neither modality has been extensively evaluated for safety during pregnancy or breastfeeding, there are no reasons to expect safety concerns so long as adequate precautions (e.g., avoidance of loud noises) are taken.

MINDFULNESS

Mindfulness, a practice derived from Buddhist theory, has also become popular for general well-being and the management of mild to moderate mental health concerns. Mindfulness involves a purposeful attention and awareness of present thoughts, emotions, and sensations without evaluation or judgment of what is occurring.

Mindfulness-based stress reduction (MBSR) is a well-studied and standardized mindfulness practice. It usually includes eight weekly 2.5-hour sessions, as well as daily home recordings of mindfulness exercises and a half-day retreat after the sixth class [40]. It includes three main components:

- Didactic material that explains the concept of mindfulness
- Practicing mindfulness exercises during group sessions and at home
- Discussing and sharing MBSR experiences with a group

In general, mindfulness seems to modestly reduce anxiety, although benefits appear to be short-term. It is unclear how mindfulness or MBSR compares with other nonpharmacologic treatment options. Meta-analyses, small clinical studies, and observational research in patients with various forms of anxiety, or without diagnosed anxiety, show that practicing MBSR or modified MBSR improves anxiety severity when compared with baseline or no intervention [41; 42; 43]. One large clinical trial shows that practicing MBSR for eight weeks may be as effective as taking escitalopram [44].

Most clinical research also shows that mindfulness can reduce symptoms of depression. These studies evaluated MBSR, as well as another form of mindfulness known as mindfulness-based cognitive therapy (MBCT) [45]. Although most studies have evaluated only the short-term effects of these modalities, MBCT does appear to reduce the risk of depressive relapse within 60 weeks of treatment [46].

Considering that MBSR has also shown benefit for the management of stress, mindfulness may be of particular interest to patients who experience mild and intermittent symptoms of anxiety or depression.

Pregnancy and Breastfeeding

Mindfulness during pregnancy or breastfeeding has not been well-researched. That being said, mindfulness is considered safe in the general population and in people with various chronic conditions, with no reason to expect adverse effects.

RELAXATION THERAPY

Relaxation therapy involves the teaching of various skills and methods to achieve relaxation, including imagery, breathing exercises, focused muscle tensing and relaxing, and cue-controlled relaxation. Patients are instructed to practice these methods on a regular basis.

Clinical research shows that relaxation therapy can improve symptoms of anxiety in people with anxiety disorders or situational anxiety and can also improve symptoms of depression in people with MDD. However, in both cases, it appears to be less effective than cognitive-behavioral therapy (CBT) or certain forms of meditation [47; 48].

Although the benefits of relaxation therapy may be modest at best, it is a generally safe modality that can be integrated into everyday life.

Pregnancy and Breastfeeding

In a small clinical study, relaxation therapy has demonstrated modest benefit for symptoms of depression and anxiety in perinatal adults [49]. Although research in those who are pregnant or breastfeeding has been limited to date, there is no reason to expect safety concerns with the use of relaxation therapy.

LIGHT THERAPY

Also known as phototherapy, light therapy involves exposing the skin to specific wavelengths of light. This modality is of particular interest, and has shown particular benefit, in the management of seasonal depression.

Clinical research shows that light therapy, delivered at a brightness of 3,000–10,000 lux, reduces symptoms of seasonal depression and may be similarly effective to fluoxetine 20 mg daily [50]. Higher intensity light therapy appears to be more effective than dimmer therapy, and blue and green wavelengths appear to be more beneficial than red wavelengths [50; 51].

In most studies, patients have been exposed to a light placed 12–18 inches away from the face for 30 minutes to 3 hours each day.

Light therapy for seasonal depression does not include ultraviolet (UV) wavelengths and is thus considered safe for use. When the appropriate wavelengths and brightness are employed, light therapy has not been associated with adverse effects.

Pregnancy and Breastfeeding

One very small clinical study suggests that light therapy may be beneficial for untreated perinatal or postpartum depression. In this study, bright light therapy was associated with remission in 42% of patients, compared with 0% of the patients who received placebo (low-light) therapy. This study was too small to determine whether there were any adverse effects to the fetus [52].

Although there is no reason to suspect that light therapy would cause harm to an unborn baby, counsel patients to ensure that light is directed to the face and used at the appropriate wavelength, brightness, and duration.

DIETARY SUPPLEMENTS

A variety of supplements, including herbal products, vitamins, minerals, and other naturally occurring chemicals, have been proposed for use in the treatment of mild-to-moderate depression and anxiety. Unfortunately, the evidence to support the use of these supplements is not typically of the same size and quality as the evidence for prescription medications. Additionally, just like prescription drugs, many supplements have the potential to cause drug interactions. These considerations should be kept in mind while reviewing the options discussed here.

HERBAL SUPPLEMENTS

St. John's Wort

St. John's wort (*Hypericum perforatum*) is a plant with a yellow, star-shaped flower. Extracts of the plant are known to affect the neurotransmitters serotonin, dopamine, and norephinephrine, possibly limiting their reuptake. It has been extensively studied for the treatment of mild or moderate depression, with most studies showing evidence of benefit.

Many individual clinical trials show that St. John's wort extracts are more effective than placebo and may be as effective as selective serotonin reuptake inhibitors (SSRIs) for treating depression. It is important to note that the benefits of St. John's wort are only seen with certain extracts that contain specific amounts of chemicals found in the plant. The extracts that have shown benefit in clinical research contain 0.3% hypericin and 1% to 4% hyperforin. If a patient purchases a St. John's wort product that contains differing quantities of these chemicals, they may have a reduced likelihood of benefit [53].

St. John's wort extracts may have a lower rate of various adverse effects than conventional antidepressants, including gastrointestinal, neurological, and sexual adverse effects [53]. That being said, St. John's wort does seem to cause adverse effects, including gastrointestinal upset, fatigue, sedation, dizziness, headache, and dry mouth. Additionally, it can cause photodermatitis, a risk that appears to increase with the dose of hypericin, with most events reported in people takin hypericin 5–10 mg daily [54].

St. John's wort is notorious for its ability to interact with many prescription drugs. This herb can induce cytochrome P450 (CYP) 3A4, which is responsible for metabolizing many drugs. This can reduce the levels and efficacy of a wide range of medications, including birth control, immunosuppressants, and certain anticoagulants [54]. Also, because St. John's wort has serotonergic activity, it can cause serious interactions with other serotonergic drugs, and even increase the risk for serotonin syndrome [54; 55].

Due to its popularity and the amount of research conducted to date, St. John's wort is discussed in some clinical guidelines, including those from the American College of Physicians (ACP). Although the ACP acknowledges the available evidence, it stops short of recommending this extract for the treatment of depression due to the fact that it may be difficult for patients to obtain a product of adequate quality and with the appropriate amount of hypericin and hyperforin. Conversely, an international guideline from the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce recommends St. John's wort at doses of 600–1,800 mg daily as monotherapy for mild-to-moderate forms of MDD [54].

Pregnancy and Breastfeeding

St. John's wort extracts may be unsafe for use during pregnancy and should be avoided. An observational study identified an association between the use of St. John's wort and birth defects, including neural tube, urinary, and cardiovascular malformations [57].

The safety of taking St. John's wort extracts while breastfeeding is unclear. Inconclusive reports suggest that infants exposed to St. John's wort via human milk may have a higher chance of colic, drowsiness, and lethargy. Until more is known, recommend that patients avoid St. John's wort while breastfeeding [58; 59].

Saffron

Which herbal supplement has shown benefits for both depression and anxiety in clinical studies?

Saffron, derived from the flower of *Crocus sativa*, is perhaps best known for its use as a vibrant red-orange spice. However, it has recently been gaining popularity for use in the treatment of both depression and anxiety.

The most extensive evidence to date is for the use of saffron extract for the treatment of depression, either alone or in combination with conventional antidepressants. Clinical research shows that taking saffron extract 30 mg daily, or taking dried saffron stigma 100 mg daily, for up to three months improves symptoms of depression when compared with a control group. When compared with a variety of antidepressants, including SSRIs, it seems to have a comparable effect [60; 61]. When used in combination with an SSRI, some research suggests that saffron may provide a further modest reduction in depressive symptoms [62].

The evidence for anxiety, on the other hand, is less robust. Only a couple of small clinical studies have evaluated saffron for this purpose. Although both suggest that saffron may modestly improve symptoms of mild-to-moderate anxiety, more research is needed to confirm this finding [63; 64].

Overall, saffron seems to be well tolerated, with the most common adverse effects including gastrointestinal complaints, nausea, vomiting, and sedation. Unlike St. John's wort, saffron has not been associated with major drug interactions to date [60].

The same international guideline that recommends St. John's wort for the treatment of depression (from WFSBP and CANMAT) also provisionally recommends saffron 30 mg daily for either monotherapy or as an adjunct treatment in mild to moderate depression [54].

Anyone who has purchased saffron as a spice knows that it can be quite expensive. In fact, saffron is one of the most expensive spices on the planet. This is because one pound of saffron requires approximately 225,000 hand-picked stigmas or 75,000 flower blossoms [65; 66].

Unfortunately, this means that saffron products are at high risk for adulteration, with some manufacturers using other ingredients (such as red-colored corn, pomegranate fruit peel, red-dyed silk fibers, and more) to replace saffron due to its high price and limited availability [67]. Caution patients to only purchase products with verified ingredients.

Pregnancy and Breastfeeding

When taken in medicinal doses, saffron may be unsafe for use during pregnancy. Although there has been little to no research conducted on this topic, there is a hypothetical concern that saffron can stimulate the uterus and increase the risk of miscarriage [68].

One small clinical study suggests that taking saffron 30 mg daily may be as effective as fluoxetine in patients with postpartum depression. However, the study lasted only six weeks, and fluoxetine may take up to six weeks to reach its full effect [69]. Additionally, this study did not evaluate whether saffron was safe while breastfeeding.

There is no reliable evidence available regarding the safety of saffron while breastfeeding. It is not known whether saffron transfers into human milk; there is also no research available on the safety of saffron in newborns. Until more is known, caution patients to avoid saffron supplements while breastfeeding.

Lavender

Lavender (*Lavandula angustifolia)*, a popular evergreen herb with a purple flower, is known for its pleasant scent, which is used in a variety of bath products and perfumes. Over the years, lavender has also gained popularity for use in the management of depression and anxiety, both when taken by mouth and when inhaled as aromatherapy.

When it comes to anxiety, the strongest available evidence has evaluated only one specific lavender oil extract (Silexan) that is taken by mouth. This extract has been studied at doses of 80–160 mg orally daily for up to 2.5 months, and research shows that it improves anxiety when compared with placebo [70; 71]. Lavender oil aromatherapy has also been evaluated for the management of both chronic and situational anxiety, for which it seems to moderately reduce symptoms when compared with a control group [70; 72; 73].

Clinical research on the use of oral lavender for depression has also shown benefits when compared with placebo. These studies have evaluated lavender in the form of a tea, a tincture, a powder, or the specific oil product that has also been studied for anxiety (Silexan) [74; 75]. Although the quality of the available research varies, oral lavender seems to modestly improve depression scores. Lavender oil aromatherapy also seems to offer some benefit for reducing symptoms of depression [75].

It is important to note that most of the available research on the use of lavender oil aromatherapy has evaluated a single dose only. Additionally, the control groups in these studies either receive no intervention at all or are asked to inhale water or lemon juice. Thus, it is difficult to ensure adequate blinding when studying the effects of aromatherapy, as patients will likely be aware of which group they have been assigned to based on the scent inhaled.

Oral lavender seems to be generally well-tolerated, although it has been reported to cause some gastrointestinal disturbance, such as constipation, diarrhea, and dyspepsia, as well as headache and breath odor. Inhaled lavender has not been associated with any serious adverse effects, although some patients who have applied lavender oil to the skin have experienced allergic reactions [76].

The international guideline from WFSBP and CANMAT provides a weak recommendation for the use of either oral lavender oil at a dose of 80–160 mg daily, or the use of dried lavender flower at a dose of 500–1,500 mg twice daily, as either monotherapy or as an adjunct for the treatment of MDD [54].

Pregnancy and Breastfeeding

There has been little to no research on the safety of lavender when taken by mouth during pregnancy or while breastfeeding. Until more is known, recommend against the use of oral lavender in people who are pregnant or planning to become pregnant, as well as people who are breastfeeding.

The safety of inhaled lavender (aromatherapy) is also unclear. Some small studies have evaluated a single inhalation of lavender aromatherapy during labor. However, these studies have not adequately evaluated assessed the newborn for any adverse effects [77].

Turmeric

Turmeric (*Curcuma longa*) is a well-known, yellow-colored spice that has gained increasing popularity over the past decade for a range of medical uses. Most of its medical benefits seem to be related to a specific chemical, curcumin, which is present in varying concentrations in turmeric.

Clinical research shows that curcumin can improve symptoms of depression when taken for at least six weeks and seems most likely to provide benefit for middle-aged patients as compared to older patients. However, the actual extent of the benefit of curcumin remains unclear. Some studies suggest that taking at least 1 gram daily is beneficial; other research suggests that curcumin 1 gram daily is only beneficial when taken along with conventional antidepressants [78; 79; 80].

Overall, turmeric is well-tolerated when taken at the doses studied for depression. The most commonly reported adverse effects are constipation, dyspepsia, diarrhea, and reflux.

Although rare, turmeric has also been associated with reports of serious liver damage. It is not entirely clear whether turmeric was the cause of liver damage in these patients; however, in most cases, the liver damage resolved after discontinuation of the supplement. Turmeric should be used with caution in people with existing liver dysfunction [81].

There are some potential drug interactions with turmeric, which should be given strong consideration in certain populations. For example, turmeric may increase the risk of bleeding in patients that are taking anticoagulants and may alter the effects of a variety of drugs used for the treatment of cancer [82; 83; 84].

The WFSBP and CANMAT international guideline provisionally recommends the use of curcumin extract 500–1,000 mg daily for mild-to-moderate depression, either as monotherapy or as an adjunct to other treatments [54].

Pregnancy and Breastfeeding

When taken in medicinal doses, turmeric may be unsafe for use during pregnancy. Although there has been little to no research conducted on the safety of turmeric supplements during pregnancy, there is a hypothetical concern that it can stimulate the uterus and increase menstrual flow [68].

There is no reliable evidence available regarding the safety of turmeric while breastfeeding. It is not known whether turmeric transfers into human milk; there is also no research available on the safety of turmeric in newborns. Until more is known, caution patients to avoid turmeric supplements while breastfeeding.

Lemon Balm

This lemon-scented herb (*Melissa officinalis)* has been used for relaxation across a variety of cultures over the last few centuries. More recently, clinical research has indicated that it may have some benefit for the treatment of depression, anxiety, and stress.

Clinical research shows that taking lemon balm orally can modestly improve depression. Most of these studies have used 1,200–3,000 mg daily for up to two months. Clinical research in adults with anxiety shows that these doses of lemon balm can also moderately improve anxiety scores when compared with a control group [85]. And in otherwise healthy adults experiencing stress, a single dose of lemon balm extract 300–600 mg seems to increase calm when compared with placebo [86].

Lemon balm is generally well-tolerated, although it has only been studied for up to two months at a time. This may be considered as a short-term, complementary therapy, particularly for patients experiencing intermittent stress or anxiety.

Pregnancy and Breastfeeding

There has been little to no research on the safety of lemon balm when taken by mouth during pregnancy or while breastfeeding. Until more is known, recommend against the use of oral lemon balm in people who are pregnant or planning to become pregnant, as well as people who are breastfeeding.

Kava

Piper methysticum is a plant that has become relatively popular as both a beverage and extract in the United States. When consumed as a beverage, it is often obtained at a "kava bar," where it is marketed as a relaxing recreational drink. When consumed as an extract, it is sold as a dietary supplement and is typically standardized to a group of chemicals called kavalactones. Most extracts evaluated in clinical research contain anywhere between 30% to 70% kavalactones [87].

The available clinical research suggests that kava extracts 150–400 mg daily, standardized to 70% kavalactones, can modestly improve symptoms of general anxiety when compared with placebo. Any effect of kava on anxiety appears to be dose-dependent; extracts that provide at least 200 mg kavalactones daily tend to be more beneficial than those that provide lower doses. Additionally, research indicates that it takes at least five weeks before benefit is obtained [88; 89].

However, kava does not appear to be beneficial in people with GAD. Some small clinical trials and one larger clinical study show that kava extracts, taken daily for four to eight weeks, are no more effective than placebo [54; 90].

Although kava appears to be generally safe when taken by mouth, it has been associated with multiple reports of hepatotoxicity. It is not entirely clear whether these cases of liver damage have been directly related to kava extracts; however, analyses of the reports suggest that the risk may be higher with higher doses and a prolonged duration of use. Some reports have also suggested that the extraction method for kava, or contamination of the kava plant, may increase the risk of liver damage [87; 91]. In general, patients with liver dysfunction, or patients who are using other medications that can cause liver damage, such as alcohol, should avoid kava.

Kava has been shown to cause central nervous system (CNS) depression and sedation and should be used with caution in patients who are taking other CNS depressants, such as opioids, alcohol, or benzodiazepines [54]. Additionally, there is some concern that kava can cause impairment when driving or operating heavy machinery. However, there is no strong evidence to indicate the level of impairment that kava may cause, and small studies evaluating its effect on reaction time and visual attention have yielded conflicting findings [92; 93]. Until more is known, patients should determine how kava affects them before driving or operating heavy machinery.

The international guideline from WFSBP and CANMAT recommends *against* the use of kava for the treatment of GAD. For practitioners that are still interested in discussing the use of kava with patients that are not at increased risk for liver damage, the group notes that only supplements standardized to a sufficient level of kavalactones should be used [54].

Pregnancy and Breastfeeding

There has been little to no research conducted on the use of kava during pregnancy or while breastfeeding. However, there is a hypothetical concern that kava may cause loss of uterine tone, which could threaten a pregnancy. There is also a hypothetical concern that certain chemicals in kava can pass into human milk [68]. Until more is known, recommend against the use of kava in those who are pregnant or trying to become pregnant, as well as those who are breastfeeding.

Ashwagandha

This shrub (*Withania somniferia*) is native to parts of India, the Middle East, and Africa and has a long history of use in traditional medicine. It has also gained widespread popularity as an adaptogen, which is a class of substances that are believed to increase the body's ability to adapt to and avoid damage from various factors, including physical, environmental, and emotional stress [94]. As a result, ashwagandha has become popular for the management of stress and anxiety.

Some small clinical studies suggest that taking ashwagandha daily for six to eight weeks can reduce the symptoms of anxiety in adults with GAD when compared with placebo. The extracts used in these studies provided 300–600 mg ashwagandha, standardized to contain 5% of a specific class of chemicals called withanolides. As a result, the international guideline from WFSBP and CANMAT provisionally recommends the use of these extracts as either monotherapy or adjunctive therapy in patients with GAD [54]. In patients with anxiety but without GAD, on the other hand, small clinical studies of ashwagandha have shown conflicting results [95; 96].

There is a growing body of research evaluating ashwagandha for the management of chronic stress, with a number of small clinical studies suggesting that taking ashwagandha daily for 8 to 12 weeks can improve stress when compared with placebo [97].

Ashwagandha appears to be generally well tolerated when taken by mouth. High doses have been reported to cause mild gastrointestinal upset, diarrhea, nausea, and vomiting. It has also been reported to cause drowsiness and should initially be used with caution with other medications that can cause CNS depression. Some research suggests that ashwagandha may increase thyroid hormone levels; use with caution in people with thyroid disorders [98].

Pregnancy and Breastfeeding

Ashwagandha extracts may be unsafe for use during pregnancy. Although there has been little to no research conducted on the safety of taking ashwagandha during pregnancy, there is a hypothetical concern that it has miscarriage-causing (abortifacient) activity [68].

There is no reliable evidence available regarding the safety of ashwagandha while breastfeeding. It is not known whether ashwagandha transfers into human milk; there is also no research available on the safety of ashwagandha in newborns. Until more is known, caution patients to avoid ashwagandha while breastfeeding.

Cannabidiol (CBD)

CBD is one of more than 100 cannabinoids found in the *Cannabis sativa* plant. Due to the passage of the 2018 Farm Bill, which legalized the use of CBD from certain types of *Cannabis* plants (known as hemp), this substance has exploded in popularity for a wide variety of indications, including anxiety.

Despite its widespread availability, research on the use of CBD for any non-prescription purpose remains limited. Although some very small studies have evaluated CBD for general anxiety, these studies have not used a placebo control group, limiting the validity of any findings [99; 100].

One small study evaluating CBD 300 mg daily for one month for social anxiety disorder found modest benefit when compared with placebo [101]. However, small studies evaluating single doses or limited doses of CBD for social anxiety or public speaking-associated anxiety have found no benefit when compared with placebo [102; 103].

CBD seems to be generally safe when taken by mouth at doses of 200–1,200 mg daily for up to 13 weeks. Prescription CBD, which is taken in much higher doses of 20 mg/kg daily, has been reported to cause somnolence and diarrhea. These high doses have also been associated with increased liver enzymes, for which the risk is especially high when used in conjunction with valproic acid [104].

Product quality is a particular concern with CBD supplements, which have been found to contain far different quantities of CBD than those listed on the label. CBD supplements have also been found to contain other ingredients which are not listed on the label, including the psychoactive cannabinoid tetrahydrocannabinol (THC). In an analysis of 84 commercially available CBD products in the United States, only 31% of products were accurately labeled and 21% of products contained unlabeled THC [105]. Another assessment of 14 products commercially available in Europe and 25 products available in the United States found that up to 90% of the products were inaccurately labeled and that up to 86% of products contained detectable quantities of THC [106].

Pregnancy and Breastfeeding

What is the main concern with using CBD supplements during pregnancy?

The U.S. Food and Drug Administration (FDA) strongly recommends against the use of CBD during pregnancy [107]. Research on the use of CBD during pregnancy is currently limited to animal studies. However, these studies have detected an increased risk of developmental toxicity [104]. Additionally, due to the widespread issues with product quality, there is a risk that taking a CBD supplement may expose the fetus to THC. THC can cause serious adverse effects to the fetus, including low birth weight, birth defects, placental abruption, and an increased risk for requiring intensive care after birth. It can also cause long-term developmental issues [108].

For similar reasons, CBD products should be avoided while breastfeeding. THC passes into human milk and can cause serious adverse effects for the newborn [109].

VITAMIN AND MINERAL SUPPLEMENTS

In a separate segment of the dietary supplement market, there has been quite a bit of interest in recent years related to the use of various vitamins and minerals for the treatment or prevention of depression and anxiety. In some cases, this supplementation is intended to treat a known deficiency. In other cases, these supplements are used regardless of whether the patient is deficient.

VITAMINS

B Vitamins

Various members of this water-soluble vitamin family have garnered attention for use in the treatment of certain mental health issues, including thiamine (B1), pyridoxine (B6), folic acid (B9), and cyanocobalamin (B12). Observational research suggests that higher dietary consumption of these vitamins is associated with a lower risk of developing depression when compared with lower consumption. However, in most cases, it is unclear whether taking supplements containing any of these B vitamins offers benefit [110].

Of these vitamins, folic acid has the most convincing evidence of benefit for the treatment or prevention of depression. Although folic acid alone does not seem to be beneficial in the management of depression, clinical studies have found that taking folic acid 0.2–15 mg daily in conjunction with a conventional antidepressant can improve treatment response in adults with MDD when compared with taking the antidepressant alone [111].

Additionally, some observational research has found that taking a folic acid supplement is associated with a reduced risk for suicidal events when compared with patients that were not taking a folic acid supplement. However, only 12% of the patients within that study were diagnosed with depression, and the cohort included people who were taking folic acid either alone or as part of a multivitamin, in doses of 0.4–5 mg daily. It is unclear if patients with a folic acid deficiency may be more likely to benefit [112].

Folic acid is available in multiple forms, all of which provide different quantities of folate. As a result, recommended daily intakes for folate are expressed in dietary folate equivalents (DFEs). Folic acid, which is found in supplements, is about 85% bioavailable; folate in foods, on the other hand, is about 50% bioavailable. Thus, 1 mcg DFE is equivalent to 1 mcg dietary folate or 0.6 mcg folic acid [113].

Although most supplements contain synthetic folic acid, a growing number of supplements contain an alternative form of folate, L-methylfolate. Some manufacturers claim that L-methylfolate has a higher bioavailability than folic acid, although blood levels appear comparable between people who take both supplements. Some manufacturers also claim that L-methylfolate is beneficial for people who lack the enzymes necessary to convert folic acid to its active form; however, there is currently no reliable evidence to support this claim [114].

Vitamin D

What is the recommended daily dose of vitamin D for adults with MDD according to the WFSBP and CANMAT guideline?

Vitamin D is a fat-soluble vitamin has been extensively evaluated for the prevention of depression, with disappointing results. A variety of studies have found that taking vitamin D 2,000 IU daily for two to five years does not reduce the risk of depression or depressive symptoms when compared with placebo [115; 116].

Vitamin D has also been evaluated for the treatment of depression, with conflicting findings. Some clinical studies have found that vitamin D does not improve depressive symptoms, whereas others have found that it may modestly improve symptoms. It is unclear whether the presence or absence of a vitamin D deficiency is responsible for these conflicting findings [117; 118; 119; 120].

Due to the limited evidence of benefit and lack of clarity as to the impact of vitamin D deficiency, the international guideline from WFSBP and CANMAT provides only a weak recommendation for the use of vitamin D, in doses of 1,500–4,000 IU daily, as an adjunct or monotherapy for adults with MDD. This recommendation also focuses on people who are likely to have a vitamin D deficiency due to inadequate sun exposure and notes that the benefits may be greater in winter months [54].

Miscellaneous Vitamins

Some limited observational research has evaluated the potential role of various other vitamins in the prevention of depression and depressive symptoms. For example, observational research suggests that higher dietary intake of vitamin E and vitamin A (individually) is associated with a reduced risk of depression when compared with lower intake. However, higher intake of vitamin E is not associated with a reduced risk of anxiety [121; 122]. Similarly, a higher dietary intake of vitamin K is associated with reduced odds of depressive symptoms when compared with lower intakes [123].

A secondary analysis of a large clinical study has also evaluated the role of vitamin C in the prevention of depression. This study, which enrolled pre- and peri-menopausal adults, identified an inverse association between vitamin C intake and depressive symptoms, which persisted regardless of age, physical activity, antidepressant use, and various other factors [124].

It is important to note that these studies are observational in nature and assess only the dietary intake of each of these vitamins. These findings do not indicate whether a supplement would be beneficial in any of these patients, nor do they assess the relevance of a vitamin deficiency. In general, patients should be counseled to consume a well-rounded, nutritious diet that provides adequate quantities of all macro- and micronutrients.

MINERALS

Magnesium

Magnesium plays an important role in a large number of cellular functions in the body and is a natural component of the diet. In recent years, it has gained popularity for the prevention and treatment of anxiety and depression.

Surprisingly, however, there is currently no reliable evidence exploring the benefits of magnesium supplements for general anxiety. As for depression, the available research is limited to lower quality studies which have yielded mostly negative findings, suggesting little to no benefit with magnesium supplements in depression [125; 126].

Zinc

This mineral has also been evaluated for use in depression, with more promising (although preliminary) findings. Observational research suggests that higher dietary intake of zinc is associated with a lower rate of depression than lower intake [127]. Additionally, some small, lower-quality studies show that taking an oral zinc supplement at doses of 7–25 mg daily for up to 12 weeks in conjunction with a conventional antidepressant may increase the benefits of the antidepressant [128].

ENDOGENOUS CHEMICAL SUPPLEMENTS

Supplements that contain chemicals which are naturally found in the human body are also commonly discussed as potential options for the management of anxiety and depression.

There has been little to no research on the safety of taking any of these endogenous chemicals in supplement form during pregnancy or while breastfeeding. Although these substances do occur naturally in the human body, the large doses found in supplements may have unanticipated effects on an unborn baby or breastfeeding newborn. Until more is known, recommend against their use in people who are pregnant or planning to become pregnant, as well as people who are breastfeeding.

5-HYDROXYTRYPTOPHAN (5-HTP)

5-hydroxytryptophan (5-HTP) is produced in the body from the essential amino acid L-tryptophan and is then converted to serotonin. Dietary supplements contain a form of 5-HTP that is derived from a shrub called *Griffonia simplicifolia*. Clinical research indicates that taking this supplement at a dose of 150–800 mg daily for up to eight weeks can improve some

symptoms of depression. Some small studies suggest that it may have similar efficacy as some conventional antidepressants [129].

This supplement is generally well tolerated when taken by mouth, although it can cause gastrointestinal upset, abdominal pain, dizziness, drowsiness, headache, and insomnia. These adverse effects appear to be dose-dependent. Due to its serotonergic activity, 5-HTP should be used with caution in combination with other serotonergic drugs, since it may increase the risk for serotonergic side effects and serotonin syndrome [130].

SAMe

S-adenosyl-L-methionine (SAMe) is naturally formed in the body, where it serves a wide variety of functions. Clinical research shows that taking SAMe 800–1,600 mg daily in divided doses for one to three months can improve symptoms of depression when compared with placebo and may be equally effective to tricyclic antidepressants [131]. Additionally, one clinical trial shows that adding SAMe 400–800 mg twice daily to a conventional antidepressant can modestly improve remission rates when compared with taking the antidepressant alone [132].

SAMe is generally well-tolerated when taken by mouth, although it has been reported to cause gastrointestinal upset, constipation, diarrhea, dizziness, dry mouth, headache, insomnia, sweating, and nervousness. It is not clear if these adverse effects are dose-dependent or how often they occur when compared with placebo. As with 5-HTP, SAMe should be used with caution in patients taking serotonergic medications.

ACETYL-L-CARNITINE

Acetyl-L-carnitine is an ester of L-carnitine, both of which occur naturally in the body, particularly in the brain, liver, and kidneys. Clinical research shows that taking acetyl-L-carnitine supplements 1-4 grams daily for up to six months may moderately reduce depressive symptoms when compared with placebo. Most of these studies have included elderly adults [133].

This supplement is generally well-tolerated and has been reported to cause agitation, dry mouth, headache, insomnia, and reduced appetite. Some people have reported a fishy odor in the urine, breath, and sweat after taking L-carnitine, to which acetyl-L-carnitine is related [134].

GABA

Gamma-aminobutyric acid (GABA) is a well-known neurotransmitter that plays a role in a variety of bodily functions. The GABA receptors in the human body are the target of prescription benzodiazepines. The known sedative and anxiolytic effects of GABA agonists has led to interest in the use of GABA supplements for the management of anxiety and/or depression. However, clinical research on this use is lacking. Additionally, it is unclear whether GABA crosses the blood-brain barrier after oral intake, which would be necessary to induce any relevant effects [135].

SUMMARY

The prevalence of mental illness continues to increase across the world and in North America, with depression and anxiety representing the most common forms of mental illness. Although the symptoms of depression and anxiety experienced by many people may not be regarded as severe, even mild to moderate symptoms can be debilitating and difficult to manage.

Many patients may be interested in pursuing alternative therapies for the management of their mild or moderate symptoms. These alternative therapies can span a wide range of options, from exercise to acupuncture, and from herbs to vitamins. They may be used in conjunction with established, evidence-based treatments or on their own.

For non-pharmacologic modalities (those that do not involve taking an oral dietary supplement), the major concerns relate to ensuring safe use, which is often guided by a trained or licensed practitioner. Some of these options, such as exercise, yoga, and mindfulness, have relatively strong evidence of efficacy and should be considered as a primary or adjunctive treatment option for most patients.

When discussing dietary supplements, on the other hand, the major concerns relate to ensuring both efficacy and safety. Although some supplements are widely discussed for these indications, the evidence does not necessarily support their use. Additionally, many of these products may carry side effects and the risk for serious drug interactions, and should always be evaluated on an individual basis, with consideration for each person's unique health situation. If a dietary supplement is recommended for a patient (or chosen by a patient), special care should be taken to ensure that a high-quality supplement is selected. This will increase the risk of efficacy by ensuring that the active chemicals are present in the right quantities and that the product is not adulterated. It will also reduce the risk of safety concerns that can be caused by unexpectedly high doses or the presence of contaminants.

Understanding the reasons that these products are used, as well as their actual risks and benefits, will allow healthcare professionals to help patients sift through the hype, avoid dangerous products, and select treatment options that are most likely to offer benefit.

Customer Information and Evaluation are located on pages 103–104.

Clinical Management of Atrial Fibrillation

Includes 6 Advanced Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, physicians, physician assistants, and other healthcare professionals working in an adult healthcare setting, where they are likely to encounter patients who are (or should be) receiving medical intervention for control of atrial fibrillation.

Course Objective
The purpose of this course is to provide a basic review of current treatment options for the management of atrial fibrillation and indications for use, risks, and criteria for evaluating the treatment's efficacy.

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

1. Describe cardiac conduction and the components of an ECG waveform.
2. Use your knowledge of the pathophysiology of atrial fibrillation, including key defining characteristics, to differentiate it from other arrhythmias and predict impact on normal functioning.
3. Outline common cardiac and noncardiac causes of atrial fibrillation.
4. List key clinical data, including subjective symptoms, past medical history, physical assessment findings, and diagnostic/laboratory tests, important to obtain when assessing a patient with atrial fibrillation.
5. Identify key components that should be considered in the development of the medical plan of care, including the issue of generic drug substitution.
6. Compare and contrast antiarrhythmic medications appropriate to use for acute and chronic rate control for patients with atrial fibrillation.
7. Outline the use of pharmacologic therapy in the restoration of normal sinus rhythm, including indications for use and procedure for administration.
8. Describe electrical cardioversion, including indications and pre- and postprocedure care.
9. Discuss antiarrhythmic medications that may be used to maintain normal sinus rhythm in a patient following successful spontaneous, electrical, or pharmacologic cardioversion.
10. Select appropriate pharmacologic measures that may be used to reduce risk of thromboembolic events in persons with atrial fibrillation.
11. Discuss the use of radiofrequency ablation of the atrioventricular (AV) node in the clinical management of atrial fibrillation.
12. Describe the causes and recommended management of atrial fibrillation in adult patients following coronary artery bypass graft surgery and in patients with Wolff-Parkinson-White syndrome.
13. Using simulated case study data, develop a best practice strategy for the clinical management of atrial fibrillation.

Faculty
Karen Majorowicz, RN, is currently employed in the Cardiac Intermediate Care Unit at Shands Healthcare at the University of Florida, Gainesville. She received her Master's in Medical-Surgical Nursing in 1978 from the University of Maryland. Karen has created numerous instructional manuals on Medicare and has conducted educational programs on cardiovascular assessment.

Faculty Disclosure
Contributing faculty, Karen Majorowicz, RN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Sarah Campbell

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

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INTRODUCTION

Atrial fibrillation is one of the most commonly sustained arrhythmias seen in medical practice. It is estimated that 12.1 million people in the United States will have atrial fibrillation in 2030 [1; 2]. Consider the following statistics [3; 4; 5; 6; 7; 8]:

- Increasing age is a major risk factor for the development of atrial fibrillation. As the American population continues to age, increasing numbers of elderly individuals will require medical care for the management of atrial fibrillation.
- Atrial fibrillation is associated with increased morbidity and mortality, especially in the elderly population.
- Elderly individuals who develop atrial fibrillation and also have a history of congestive heart failure, myocardial infarction, and/or left ventricular dysfunction are at increased risk for poor outcomes and complications.
- Atrial fibrillation is a major independent risk factor for thromboembolic cerebrovascular accidents (CVAs). CVAs may result in death or serious disability.
- Hospital stays for management of atrial fibrillation are longer than hospital stays for the treatment of other arrhythmias.

The clinical management of atrial fibrillation presents a complex challenge to the clinician. A wide variety of pharmacologic and nonpharmacologic therapies is available for the treatment of atrial fibrillation. Therapy should be individualized to each specific patient. Carefully assess the patient's status and past medical history with an emphasis on the patient's specific pattern of atrial fibrillation, including its onset, duration, and precipitating factors, the symptoms experienced during

atrial fibrillation, the impact of the arrhythmia on the patient's activities of daily living, risk factors for atrial fibrillation, findings from laboratory and diagnostic tests, and history of cardiovascular disease.

It is important to match patient assessment data with an appropriate medical management plan. Common goals seen in the management of atrial fibrillation include rate control, restoration of normal sinus rhythm, maintenance of normal sinus rhythm, and prevention of thromboembolic complications.

The selection of appropriate pharmacologic and nonpharmacologic therapies for the patient should be based on the identified goal(s) and patient assessment data. A wide range of antiarrhythmic medications is available with varying effects on the electrical conduction system in the heart. Some are contraindicated in the presence of concurrent illnesses, such as hypertension and asthma. Nonpharmacologic therapies include direct current (electrical) cardioversion, radiofrequency ablation, and atrial or dual chamber pacemakers.

Regular follow-up is required to monitor the effectiveness of the therapy in meeting the identified medical goals. Evaluation criteria include a rate that is controlled within desired parameters, increased ability to perform activities of daily living, reduction in severity of attacks of atrial fibrillation, absence of undesired side effects of prescribed antiarrhythmic medications, and absence of any thromboembolic complications.

A BRIEF REVIEW OF NORMAL ELECTRICAL CONDUCTION

In the normal heart, the heartbeat is initiated by the sinoatrial (SA) node. From the SA node, the electrical impulse travels through both the right and left atria, causing depolarization of the atria. Atrial depolarization is followed by atrial contraction and atrial repolarization. The electrical impulse travels from the atria to the atrioventricular (AV) node located in the inferior wall of the right atrium. The speed of conduction slows in the AV node to allow time for the atria to depolarize, contract, and complete ventricular filling. From the AV node, the electrical impulse travels through the bundle of His located in the septum of the heart. The bundle of His divides into the right and left bundle branches. These branches divide further into the smaller fibers of the Purkinje system. Electrical conduction through the His-Purkinje system is rapid, causing rapid depolarization of both the right and left ventricles. Depolarization of the ventricular cells spreads from the apex of each ventricle to the base and moves from the endocardium to the epicardium. Ventricular depolarization is followed by ventricular contraction and ventricular repolarization [9; 10; 11].

CELLULAR EVENTS IN NORMAL CARDIAC CONDUCTION (THE ACTION POTENTIAL)

When an electrical impulse stimulates a cardiac cell, a series of events is initiated that causes the cell to depolarize and repolarize. This generates an action potential that allows the electrical impulse to propagate, ultimately resulting in the contraction of the cells of the myocardium. The basic events that occur during the formation of the action potential are as follows:

- When an electrical impulse stimulates a cardiac cell, the cell depolarizes. Positively charged sodium ions from the extracellular space flood rapidly into the intracellular space. This increases the total number of positively charged ions in the intracellular space, and the charge in the intracellular space becomes less negative. The potential or voltage in the cell increases. This is phase 0 of the development of the action potential.
- The flood of sodium ions into the intracellular space stops very quickly. It is followed by a brief and incomplete period of repolarization. This period is mediated by a temporary movement of potassium ions from the intracellular to the extracellular space. This brief period of repolarization is referred to as phase 1 of the action potential.
- Phase 2 of the action potential is characterized by a balance of inward and outward movement of ions. Calcium ions move slowly through select channels into the intracellular space while potassium ions move out through multiple channels into the extracellular space. This initiates a slow repolarization and creates a plateau in the action potential. Cardiac contraction is mediated by phase 2.
- In phase 3, the calcium channels close. The process of repolarization is accelerated.
- In phase 4, electrical diastole occurs. Except for the SA node, the heart rests. The SA node begins the process of initiating the next electrical impulse.

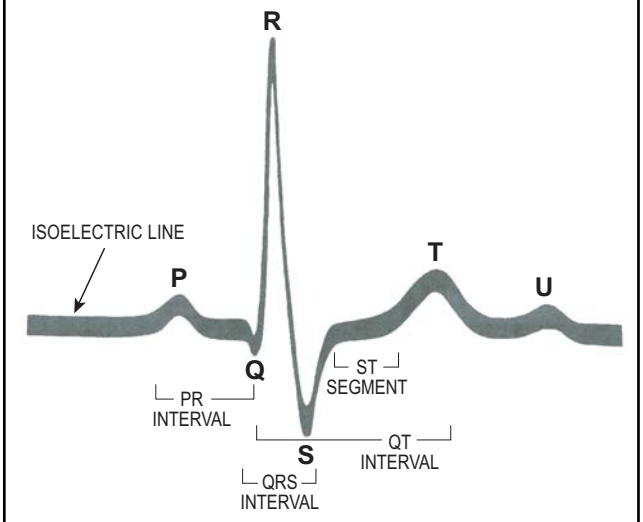
After the myocardial cell has depolarized, there is a period of time during which the cell cannot generate an action potential in response to another electrical impulse; this is referred to as the "absolute refractory period." As the cell continues to repolarize, an "effective refractory period" occurs in which the cell can transiently depolarize in response to an electrical impulse but generally will not develop enough of an action potential to propagate the impulse to surrounding cells. As repolarization nears completion, the cell is said to be in a "relative refractory period." In this period, a strong electrical stimulus can trigger the cell to depolarize and create another action potential [12; 13; 14].

A REVIEW OF ELECTROCARDIOGRAM WAVEFORM

The electrical events that occur in the heart are reflected in the electrocardiogram (ECG) waveform. The components of a normal beat are (***Figure 1***)**:**

- The **P wave** represents atrial depolarization.

COMPONENTS OF A NORMAL HEARTBEAT



Source: Created by Author *Figure 1*

- The **PR interval** represents the amount of time the electrical impulse takes to travel from the SA node through the AV node. The normal PR interval is 0.12 to 0.20 seconds.
- The **QRS interval** represents the amount of time it takes the ventricles to depolarize. In normal conduction, ventricular depolarization occurs rapidly. This rapid conduction is reflected in a narrow QRS interval. The normal duration of a QRS interval is <0.10 seconds.
- The **T wave** represents ventricular repolarization.
- The **QT interval** represents the amount of time that it takes the ventricles to depolarize and repolarize; it is measured from the beginning of ventricular depolarization (i.e., the start of the QRS interval) to the end of repolarization (i.e., the end of the T wave). During the early part of the QT interval, the ventricles are completely refractory and unable to respond to another electrical impulse. During the latter part of the interval, the ventricles are only partially refractory and may respond to some impulses but not to others. The normal QT interval is <0.44 seconds.

ABNORMAL ECG WAVEFORM

What does a prolonged QT interval indicate?

When changes occur in the normal cardiac cycle, the normal ECG waveform is altered to reflect them. For example, prolonged repolarization is reflected in a prolonged QT interval. A slowing of conduction from the SA node through the AV node may be reflected in a prolonged PR interval. Abnormal conduction of the electrical impulse through the ventricles results in a QRS interval that is wider than usual or bizarre in shape. Careful analysis of the changes in a patient's ECG can provide valuable information in the diagnosis and treatment of the arrhythmia [6; 15].

ANTIARRHYTHMIC DRUGS AND CARDIAC ELECTROPHYSIOLOGY

Antiarrhythmic medications interrupt or prevent arrhythmias by altering electrical conduction in the heart. Some antiarrhythmic medications have a single mechanism of action, but many have multiple mechanisms. In general, antiarrhythmic medications may act by:

- Prolonging the normal development of the action potential
- Inhibiting or slowing the movement of sodium or calcium ions into the intracellular space
- Altering the movement of potassium ions out of the intracellular space
- Altering the speed at which the impulse is conducted through the AV node
- Prolonging ventricular repolarization and the refractory period

Because antiarrhythmic medications impact specific events in cardiac conduction, they run the risk of creating new arrhythmias or worsening existing arrhythmias. Arrhythmias caused by the administration of an antiarrhythmic medication are referred to as proarrhythmias. Proarrhythmias can range from mild to severe. Serious proarrhythmias include ventricular tachycardia, torsades de pointes, and ventricular fibrillation. We will look at the actions and properties of specific antiarrhythmic agents in more detail in later sections.

ATRIAL FIBRILLATION

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Atrial fibrillation is an arrhythmia characterized by rapid, disorganized electrical activity in the atria. Instead of the SA node depolarizing to initiate a heartbeat, ectopic (or abnormal) areas in the atria depolarize rapidly and irregularly, resulting in chaotic atrial activity. Because of the chaotic electrical activity, normal atrial depolarization does not occur. Patchy areas of the atria may attempt to contract, giving the atria a "quivering" appearance, but the unified contraction of both the right and left atria (needed to complete active filling of the ventricles) cannot occur. One theory suggests that the mechanism underlying atrial fibrillation is the development of multiple impulses or "wavelets" in the atria. These impulses wander around and through the atria, getting caught in a cycle that continuously circulates in the atria, triggering small, erratic areas of depolarization. In atrial fibrillation, atrial impulses may be generated at a rate as high as 300 impulses per minute. Atrial impulses bombard the AV node. However, because of its inherent characteristics, the AV node tends to limit ventricular response to the atrial stimulation. Because the AV node is less

excitable than the nearby atrial or ventricular cells, it conducts impulses more slowly, and its refractory period (when it cannot respond to another electrical stimulus) is relatively prolonged. Recently, there has been a re-assessment of the multiple wavelet hypothesis, demonstrating that the substrates of atrial fibrillation at the clinical level are focal trigger sites of action potentials rather than multiple micro re-entry sites [16].

Conduction in the AV node is also "decremental." This means that, as the impulse is conducted through the AV node, the action potentials that are generated have less and less ability to stimulate new action potentials. In atrial fibrillation, some atrial impulses are "blocked" or lost in the AV node because the action potentials that are generated are insufficient to stimulate further electrical activity.

Finally, the AV node has the property of concealed conduction. An atrial impulse may enter the AV node, stimulate depolarization of initial cells in the node, and be blocked from further conduction. Although the impulse is not sufficient to generate ventricular depolarization, it depolarizes enough cells in the AV node to create a refractory period. Subsequent impulses entering the AV node immediately following that impulse will be blocked. The AV node will be unable to accept or respond to them until repolarization has occurred. Due to the combination of slowed, decremental, and concealed conduction, the AV node can limit ventricular rate in atrial fibrillation to less than 200 beats per minute (bpm). It is important to note that these properties of the AV node create a relationship between atrial and ventricular rates in atrial fibrillation: when the atrial rate increases, the ventricular rate decreases. However, when the atrial rate slows, the ventricular rate may actually increase. At a slower rate, more atrial impulses are likely to stimulate the AV node at a time when the impulse can be conducted through the AV node to the ventricles [17; 18; 19].

Clinicians who work with patients who have atrial fibrillation are aware that the longer atrial fibrillation persists, the harder it becomes to terminate the arrhythmia and maintain normal sinus rhythm. Research suggests that atrial fibrillation triggers a process known as "atrial remodeling." In atrial remodeling, electrical, histologic, anatomic, and autonomic nervous system changes occur in the atria that facilitate the continuation of atrial fibrillation and impair the heart's ability to return to normal sinus rhythm [20; 21; 22]. Changes that have been hypothesized include:

- Gradual enlargement of the atria through dilation and stretching. Atrial hypertrophy may increase the vulnerability of the atria to abnormal electrical impulses and may shorten the atrial refractory period. A shortened refractory period facilitates development of the continuous loop or cycle of impulses (also called a re-entry mechanism) that sustains atrial fibrillation.
- Alteration in the normal flow of one or more ions (especially calcium ions) across the cardiac cell membrane, leading to generation of a cellular substrate that facilitates the onset of arrhythmia.
- Progressive shortening of the effective refractory period in the atria.
- Adrenergic activation may contribute to the initiation of ectopic activity

Additional factors have emerged to complement the arrhythmogenic substrate that shed light on the perpetuation of arrhythmia. These include inflammation, fibrosis, altered gap junctions, and genetic predisposition, which are yet to be fully characterized across the different stages of atrial fibrillation [23; 24; 25; 26; 27].

KEY DEFINING CHARACTERISTICS OF ATRIAL FIBRILLATION

What is a key defining characteristic of atrial fibrillation?

The two key defining characteristics of atrial fibrillation are (***Figure 2)*** [5; 17; 19]:

- Total absence of normal sinus P waves. The absence of P waves indicates that the heartbeat was not initiated in the SA node, or normal pacemaker, of the heart. The P waves are replaced by fibrillatory (fib) waves. These fib waves may be so fine that they are indiscernible or barely discernible; or, they may be very coarse and more clearly seen on the ECG tracing.
- An irregularly irregular ventricular response when conduction through the AV node is normal.

Additional characteristics associated with atrial fibrillation include:

- A variable ventricular rate. The rate may range from less than 60 bpm to as high as 160 bpm.
- A QRS interval that is usually (but not always) normal in configuration and duration.

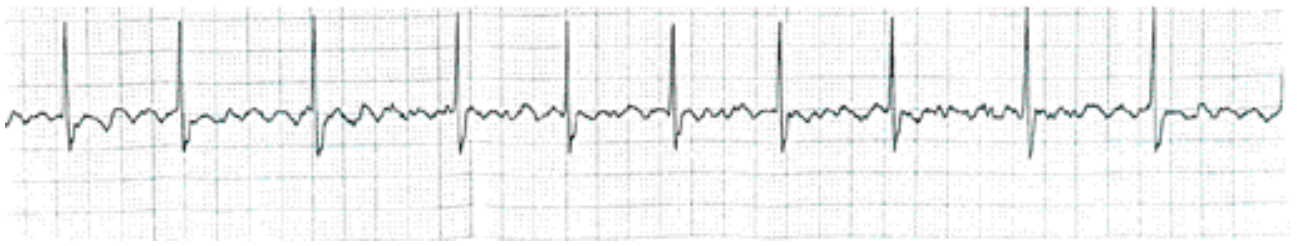
TYPES OF ATRIAL FIBRILLATION

The types of atrial fibrillation may be described in terms of onset or duration of rate. Descriptions based on rate include the following [17]:

- Rapid ventricular response: atrial fibrillation with a ventricular rate greater than 120 bpm.
- Controlled ventricular response: atrial fibrillation with a ventricular rate between 60 bpm and 110 bpm.
- Slow ventricular response: atrial fibrillation with a ventricular rate of less than 60 bpm.

Descriptions based on onset and duration have not been standardized throughout medical literature. Terms such as acute onset, chronic, and others have been used. In its published practice guidelines, the American College of Cardiology, the American Heart Association, and the European Society for Cardiology (ACC/AHA/ESC) Task Force recommends the following simplified terminology for episodes of atrial fibrillation that last more than 30 seconds and are not caused by another, reversible medical cause [28]:

RHYTHM STRIP OF ATRIAL FIBRILLATION



Source: Created by Author *Figure 2*

- First-detected: the first diagnosed or known episode of atrial fibrillation that a patient experiences. A first-detected episode may be symptomatic or asymptomatic; it may or may not be self-limited. It may or may not actually be the patient's first episode of atrial fibrillation; however, it is the first episode that is formally identified as atrial fibrillation.
- Paroxysmal: recurrent atrial fibrillation that spontaneously terminates or terminates with intervention within seven days of onset, and episodes may recur with variable frequency.
- Persistent: recurrent atrial fibrillation that is sustained beyond seven days; it may include atrial fibrillation that is terminated by electrical cardioversion or pharmacologic therapy. This category also includes cases of long-standing atrial fibrillation (e.g., longer than one year) that usually lead to permanent atrial fibrillation.
- Permanent: paroxysmal or persistent atrial fibrillation in which pharmacologic and/or electrical cardioversion is not attempted or is not successful.
- Nonvalvular: atrial fibrillation in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

DIFFERENTIATING ATRIAL FIBRILLATION FROM OTHER SUPRAVENTRICULAR TACHYCARDIAS

Atrial fibrillation is one of several arrhythmias in which the electrical impulse is initiated at or above the AV node. These arrhythmias are usually referred to using the umbrella term, supraventricular tachycardias (SVT). Other common SVTs include atrial flutter and AV nodal re-entrant tachycardia.

In atrial flutter, the heartbeat originates in the atria somewhere outside the SA node. More organized than fib waves, atrial flutter (F) waves have a characteristic sawtooth appearance. Early studies designated atrial flutter with rates between 240 and 340 bpm as "type I flutter," and this term has commonly been applied to typical atrial flutter. An electrocardiographic appearance of atrial flutter with a rate faster than 340 bpm was designated as "type II flutter;" the mechanisms for type II flutter remain undefined [28]. The atrial rate is typically 240 to 300 bpm, but conduction delays in the atrial circuit due to scars from prior ablation, surgery, or antiarrhythmic drugs can slow the rate to less than 150 bpm in some patients [28]. One or more flutter waves may be present before each QRS interval. Conduction through the AV node is often regular (i.e., every second or third or fourth flutter wave is conducted). The most common pattern is 2:1 conduction, which results in a ventricular rate of 150 bpm. Flutter waves do not result in organized contraction of the atria, but they may increase atrial oxygen demands by triggering "near contractions." Atrial flutter is generally differentiated from atrial fibrillation by the presence of flutter waves that are more defined than fib waves and occur at regular intervals and regular ventricular rhythm [29]. The relationship between atrial fibrillation and atrial flutter may explain why 80% of patients who undergo radiofrequency catheter ablation of typical atrial flutter will have atrial fibrillation within the following five years [28].

In AV nodal re-entrant tachycardia, the ventricular rate falls between 150 and 250 bpm. Because of the abrupt onset and termination of the re-entrant SVT, the nonspecific term paroxysmal supraventricular tachycardia has been used to refer to these tachyarrhythmias. With improved knowledge of the electrophysiology of re-entrant SVT, greater specificity in nomenclature, based on the mechanisms of re-entry, has been possible [30]. With AV nodal re-entrant tachycardia, no evidence of atrial activity is present. The ventricular rhythm is regular. The arrhythmia has an abrupt onset and termination, with episodes lasting from seconds or minutes to days, and may occur in persons with no history of heart disease as well as in elderly persons with chronic heart disease. The arrhythmia may be differentiated from sinus tachycardia by rate; sinus tachycardia rarely exceeds a rate of 150 to 160 bpm in an adult at rest. It may also be differentiated from atrial fibrillation because the rhythm is regular. It may be differentiated from atrial flutter by rate; the usual rates associated with AV nodal re-entrant tachycardia are too slow for 1:1 (atrial to ventricular) conduction in atrial flutter and too fast for 2:1 conduction [17; 30].

Differential diagnosis of atrial fibrillation is based on ECG analysis combined with patient history, description of symptoms, current medications, and past medical history [31]. At a

controlled rate, atrial fibrillation is usually readily recognizable because of the absence of sinus P waves and the irregularly irregular rhythm. However, at higher rates, identification of these key characteristics may become more difficult. The physician may choose to facilitate diagnosis through the use of intravenous adenosine. Adenosine is a medication that may be administered intravenously to aid in the differential diagnosis of a narrow complex SVT [32]. Adenosine should not be administered in the presence of a wide QRS complex tachyarrhythmia, nor should it be administered if the arrhythmia's underlying mechanism has already been identified [31]. Adenosine has an immediate onset of action and an extremely short half-life (i.e., <10 seconds) [33]. Care should be taken to administer the medication rapidly enough to ensure that the medication reaches the systemic circulation before its half-life expires. Due to its extremely short half-life, adenosine is not effective for pharmacologic cardioversion; as soon as the effects wear off, the original arrhythmia resumes. Adenosine acts by interrupting re-entry pathways and slowing conduction through the AV node; it slows the ventricular rate to permit analysis and identification of the exact arrhythmia. Side effects include bradycardia, a brief period of asystole that does not exceed 15 seconds, and a sense of flushing and lightheadedness. It is a potent vasodilator and may cause hypotension. The side effects may be uncomfortable for the patient but are usually short and self-limiting [12; 14; 19; 34]. In 2013, the U.S. Food and Drug Administration (FDA) issued a warning of a rare but serious risk of myocardial infarction and death with the use of adenosine [35]. Adenosine should be avoided in patients with unstable angina or cardiovascular instability. When administering adenosine, follow these tips [12; 14; 19; 33; 36]:

- Make sure that the patient has a good IV access.
- Administer adenosine undiluted through a proximal IV access.
- Administer an initial dose of 6 mg over one to two seconds. Follow the medication quickly with a rapid normal saline flush to make sure that the entire dose reaches systemic circulation. Remember that the rapid administration rate is vital for effectiveness. If adenosine is administered too slowly, it may have the adverse effect of further increasing heart rate.
- Continuously monitor ECG and heart rate before, during, and after administration. Record a continuous strip during administration to assess the arrhythmia when the rate slows or the arrhythmia breaks and resumes.
- After one to two minutes, if the initial dose is ineffective, a second dose of 12 mg may be given as a rapid one- to two-second bolus. The second dose should also be followed with a rapid saline flush.
- Note that a single dose should not exceed 12 mg.
- If the second dose is ineffective, another 12 mg dose may be given after several minutes, to a maximum of 18–24 mg.

EFFECTS OF ATRIAL FIBRILLATION ON SYSTEMIC FUNCTIONING

Atrial fibrillation causes a drop in cardiac output. Atrial contraction does not occur, thereby reducing ventricular filling during mechanical diastole. Loss of atrial contraction (or "atrial kick") may reduce cardiac output from 5% to 40%. Symptoms of decreased cardiac output may develop; how severe these symptoms are depends on multiple factors, including the person's age, overall health, and presence of structural heart disease. If atrial fibrillation occurs at a rapid ventricular rate, cardiac output is reduced further. Any tachycardia reduces ventricular filling time. When ventricular filling is already reduced due to the loss of atrial kick, further reduction in filling time from a rapid heart rate may greatly exacerbate signs of reduced cardiac output. Over time, atrial fibrillation with a rapid ventricular response may cause a tachycardia-induced cardiomyopathy. This cardiomyopathy may be reversible when the heart rate is controlled [17; 19]. Loss of atrial contraction also causes stasis of blood in the atria. Stasis of blood increases the risk of thrombus formation and can lead to the development of thromboembolic complications such as CVAs [17; 29].

CAUSES OF ATRIAL FIBRILLATION

Which cardiac problems are linked to the development of atrial fibrillation?

The causes of atrial fibrillation may be grouped into three major categories [5; 37]:

- Primary arrhythmia in the absence of structural heart disease or other precipitating causes
- Secondary arrhythmia associated with a range of cardiovascular diseases
- Secondary arrhythmia in the absence of heart disease but in the presence of a systemic problem that precipitates the arrhythmia

Historically, atrial fibrillation, as a primary arrhythmia, was thought to develop in isolation, with no known precipitating cause. Called "lone atrial fibrillation," this type of atrial fibrillation was defined as occurring in the presence of documented normal left ventricular function, typically in people 60 years of age or younger. It was characterized by a paroxysmal onset and termination and frequent recurrence. However, a Working Group of the American College of Cardiology suggests that the category of lone (idiopathic) atrial fibrillation is no longer mechanistically or clinically useful [2]. The Working Group posits several reasons for avoiding use of the term "lone atrial fibrillation," including [2]:

- Outdated terminology, as the term "lone atrial fibrillation" predates current understanding of the many disorders that may contribute to the initiation of atrial fibrillation
- Broad definition of and variation in what investigators have termed "lone atrial fibrillation," leading to confusion and diminished usefulness of the term

- Wide variation in the reported prevalence (0.2% to 68%) of lone atrial fibrillation
- No specificity in requirement for extensiveness and interval of baseline imaging to exclude heart disease
- Well-established heritability of atrial fibrillation not taken into account when classifying an individual as having lone atrial fibrillation
- Lack of unique pathophysiologic mechanisms attributed to lone atrial fibrillation

Instead, the term "paroxysmal atrial fibrillation" should be used.

As a secondary arrhythmia, atrial fibrillation may be caused by cardiac and noncardiac causes. Common cardiac causes include [37; 38; 39]:

- Hypertension
- Rheumatic heart disease
- Mitral valve disease (e.g., mitral stenosis, mitral valve prolapse, mitral valve annular calcification)
- Congestive cardiomyopathy/congestive heart failure
- Acute myocardial infarction
- Sick sinus syndrome
- Pericarditis
- Hypertrophic cardiomyopathy
- May occur following cardiac/coronary artery bypass graft (CABG) surgery

The persons at highest risk to develop atrial fibrillation are those with long-standing hypertension, valvular heart disease, left ventricular hypertrophy, depressed left ventricular function, and coronary artery disease. Atrial fibrillation associated with cardiovascular disease may initially have a paroxysmal onset; however, the arrhythmia can continue to progress to persistent or chronic atrial fibrillation. Noncardiac, systemic diseases may also cause atrial fibrillation. Diabetes mellitus is a major risk factor for the development of atrial fibrillation. Other noncardiac causes include [2; 37; 38; 39]:

- Hyperthyroidism
- Male sex
- Advancing age
- Obesity
- Obstructive sleep apnea
- Genetic factors
- Alcohol and drug use
- Noncardiac surgery
- Noncardiac diagnostic procedure
- Pulmonary conditions/hypoxemia caused by pulmonary conditions (e.g., pneumonia, chronic obstructive pulmonary disease [COPD])
- Pulmonary embolus
- Over-the-counter use of some herbs, such as ephedra or ginseng

Emerging risk factors for atrial fibrillation include [2]:

- Subclinical atherosclerosis
- Chronic kidney disease
- Inflammation
- Increased height, birth weight
- Smoking
- Caffeine intake
- Ethnicity

Atrial fibrillation caused by noncardiac causes is frequently reversible once the underlying condition is resolved. In some instances, the atrial fibrillation may spontaneously convert to normal sinus rhythm. In other cases, the arrhythmia responds well to pharmacologic or electrical cardioversion to restore normal sinus rhythm [37].

ASSESSMENT OF THE PATIENT WITH ATRIAL FIBRILLATION

CLINICAL SIGNS AND SYMPTOMS

Patients in atrial fibrillation can present with symptoms that range from asymptomatic to severely incapacitating. Consider these patient examples:

- Patient K is 68 years of age. He is found to be in controlled atrial fibrillation during a routine physical before surgery for a total knee repair. He reports that he has experienced no symptoms and has never before been told that he has an irregular heartbeat or arrhythmia.
- Patient J is 45 years of age. She presents to the emergency department with atrial fibrillation with rapid ventricular response. An ECG shows her heart rate to be 160 bpm. She complains of feeling palpitations and slightly short of breath. She gives a history of intermittent episodes of palpitations and dyspnea that start and stop abruptly. She reports feeling frightened and out of control because her symptoms occur without warning and without obvious precipitating cause.
- Patient W is 76 years of age. He presents to the emergency department with severe dyspnea and dizziness. His blood pressure is hypotensive at 85/50 mm Hg. His respirations are 32 breaths per minute, and he has rales in both lung bases. His oxygen saturation on room air is 87%. His ECG shows atrial fibrillation with rapid ventricular response at a rate of 140–160 bpm. Patient W gives a history of coronary artery disease, previous myocardial infarction, and long-standing hypertension. He reports that his symptoms started about a week earlier and have gradually grown worse.

- Patient C is 58 years of age. She makes an appointment to see her physician and reports that she has been experiencing a "pounding heartbeat" intermittently for the last few days. She denies other symptoms but admits that she has been "more tired" than usual and that she has not "gotten as much done during the day as usual." Patient C has a history of mitral valve disease and a mitral valve replacement several years earlier. She also has mild (Class I/II) congestive heart failure. An ECG shows Patient C to be in atrial fibrillation at a relatively controlled rate of 80–90 bpm.

As the simulated patient examples show, symptoms of atrial fibrillation may include one or more of the following [37; 38; 39]:

- Palpitations
- Decreased blood pressure
- Fatigue
- Dizziness
- Shortness of breath
- Exacerbation of congestive heart failure
- Chest pain (angina)
- Syncope or near syncope
- Reduced exercise tolerance

Because of the unpredictable pattern of paroxysmal atrial fibrillation, patients with this type of atrial fibrillation may feel frightened and out of control. They may choose to curtail their usual level of activity in an attempt to prevent the arrhythmia from occurring. Depression and a sense of helplessness may occur.

Atrial high-rate episodes may be detected by a cardiac implantable electronic device. These cases should result in further evaluation to establish the diagnosis and guide treatment decisions [40].

PHYSICAL ASSESSMENT

What physical assessment finding is commonly associated with atrial fibrillation?

Physical assessment findings in atrial fibrillation may include the following [28; 37]:

- Rapid heart rate and irregularly irregular heart rhythm
- Irregular jugular venous pulsations
- Variable loudness of S1
- Variable pulse pressure. This results from the variable ventricular filling caused by the irregular conduction of atrial impulses through the AV node to the ventricles.
- A blood pressure that appears to vary widely. In atrial fibrillation with a controlled or slow ventricular response, there may be long pauses between some beats. When an electronic, noninvasive blood pressure device is used (or when the pressure is released too rapidly during manual auscultation of blood pressure), the systolic blood pressure reading may vary widely. Taking serial blood pressure readings and using an average of readings to estimate the patient's actual blood pressure may be needed.
- Hypotension, especially if cardiac output is significantly reduced
- Signs of congestive heart failure, such as decreased oxygen saturation and rales/crackles in lung fields
- Signs of poor peripheral perfusion, such as diminished peripheral pulses and impaired capillary filling

RELATED LABORATORY AND DIAGNOSTIC TESTS

Assessment of the patient with atrial fibrillation should include laboratory and diagnostic tests to identify any factors that may be contributing to the development of the arrhythmia as well as to rule out any noncardiac causes of the arrhythmia. Appropriate laboratory and diagnostic tests may include the following [10; 28; 37; 38; 39]:

- Serial cardiac enzymes to evaluate for possible acute myocardial infarction
- Arterial blood gases to assess for hypoxia
- Thyroid function studies to evaluate for hyperthyroidism
- Serum electrolytes, particularly imbalances in sodium, potassium, or magnesium
- Complete blood count to evaluate hematocrit and hemoglobin. Anemia may aggravate angina and signs of decreased cardiac output.
- Chest x-ray to evaluate for signs of congestive heart failure or underlying pulmonary disease/pneumonia
- Ultrasound studies (i.e., echocardiography [ECHO]) to identify valvular disease and evaluate left ventricular function
- Transesophageal ECHO (TEE) to evaluate for presence of clots in atria (most sensitive and specific technique for this purpose)
- 12-lead ECG to evaluate arrhythmia
- Continuous ambulatory ECG monitoring for patients who complain of symptoms associated with atrial fibrillation but are in normal rhythm upon presentation to healthcare system/emergency department
- Nuclear medicine cardiac studies

ASSESSING NON-ENGLISH-PROFICIENT PATIENTS

When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A systematic review of the literature has shown that the use of professional interpreters provides better clinical care than the use of "ad hoc" interpreters, with the

former improving the quality of care for patients with limited English language skills to a level equal to that for patients with no language barriers [41; 42]. Use of professional interpreters has been associated with improvements in communication (errors and comprehension), utilization, clinical outcomes, and satisfaction with care [41; 42]. Individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [43].

ESTABLISHING THE MEDICAL PLAN OF CARE

Effective clinical management of the patient with atrial fibrillation is based on evaluation of the patient's status, identification of appropriate medical goals, and determination of which specific therapies will be most effective in assisting the patient to reach the identified goal(s).

Until the 2000s, no consensus existed about what therapy or combination of therapies is the most effective in the clinical management of atrial fibrillation. In 2001, the ACC/AHA/ESC task force was formed to make recommendations for the management of persons with atrial fibrillation. Through a process of rigorous and expert evaluation of published data, the Task Force derived specific guidelines that have been published in the *American Journal of Cardiology* and are available on the AHA website [44]. The Task Force updated these guidelines in 2014 and again in 2019 [28; 40]. Effective clinical management of the person with atrial fibrillation begins with a thorough history and assessment of the patient to identify the patient's type and pattern of atrial fibrillation [28; 40]. Based on the patient's type and pattern of atrial fibrillation, symptoms, and underlying cause, appropriate medical goals should be identified. Specific therapies are then selected based on the identified goals [45].

PATIENT FACTORS

Adequate patient assessment should focus on the patient's symptoms, past medical history, any concurrent illnesses, and psychosocial issues. When assessing the patient, consider the following [46]:

- What type of atrial fibrillation does the patient have? Is this a first detected episode? Does the patient have recurrent paroxysmal, recurrent persistent, or permanent atrial fibrillation?
- How often does the patient experience atrial fibrillation? How long does it last? What precipitates it? What terminates it?
- What specific symptoms does the patient have?
- What impact do the symptoms have on the patient's ability to work? Take care of himself/herself? His/her activity tolerance? Does the patient feel frightened? Disabled by the symptoms?
- What impact is the atrial fibrillation having on any other medical problems that the patient has? Is it exacerbating his/her angina? Is it exacerbating his/her congestive heart failure?
- Does the patient have some type of cardiovascular disease? Coronary artery disease? Hypertension? Valvular heart disease? History of myocardial infarction? History of congestive heart failure?
- Does the patient have some other systemic problem that is precipitating the atrial fibrillation?
- Is the patient elderly?
- Has the patient been treated for atrial fibrillation? What treatment was prescribed? How effective was that treatment? Did the patient follow the prescribed treatment? Did it work? Did side effects develop?
- How will the patient pay for his/her medical care and medications? What medications and treatments will his/her insurance pay for?
- Is the patient able and willing to comply with prescribed medication therapy? Has the patient been compliant with medication therapy in the past?
- What is the patient's renal and hepatic function? Are these normal?

IDENTIFICATION OF APPROPRIATE MEDICAL GOALS

What is the initial goal for a patient with atrial fibrillation with a rapid ventricular response?

Based on a thorough evaluation of the patient's status and other factors, one or more medical goals should be identified. The initial goal for a patient who is hemodynamically unstable is the immediate restoration of normal sinus rhythm through electrical cardioversion. The initial goal for patients who present with atrial fibrillation with a rapid ventricular response is rate control. Once the patient's status has stabilized, long-term goals may be developed. When developing long-term goals, consider the following points [17; 28; 40; 45; 46; 47; 48; 49]:

- Use of antiarrhythmic therapy may not be necessary for persons with asymptomatic paroxysmal atrial fibrillation.
- Use of antiarrhythmic therapy is indicated for persons who experience severe symptoms with paroxysmal atrial fibrillation.
- Long-term rate control is indicated for persons with paroxysmal, persistent, or permanent atrial fibrillation.
- Long-term rate control is also indicated for patients who have repeatedly reverted to atrial fibrillation following electrical or pharmacologic cardioversion. Ablation for symptomatic persistent atrial fibrillation and for severely symptomatic recurrent atrial fibrillation may be indicated. AV nodal ablation is usually reserved for elderly patients, because it leads to pacemaker dependency.

RECOMMENDED MANAGEMENT FOR PERSONS WITH ATRIAL FIBRILLATION	
Type of Atrial Fibrillation	**Recommended Management Strategy**
First-detected, self-limiting	Assess severity of symptoms Therapy only indicated if symptoms are severe (e.g., hypotension, heart failure, angina pectoris) Consider anticoagulation on individual basis
First-detected, persistent	Assess symptoms Control ventricular rate Anticoagulate as needed Consider antiarrhythmic therapy Consider cardioversion to restore normal sinus rhythm Long-term antiarrhythmic drug therapy unnecessary
Recurrent paroxysmal	Assess symptoms Control rate and anticoagulate as needed If severely symptomatic, consider antiarrhythmic therapy to maintain normal sinus rhythm and decrease frequency of recurrent episodes of atrial fibrillation Consider ablation if antiarrhythmic treatment fails
Recurrent persistent	Assess severity of symptoms Control ventricular rate Anticoagulate as indicated For severe symptoms, consider antiarrhythmic therapy to restore or maintain normal sinus rhythm and electrical cardioversion to restore sinus rhythm Consider electrical cardioversion as needed Continue anticoagulation as needed and therapy to maintain sinus rhythm Consider ablation for severely symptomatic recurrent atrial fibrillation after failure of more than one antiarrhythmic drug plus rate control
Permanent	Pharmacologic therapy for rate control Anticoagulate as indicated If symptomatic with medication, consider more aggressive therapy
Source: [20; 49]	*Table 1*

- Catheter ablation performed in experienced centers may be indicated to maintain sinus rhythm in select patients with significantly symptomatic, paroxysmal atrial fibrillation who have failed treatment with an antiarr-hythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.
- Catheter ablation is indicated for symptom-atic patients with atrial fibrillation who have Wolff-Parkinson-White (WPW) syndrome. Prompt direct-current cardioversion is recommended for patients with WPW syndrome and rapid ventricular response who are hemodynamically compromised.
- Restoration of normal sinus rhythm is indicated for those who have persistent signs of decreased cardiac output during episodes of atrial fibrillation.
- Direct-current cardioversion may be indicated as part of a long-term management strategy to restore sinus rhythm in patients with atrial fibrillation.
- Maintenance of normal sinus rhythm may be indicated for persons who spontaneously convert from atrial fibrillation to sinus rhythm.
- Maintenance of normal sinus rhythm is indicated for persons who are successfully converted by pharmacologic or electrical means.
- Elimination or interruption of the arrhythmia through radiofrequency ablation (of the focal source of the arrhythmia or the AV node) is indicated for patients who cannot tolerate antiarrhythmic therapy, whose arrhythmia is not successfully controlled by optimal doses of antiarrhythmic therapy, or who cannot be successfully cardioverted through pharmacologic or electrical means. Some patients with atrial fibrillation who also have atrial flutter may benefit from treatment with radiofrequency ablation.

To assist the clinician in selecting and prioritizing appropriate medical goals, the ACC/AHA Task Force established recommendations for the management of various types of atrial fibrillation. These recommendations are summarized in ***Table 1.***

SELECTION OF SPECIFIC THERAPIES

Antiarrhythmic medications are the mainstay of treatment for atrial fibrillation. They may be used for acute and chronic rate control. They also may be used for pharmacologic cardioversion of atrial fibrillation to normal sinus rhythm and maintenance of normal sinus rhythm following successful conversion; however, their use for achieving rhythm control has decreased due to evidence of greater safety and lower costs for hospitalization obtained from the use of rate-control strategies [28; 50]. The AHA/ACC/HRS recommends treating the precipitating or reversible causes of atrial fibrillation prior to initiating antiarrhythmic drug therapy [28]. Whatever the goal of treatment, selection of specific antiarrhythmic medications should be guided by the following [28; 50]:

- Patient characteristics (e.g., age, disease states, renal function, concurrent drug therapies)
- Effectiveness of the medication in meeting identified goals (i.e., controlling rate within desired parameters, limiting episodes of atrial fibrillation)
- Specific action of the medication on the cardiac cycle and its risk of proarrhythmias and other serious side effects
- Medical contraindications to the use of some antiarrhythmic medications in the presence of specific cardiovascular disorders
- Convenience of administration (i.e., dosing, frequency, schedule of doses)
- Cost and ready availability of the medication(s)

AN ISSUE IN THE SELECTION OF ANTIARRHYTHMIC MEDICATIONS: PRODUCT SUBSTITUTION

With the increasing emphasis on reduction of healthcare costs, there has been an increase in the use of generic (as opposed to proprietary) medications. Almost every state has passed regulations encouraging the substitution of less expensive drug products for more expensive proprietary products. State regulations may approve substitutions only for medications on an approved list, or the regulations may permit the substitution of any medication, except those specifically listed on a list of exclusions. On the national level, the FDA provides a specific list of approved drugs. This list is updated on a monthly basis [51].

When a pharmaceutical company develops a new drug, the company may apply for one or more patents for (1) the drug itself; (2) the manufacturing process; (3) how the drug is delivered to the bloodstream; or (4) how the medication is to be used. Although the patent gives the company exclusive rights to the new drug for 17 years, this period often involves at least 10 years of development. In reality, the company may have only seven years to exclusively sell the drug. A newly developed drug is given several names. The generic name, which is the medication's official name (derived from the drug's chemical name, structure, and/or formula), must be unique. Generic names are frequently difficult to pronounce, remember, and spell. The new drug is also given a trade name or proprietary name that signifies that the drug is the exclusive property of its company. Trade names are simpler, easier to remember, and often emphasize an attribute of the medication. Trade names must also be unique. After the patent on a specific drug has expired, other companies may manufacture and sell that drug under its generic name. Generics are frequently sold at a lower price than trade/proprietary drugs. Generic versions of a drug must meet FDA approval, specifically the following three points [51; 52]:

- The generic preparation must contain the same amount of active drug ingredient as the original proprietary preparation.
- The generic must be manufactured according to federal standards as defined in the Good Manufacturing Practices.
- In the human body, the generic medication must be released in equivalent fashion (i.e., same rate, to same extent) as the proprietary drug. This is referred to as "bioequivalence." Bioequivalence is established by a drug company through the use of small research studies. For time-release medications, the process of establishing bioequivalence is more strict, extensive, and time-consuming. Because there is more variation inherent in the use of time-release forms, more extensive testing is required to ensure bioequivalence. Because of the cost and extensiveness of the process, very few time-release generic drugs are available.

Proprietary and generic versions of a medication may vary in several respects [33; 52]:

- Appearance of the medication. By law the size, color, and shape of the generic must significantly differ from the proprietary. Patients will notice the difference.
- Different inactive ingredients. While the active ingredients must be the same, the inactive components may vary. Inactive ingredients are routinely used in medications to add bulk, to keep the tablet from crumbling/disintegrating until use, to help the medication dissolve, or to provide a pleasant taste. There have been instances in which the difference in inactive ingredients has changed the absorption of the active ingredients.
- Variable bioequivalence. Regulations permit as much as a 20% variation in bioequivalence. For medications, such as antiarrhythmic medications that may have a very narrow margin for therapeutic effect, this variation may alter how effective the generic medication is in managing the patient's arrhythmia.

Practically speaking, the use of a generic substitution means that the patient could experience different effectiveness with different preparations. Random switching from proprietary to generic or from one generic to another could increase side effects, decrease rate control, and cause more frequent relapse

from normal sinus rhythm to atrial fibrillation. For that reason, any generic substitution of antiarrhythmic medications should be done very carefully. With many antiarrhythmic medications, very small variations in the serum blood level may influence the effectiveness of the medication in controlling the arrhythmia and significantly increase the risk of proarrhythmias and serious side effects. Physician groups have made the following recommendations regarding the use of generic antiarrhythmic medications [46]:

- Regardless of the preparation used, closely monitor the patient's status and serum drug levels. Adjust dosage as indicated by data.
- Avoid substitution of antiarrhythmic medications for patients with life-threatening arrhythmias, arrhythmias that cause loss of consciousness, or when a change in drug level (increase) can cause life-threatening proarrhythmias.
- Use a generic for less serious arrhythmias if an easy, reliable assay is available and a therapeutic drug level is stable and sustained over time.
- If generic substitution is necessary, give preference to generic medications that have only one preparation available, thus avoiding multiple switches from one generic product to another. Also give preference to a generic preparation that is widely available in hospital and outpatient pharmacies.
- If switching from a proprietary to a generic medication, re-establish effectiveness and proper dose with the new preparation.
- The physician may wish to specify on the prescription the exact preparation of a medication to be dispensed. Some states have regulations that limit the physician's ability to specify preparations. Also, specifying a proprietary medication may present a financial issue for the patient; insurance companies may not cover the higher cost preparation.

PHARMACOLOGIC THERAPY

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

A classification system for antiarrhythmic drugs was developed in the early 1970s. An antiarrhythmic medication was classified according to its specific effect on the normal cardiac cycle. When the classification system was developed, it was believed that each antiarrhythmic medication had only one action. Electrophysiologic research has shown that the mechanisms involved in the generation and spread of an electrical impulse throughout the heart are complex, and that antiarrhythmic medications may impact more than one of these mechanisms. Although the classification system does not reflect the advances in the understanding of electrophysiology, it is still in common use today. ***Table 2*** summarizes the classification system [53; 54].

SITE OF CARE DECISIONS FOR ANTIARRHYTHMIC THERAPY

When selecting and initiating (or changing) antiarrhythmic therapy, the site of care should be considered. Sites of care may include the patient's home, a physician's office, an outpatient clinic, or an inpatient setting. Some antiarrhythmics, such as dofetilide, can only be initiated in an inpatient setting. For others, inpatient initiation is strongly recommended if risk of proarrhythmia is high. Proarrhythmic risk is increased in persons with structural heart disease, congestive heart failure, and those who already have a prolonged QT interval. Persons who have no structural heart disease and whose QT interval is normal are considered to be at low risk for development of proarrhythmias. In these cases, antiarrhythmic therapy may be initiated in outpatient settings. If antiarrhythmic therapy is initiated outside the hospital setting, transtelephone monitoring may be used to intermittently assess the patient's heart rate and rhythm for any undesired changes [55].

DRUG INTERACTIONS

When selecting antiarrhythmic agents, potential drug interactions should be considered. Serious interactions may occur between two antiarrhythmic medications, between an antiarrhythmic and other cardiovascular medications, and between antiarrhythmics and noncardiac medications. Interactions that may occur include the following [12; 14; 19; 33; 52]:

- Other drugs may potentiate or inhibit the effectiveness of antiarrhythmic drugs.
- Other drugs may interfere with the normal absorption of antiarrhythmic drugs, thus reducing the serum level and the drug's effectiveness in controlling an arrhythmia.
- Other drugs may interfere with the normal metabolism or excretion of another medication, thus increasing the serum levels and increasing the risk of toxicity.
- Antiarrhythmic drugs may potentiate or inhibit the therapeutic effects of other medications.
- Antiarrhythmic drugs may interfere with the normal absorption, metabolism, or excretion of another medication, thus reducing the serum level and the drug's effectiveness.
- When given concurrently with other antiarrhythmic drugs, an antiarrhythmic drug may have cumulative effects on heart rate and blood pressure.

Table 3 lists some common drug to drug interactions.

CLASSIFICATION OF ANTIARRHYTHMIC MEDICATIONS			
Class	**Action/Properties**	**Class Proarrhythmic Effects**	**Specific Agents**
Ia	Blocks the rapid influx of sodium Slows rate of development of phase 0 of the action potential Slows conduction velocity; QRS complex widens Prolongs repolarization; QT interval lengthens	Torsades de pointes (quinidine) Ventricular fibrillation or asystole Second-degree heart block	Quinidine Procainamide Disopyramide
Ib	Sodium channel blocker Shortens action potential duration Shortens repolarization Used only for management of ventricular arrhythmias	Increased premature ventricular contractions (rare) AV block/conduction disturbances	Lidocaine Mexiletine
Ic	Significant block of sodium channel Slows conduction velocity; QRS complex widens Has no effect on repolarization; QT interval unaffected	Re-entry arrhythmias	Flecainide Propafenone
II	Beta adrenergic blockers Slows AV node conduction Slows sinus rate Decreases myocardial oxygen consumption	Sinus bradycardia AV block	Metoprolol Acebutolol Propranolol Esmolol
III	Blocks outward movement of potassium ions in phase 3 of the action potential Prolongs repolarization; lengthens QT interval Prolongs cardiac action potential and effective refractory period At increased heart rates, has reduced ability to affect/slow the cardiac action potential	Sinus bradycardia Torsades de pointes	Amiodarone Sotalol Dofetilide Ibutilide
IV	Calcium channel blockers Blocks slow inward movement of calcium ions into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period	Sinus bradycardia AV block	Verapamil Diltiazem
AV = atrioventricular; SA = sinoatrial.			
Source: [53; 54]			*Table 2*

PHARMACOLOGIC THERAPY FOR RATE CONTROL

ACUTE INTERVENTION

When a person presents with uncontrolled atrial fibrillation, his/her ventricular rate may reach 160 bpm. The immediate goal of medical therapy is to control the heart rate to decrease acute symptoms, relieve hypotension, reduce signs of ischemia, and reduce or prevent signs of congestive heart failure from developing. No single agent has been found to be more effective than others in controlling rapid rates. For acute rate control, the administration route of choice is intravenous. Antiarrhythmic drugs commonly prescribed for acute rate control include diltiazem, verapamil, esmolol, metoprolol, and digoxin [49].

Diltiazem

Diltiazem acts by blocking calcium transport into the myocardial and vascular smooth muscle cells. As a result, conduction through the SA and AV nodes is slowed, and the refractory period of the AV node is prolonged. Ventricular rate is slowed, but the underlying atrial arrhythmia is not corrected. Diltiazem should be administered initially as an IV bolus. The usual dose is a 0.25 mg/kg bolus administered over a two-minute period. Diltiazem has a rapid onset of action. If effective, it should slow the patient's heart rate within three to seven minutes of administration. If the initial dose is ineffective in slowing the patient's heart rate, the bolus may be repeated at a higher dose of 0.35 mg/kg over two minutes. The patient's heart rate and rhythm and blood pressure should be monitored during administration. Bradycardia, bradyarrhythmias such as heart block, and hypotension may occur. To achieve or maintain

COMMON DRUG TO DRUG INTERACTIONS OF ANTIARRHYTHMIC DRUGS (AADs)					
AAD	**AAD Increases the Level of Action**	**AAD Inhibits the Action**	**AAD Serum Levels Increased**	**AAD Serum Levels Decreased**	**Other Considerations and Comments**
Amiodarone	Warfarin sodium Quinidine Procainamide Disopyramide Cyclosporine Flecainide Digoxin	—	Cyclosporine Flecainide Digoxin	—	Additive effects on heart rate, blood pressure, force of cardiac contraction can occur when administered concurrently with calcium channel blockers, beta blockers Significant drug-food interaction when administered with grapefruit juice
Digoxin	—	—	Erythromycin Tetracycline Quinidine Amiodarone Diltiazem Verapamil Propafenone Itraconazole Alprazolam Spironolactone Nicardipine Indomethacin Rifampin	Cholestyramine Antacids Bismuth Neomycin Sulfasalazine Select anticancer drugs Metoclopramide	Concurrent administration of medications such as thiazide diuretics, ticarcillin, or amphotericin B that cause hypokalemia can increase risk of digitalis toxicity
Diltiazem	Digoxin Cyclosporine	—	Cimetidine Propranolol Carbamazepine	Phenytoin Phenobarbital	Additive effects on heart rate, blood pressure, force of cardiac contraction can occur with administration concurrently with calcium channel blockers, or beta blockers
Disopyramide	Warfarin	—	Quinidine Cimetidine Erythromycin	Phenobarbital Phenytoin Rifampin Quinidine	Additive effects on heart rate, blood pressure, force of cardiac contraction can occur when administered concurrently with calcium channel blockers, beta blockers, or flecainide Should not be administered within 48 hrs before or 24 hrs after administration of verapamil
Dofetilide	—	—	Cimetidine Ketoconazole Trimethoprim Verapamil	—	Significant risk of dangerously prolonged QT intervals when administered concurrently with other medications that prolong QT intervals (e.g., hydrochlorothiazide) Significant drug-food interaction when administered with grapefruit juice
Esmolol	Succinylcholine	Theophylline	Digoxin	Thyroid preparations	Potentiates effect on heart rate, AV conduction, blood pressure and risk for heart failure when given concurrently with negative inotropes, calcium channel blockers, or digoxin IV preparation physically incompatible with IV sodium bicarbonate, furosemide, or diazepam

Table 3 continues on next page.

COMMON DRUG TO DRUG INTERACTIONS OF ANTIARRHYTHMIC DRUGS (AADs) *(Continued)*					
AAD	**AAD Increases the Level of Action**	**AAD Inhibits the Action**	**AAD Serum Levels Increased**	**AAD Serum Levels Decreased**	**Other Considerations and Comments**
Flecainide	Digoxin	—	Cimetidine Amiodarone Propranolol	—	Additive effects on heart rate, blood pressure, force of cardiac contraction when given concurrently with beta blockers or calcium channel blockers Neither disopyramide nor verapamil should be coadministered unless the benefit is judged to outweigh the risk
Ibutilide	—	—	—	—	Significant risk of dangerously prolonged QT intervals when administered concurrently with other medications that prolong QT interval
Metoprolol	May alter effectiveness of insulin and oral hypoglycemic agents	Theophylline Negates positive action of dopamine, dobutamine	—	Thyroid preparations	Additive myocardial depression possible when administered concurrently with general anesthesia, IV phenytoin, or verapamil Concomitant use with beta blockers can increase the risk of bradycardia
Procainamide	—	—	Cimetidine Amiodarone	—	Additive effect if administered with other AADs
Propafenone	Warfarin Cyclosporine Digoxin	—	Cimetidine Desipramine Imipramine Haloperidol Venlafaxine Propranolol	Etravirine	Concomitant use of propafenone and quinidine is not recommended Concomitant administration of propafenone and amiodarone can affect conduction and repolarization and is not recommended
Propranolol	May alter effectiveness of insulin and oral hypoglycemic agents	Theophylline Negates positive action of dopamine, dobutamine	—	Thyroid preparations	Additive myocardial depression possible when administered concurrently with general anesthesia, IV phenytoin, or verapamil
Quinidine	Warfarin Digoxin	—	Cimetidine Amiodarone	Phenytoin Phenobarbital Rifampin Nifedipine Sodium bicarbonate Thiazide diuretics	—

Source: [12; 20; 33; 45; 56; 57; 58; 59] *Table 3*

rate control, a continuous infusion may be started following bolus administration. The infusion may be started at 10 mg/hour and increased in increments of 5 mg/hour to achieve rate control if no undesirable side effects occur. Diltiazem should be used with caution in patients with congestive heart failure, known pre-existing conduction defects, and significant hypotension [33; 60].

Verapamil

Verapamil, another calcium channel blocker, also slows ventricular rate by slowing conduction through the AV node and prolonging the refractory period of the AV node. Revised guidelines published by the AHA/ACC/HRS recommend a loading or bolus dose of 0.075–0.15 mg/kg administered over two minutes; no maintenance or continuous drip is included in the recommendations [28]. If ineffective in achieving rate

control and if no untoward effects occur, the bolus may be repeated at a higher dosage of 10 mg administered 30 minutes after the initial dose [28]. Verapamil should not be used for patients with atrial fibrillation secondary to WPW syndrome or patients who have a wide QRS complex tachyarrhythmia. Verapamil should be used with caution for persons with pre-existing conduction disturbances or left ventricular dysfunction. The patient's heart rate and rhythm and blood pressure should be monitored during and following administration. Bradycardia, heart block, and hypotension may occur [33; 61].

Esmolol

Esmolol is a short-acting beta-adrenergic blocker that slows ventricular rate in atrial fibrillation by slowing conduction through the AV node. Initial administration is an IV bolus dose/loading dose of 0.5 mg/kg administered over one minute [28]. The bolus should be followed with an infusion of 0.05 mg/kg/min for four minutes. If the desired rate control is achieved, the infusion should be continued at that rate. If adequate rate control is not achieved at that dose, the bolus should be repeated followed by an infusion of 0.1 mg/min for four minutes. The total dose should not exceed 200 mcg/kg/min [33]. This procedure may be repeated until rate control is achieved or undesirable side effects occur. The patient's heart rate, ECG rhythm, and blood pressure should be monitored during the administration. Hypotension may occur. Once rate control is achieved, the infusion should be reduced to 0.025 mg/kg/min. Because esmolol has a short half-life, the therapeutic effects and side effects usually reverse within 10 to 20 minutes after the infusion is stopped. Because the therapeutic effects wear off quickly, care should be taken when switching the patient to an oral preparation to prevent relapse/loss of rate control. To transition the patient to oral medication, the first dose of the oral medication should be administered while the patient is still receiving esmolol. Thirty minutes after the first oral dose is given, the esmolol infusion should be reduced by one-half. The second dose of the oral agent should be administered at its scheduled time. One hour after the scheduled administration of the second oral dose, assess the patient's heart rate, ECG rhythm, and blood pressure. If rate control is maintained, the esmolol infusion may be discontinued. Note: Esmolol has no oral preparation; long-term control by oral agent requires a different agent [33].

Metoprolol

Metoprolol is a longer acting beta-adrenergic blocking agent that decreases conduction through the AV node. Although metoprolol is not labeled for use in the management of atrial arrhythmias, it is used by some clinicians to control/slow ventricular rate in atrial fibrillation with a rapid ventricular response. For acute rate control, an IV bolus of 2.5–5 mg may be given over two minutes and repeated every two to five minutes up to a total of 15 mg in a 10- to 15-minute period. The patient's heart rate, ECG rhythm, and blood pressure should be monitored closely. Bradycardia, bradyarrhythmias, heart block, and hypotension may occur. Use of metoprolol is contraindicated for persons with bradycardia, AV conduction problems, uncompensated congestive heart failure, or asthma [33; 62].

Digoxin

Digoxin is an older agent that may be used to control ventricular rate in some patients. Once considered a leading treatment for rate control in atrial fibrillation, digoxin is primarily recommended for persons with atrial fibrillation who also have congestive heart failure caused by systolic dysfunction. Digoxin acts by prolonging the refractory period of the AV node as well as slowing conduction through SA and AV nodes. Digoxin therapy is initiated by either an oral or intravenous loading dose protocol. Intravenous administration should be used in an acute situation. The revised AHA/ACC/HRS guideline notes that one-half the total digitalizing dose (TDD) of 9–12 mcg/kg may be administered over five minutes with the remaining portion as 25% fractions at four- to eight-hour intervals or 0.25 mg may be given intravenously every two hours up to a total of 1.5 mg over 24 hours followed by an oral maintenance regimen [28]. These doses should be given at six- to eight-hour intervals. The usual protocol for an oral loading dose is 0.75–1.5 mg given in three to four doses every six to eight hours. The maintenance oral dose is 0.125–0.25 mg once daily [28]. Careful monitoring of serum digoxin levels is recommended. For digoxin to achieve a therapeutic effect, the serum digoxin level must fall within the therapeutic level of 0.5–2 ng/mL. The therapeutic range for digoxin is very narrow. Serum levels in excess of 2 ng/mL are considered toxic and may cause tachyarrhythmias, bradycardia, heart block and bradyarrhythmias, and other symptoms [12; 14; 19; 33; 37; 47; 63]. ***Table 4*** summarizes information about antiarrhythmic medications used for acute rate control.

CHRONIC RATE CONTROL

If the long-term goal of clinical management is rate control, there are a number of oral preparations to choose from. Clinical decision making includes selecting the category, specific agent, effective dose, and preparation (e.g., short-acting, extended-release). As with acute rate control, no consensus exists on the best medication(s) for every patient. Specific antiarrhythmic agents should be selected on the basis of patient assessment. Again, factors to consider include the cost and complexity of the prescribed regimen, the risk of proarrhythmic effects, concurrent cardiovascular disease, and the risk of other troublesome or serious side effects. When choosing long-term therapy, the patient's lifestyle should be considered as well. Some medications provide effective rate control when the patient is at rest but do not provide adequate rate control during activity or exercise. A heart rate is considered "controlled" if it falls between 60 to 80 bpm at rest and 90 to 115 bpm with moderate exercise [20]. Adequate rate control may be achieved by a single antiarrhythmic drug, or it may require a combination of drugs. Antiarrhythmic drugs commonly used for long-term rate control include calcium channel blockers, beta blockers, and digoxin [49].

PHARMACOLOGIC THERAPY FOR ACUTE RATE CONTROL IN ATRIAL FIBRILLATION

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Diltiazem	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate Controls ventricular rate in atrial fibrillation	IV: 0.25 mg/kg bolus over 2 mins If needed, may repeat after 15 mins with dose of 0.35 mg/kg IV over 2 mins May be followed by continuous infusion at 10 mg/hour May increase to 15 mg/hour	Bradycardia Heart block CHF Hypotension Flushing Angina Syncope Insomnia Nausea	Rapid onset of action Onset: 3 to 7 mins Duration of IV bolus may last more than 30 mins
Verapamil	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate May reduce atrial electrophysiologic remodeling	IV loading dose: 0.075–0.15 mg/kg over 2 mins	AV block Hypotension Bradycardia Heart failure Dizziness Fatigue CHF	Use with caution for patients with conduction disturbances Negative inotrope; may make left ventricular dysfunction worse Should not be used for patients with accessory conduction pathways Rapid onset of action (3 to 5 mins) Duration of IV bolus may last more than 30 mins
Esmolol	II	Beta adrenergic blocker Decreases AV nodal conduction Can rapidly slow ventricular response in atrial fibrillation	IV dosing only: Administer loading dose of 0.5 mg/kg over 1 min Follow with infusion at rate of 0.05 mg/kg/min for 4 mins; if adequate rate control is achieved, continue at the same rate. If adequate rate control is not achieved, repeat the same procedure, increasing the rate by 0.05 mg/kg/min every 4 mins until the rate control is achieved (or side effects occur). Maximum: 200 mcg/kg/min When the rate control is achieved, omit loading dose and reduce infusion rate to 0.025 mg/kg/min. Begin transition to another antiarrhythmic: administer first dose; 30 mins later, reduce infusion rate by one-half. Administer 2nd dose of new agent when scheduled. If rate control is maintained 1 hour after 2nd dose, stop infusion.	Hypotension Dizziness Diaphoresis Nausea and vomiting Fatigue	Short half-life (9 mins) Contraindicated for patients with bradycardia, uncompensated CHF, and conduction problems

Table 4 continues on next page.

PHARMACOLOGIC THERAPY FOR ACUTE RATE CONTROL IN ATRIAL FIBRILLATION *(Continued)*

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Metoprolol	II	Beta adrenergic blocker Decreases AV nodal conduction Slows ventricular rate in atrial fibrillation	IV loading dose: 2.5–5 mg over 2 mins and repeated every 2 to 5 mins up to a total dose of 15 mg in a 10- to 15-min period	Bradycardia Heart block CHF Hypotension Flushing Angina Syncope Insomnia Nausea	Rapid onset of action Onset: 5 mins Duration of IV bolus may last more than 30 mins Contraindicated for patients with bradycardia, AV conduction abnormalities, uncompensated CHF, and asthma
Digitalis (Digoxin)	None	Prolongs AV node refractory period Slows conduction through the SA and AV nodes Slows ventricular rate in atrial fibrillation	IV loading dose 0.25 mg IV every 2 hours up to total dose of 1.5 mg Oral loading dose: 0.75–1.5 mg every 6 to 8 hours Oral maintenance dose: 0.125–0.375 mg/day	Bradycardia AV block Signs of dig toxicity: Multiple tachyarrhythmias Bradyarrhythmias Visual disturbances Anorexia Nausea and vomiting Malaise Headache Weakness Seizures	Onset: 2 hours Consider as first line of treatment for patients with CHF secondary to systolic dysfunction Serum digoxin levels should be periodically monitored; therapeutic level is 0.5–2 ng/mL Dig toxicity often occurs with dig levels >2 ng/mL Dig toxicity is more likely to occur with hypokalemia, renal failure, combination therapy, elderly Excessively high dig levels may be reversed with use of digoxin immune Fab

AV = atrioventricular; CHF = congestive heart failure; SA = sinoatrial; TDD = total digitalizing dose.

Source: [4; 12; 20; 28; 33; 51; 53; 56; 57; 64; 65; 66] *Table 4*

See ***Table 5*** for a summary of antiarrhythmic medications that may be used for long-term rate control in atrial fibrillation.

Diltiazem

What is a drug of choice for chronic rate control for persons in atrial fibrillation who also have an active lifestyle?

Oral diltiazem preparations provide chronic rate control in atrial fibrillation and are a drug of choice for persons who have a physically active lifestyle; however, their use for rate control is unlabeled [33]. Diltiazem comes in immediate- and extended-release forms. Immediate-release doses must be taken three to four times per day; extended-release forms require only daily dosing. In addition to bradycardia, hypotension, and heart block, other side effects of oral diltiazem include flushing, angina, insomnia, headache, nausea, syncope, and signs of congestive heart failure. Care should be taken when diltiazem is combined with negative inotropic drugs, other calcium channel blockers, and digoxin. Combination therapy increases the risk of bradycardia, conduction abnormalities, hypotension, and signs of congestive heart failure [33; 60].

Verapamil

Oral verapamil preparations may also be prescribed for chronic rate control. Available in immediate- and extended-release forms, oral verapamil can control ventricular rate at rest and with activity. In addition, research has shown that verapamil may have the additional benefit of reducing atrial electrophysiologic remodeling (the process thought to be responsible for frequent recurrence of atrial fibrillation and resistance to successful cardioversion). Immediate-release preparations must be taken three to four times per day at evenly spaced intervals; extended-release dosing may be administered once per day. Oral verapamil should be used with caution in persons with conduction defects and left ventricular dysfunction. Oral verapamil should not be prescribed for persons with WPW syndrome. There is increased risk of bradycardia, bradyarrhythmias, conduction abnormalities, hypotension, and development of congestive heart failure when combined with administration of other calcium channel blockers, negative inotropes, or digoxin [33; 61].

Digoxin

Oral digoxin may be the first drug of choice for patients with atrial fibrillation and congestive heart failure caused by systolic dysfunction [67]. Digoxin does not provide adequate

ANTIARRHYTHMIC AGENTS USED FOR LONG-TERM RATE CONTROL IN ATRIAL FIBRILLATION

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Diltiazem[a]	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate Controls ventricular rate in atrial fibrillation	Oral maintenance dose: 120–360 mg daily in divided doses Sustained-release form: 60–120 mg twice daily Extended-release form: 120–240 mg daily	Bradycardia Heart block CHF Hypotension Flushing Angina Syncope Insomnia Headache Nausea	Effective in controlling ventricular rates in patients during exercise May also be used in the management of hypertension, angina pectoris, and vasospastic angina
Verapamil	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate May reduce atrial electrophysiologic remodeling	Oral maintenance dose: 120–360 mg daily in divided doses Extended release: 120–360 mg daily Immediate release: 240–480 mg daily in 3 to 4 divided doses	AV block Hypotension Bradycardia Heart failure Dizziness Fatigue CHF	Effective in controlling ventricular rates in patients during exercise May also be used in the management of hypertension, angina pectoris, and vasospastic angina Use with caution for patients with conduction disturbances Negative inotrope; may make left ventricular dysfunction worse Should not be used for patients with accessory conduction pathways
Digitalis (Digoxin)	None	Prolongs AV node refractory period Slows conduction through the SA and AV nodes Slows ventricular rate in atrial fibrillation	Half the TDD of 0–12 mcg/kg over 5 mins followed by 25% fractions of TDD at 4- to 8-hr intervals, or IV loading dose 0.25 mg IV every 2 hours up to total dose of 1.5 mg over 24 hrs at 6- to 8-hour intervals[b] Oral loading dose: 0.75–1.5 mg every 6 to 8 hours Oral maintenance dose: 0.125–0.25 mg/day	Bradycardia AV block Signs of digitalis toxicity (sinus bradycardia, multiple tachyarrhythmias, heart block) Visual disturbances Anorexia Nausea, vomiting Malaise Headache Weakness Seizures	Digoxin may also be used in the management of congestive heart failure First drug of choice for patients with CHF and atrial fibrillation Ineffective in controlling ventricular rates in patients during activity/exercise Serum digoxin levels should be periodically monitored; therapeutic level is 0.5–2 ng/mL Dig toxicity often occurs with dig levels >2 ng/mL Dig toxicity is more likely to occur with hypokalemia, renal failure, combination therapy, elderly Serious or life-threatening dig toxicity may be reversed with the use of digoxin immune Fab

Table 5 continues on next page.

ANTIARRHYTHMIC AGENTS USED FOR LONG-TERM RATE CONTROL IN ATRIAL FIBRILLATION *(Continued)*

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Metoprolol[a]	II	Beta adrenergic blocker Decreases AV nodal conduction Slows ventricular rate in atrial fibrillation	Oral maintenance dose: 25–100 mg twice daily Extended-release preparations are administered once daily	Bradycardia Hypotension Fatigue Weakness Insomnia CHF Bronchospasm Impotence	May be also prescribed for the management of hypertension, angina, prevention of MI, and management of acute MI Effective in controlling ventricular rate in patients during activity/exercise Contraindicated for patients with bradycardia, AV conduction abnormalities, uncompensated CHF, and asthma
Propranolol	II	Beta adrenergic blocking agent Controls ventricular rate in atrial fibrillation	Oral maintenance dose: 30–160 mg daily in divided doses	Bradycardia Heart block Hypotension CHF Nausea and vomiting Diarrhea Constipation Insomnia Depression Bronchospasm Hypoglycemia Fatigue Impotence	Propranolol may also be used in the management of angina, hypertension, prevention and management of MI

AV = atrioventricular; CHF = congestive heart failure; MI = myocardial infarction; SA = sinoatrial; TDD = total digitalizing dose.
[a] Off-label use
[b] Unlabeled dose

Source: [4; 12; 20; 28; 33; 53; 56; 57; 64; 65; 66] *Table 5*

rate control during exercise or activity. The usual oral maintenance dose of digoxin is 0.125–0.25 mg daily. Serum digoxin levels should be monitored periodically. The patient should be monitored for signs of digitalis toxicity. The patient and/or family should be taught to recognize key signs of toxicity. These include nausea and vomiting, headache, unexplained weakness, malaise, and visual disturbances as well as slow heart rate. ECG changes that may occur with digitalis toxicity include sinus bradycardia, heart block, and multiple tachyarrhythmias. Digitalis toxicity is more likely to occur in elderly persons. Electrolyte imbalances such as hypokalemia, renal failure, or combined therapy with other antiarrhythmic agents may potentiate the effects of digoxin and increase the risk of digitalis toxicity. Severe digitalis toxicity may be treated with digoxin immune Fab [33].

Fab is an antibody produced in sheep. When Fab is administered intravenously, it binds to unbound digoxin in the bloodstream and facilitates its removal, thus reducing the serum digoxin level. The precise dose of Fab may be calculated on the basis of the amount of digitalis ingested or on the patient's serum digoxin level. In emergency situations when the amount of digoxin ingested is not known and a serum digoxin level is not available, a Fab dose of 800 mg in two divided doses may be administered IV. This dose should be diluted according to package instructions and administered over 15 to 30 minutes. Continuous monitoring of ECG, pulse, blood pressure, and temperature before and during infusion should be done. Following the administration of Fab, persons with atrial fibrillation (or a history of atrial fibrillation) may experience recurrence of the arrhythmia or a loss of rate control, and persons with congestive heart failure may develop signs of an exacerbation such as dyspnea, hypotension, or rales [33].

Metoprolol

Oral metoprolol is not labeled for management of atrial fibrillation; however, in patients with coronary artery disease, hypertension, and angina, it may be prescribed for rate control plus its other therapeutic effects. Its off-label use for rate control in patients with paroxysmal, persistent, or permanent atrial fibrillation is recommended by the AHA/ACC/HRS [28]. It

may exert cumulative effects on heart rate, rhythm, and blood pressure when given in combination with calcium channel blockers, other beta blockers, or disopyramide resulting in bradycardia, bradyarrhythmias/heart block, and hypotension. The usual oral dose may range from 25–100 mg twice daily. Metoprolol is available in short-acting and extended-release preparations. Extended-release preparations are administered only once per day. Side effects include those common to beta blockers [33].

Propranolol

Oral propranolol, another beta-adrenergic receptor antagonist, may also be prescribed for long-term rate control in atrial fibrillation. Unlike metoprolol, propranolol is approved for use in atrial fibrillation. The usual oral maintenance dose is 30–160 mg per day in divided doses. Side effects include nausea, vomiting, diarrhea, constipation, insomnia, depression, bronchospasm, hypoglycemia, fatigue, and impotence [33].

PHARMACOLOGIC CARDIOVERSION

Based on the assessment of a patient's status, it may be determined that restoration of normal sinus rhythm is a major goal. Persons who continue to demonstrate signs of decreased cardiac output from loss of atrial kick, such as continuing shortness of breath, fatigue, signs of congestive heart failure, and diminished exercise tolerance despite adequate rate control, may require restoration of sinus rhythm to alleviate symptoms and improve quality of life. Restoring normal sinus rhythm can be done using a combination of approaches, including chemically through the use of intravenous or oral medications, through direct current electrical cardioversion, or through the use of radiofrequency catheter ablation in the setting of appropriate anticoagulation and rate control [28]. Although pharmacologic cardioversion remains more popular, it appears to be most effective when initiated within seven days of the onset of atrial fibrillation [28]. Unlike electrical cardioversion, pharmacologic cardioversion requires no anesthesia, has fewer risks, and is less costly. This section will review the antiarrhythmic medications that may be used for pharmacologic cardioversion, including ibutilide, dofetilide, amiodarone, propafenone, procainamide, quinidine, and flecainide [5; 19; 20; 28; 37; 45; 46; 49; 53; 68; 69]. See ***Table 6*** for a summary of select antiarrhythmic agents that may be used for pharmacologic cardioversion.

IBUTILIDE

Ibutilide is a drug approved by the FDA for the acute termination of atrial fibrillation and atrial flutter. A Class III antiarrhythmic, ibutilide acts by prolonging the duration of the action potential, the atrial refractory period, and the ventricular refractory period. It also slightly slows the sinus rate and conduction through the AV node. Ibutilide's exact mechanism of action is unknown [33]. On a cellular level, it has been reported to exert its effects by both blocking repolarizing potassium currents and initiating an inward depolarizing sodium current [56]. Ibutilide does not appear to have a direct impact on cardiac output, but monitoring for conduction disturbances and heart block is recommended [33].

Proarrhythmic Effects

What is the treatment of choice for torsades de pointes?

Because ibutilide prolongs the ventricular refractory period (reflected by a prolonged QT interval), the risk of torsades de pointes is significant. Torsades de pointes is a rapid, polymorphic form of ventricular tachycardia. See ***Figure 3*** for more information about torsades de pointes. With ibutilide administration, the risk of torsades de pointes is dependent on the dose of ibutilide administered; the higher the dose, the greater the risk.

Dosage

For an adult weighing 60 kg or more, the initial dose is 1 mg diluted to a total volume of 50 mL administered over 10 minutes. If conversion to normal sinus rhythm does not occur, the dose may be repeated 10 minutes after completion of the first dose. For patients who weigh less than 60 kg, the dose of ibutilide should be reduced to 0.01 mg/kg administered over 10 minutes [33].

Drug Interactions

If administered with other antiarrhythmics and medications (e.g., tricyclic antidepressants, dronedarone) that prolong the QT interval, ibutilide can interact with these medications to create a dangerously prolonged QT interval [33].

Preprocedure Assessment

Prior to administering ibutilide, the patient should be assessed and the following data obtained [28]:

- When did the patient's arrhythmia begin? Ibutilide has been found to be most effective in patients with atrial fibrillation of less than two months duration.
- What medications is the patient currently taking? Other antiarrhythmic medications that prolong the QT interval should be discontinued before ibutilide administration to reduce the risk of excessive QT prolongation and torsades de pointes.
- Is the patient adequately anticoagulated? Because of the risk that cardioversion can cause small pieces of an atrial thrombus to break loose and cause embolization, patients should be adequately anticoagulated prior to receiving ibutilide.
- Does the patient have any history of polymorphic ventricular tachycardia (torsades de pointes)? Persons with a past history of torsades de pointes should not be given ibutilide.

ANTIARRHYTHMIC AGENTS USED FOR PHARMACOLOGIC CARDIOVERSION

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Ibutilide	III	Used for rapid conversion of atrial fibrillation/atrial flutter of recent (<3 months) duration Prolongs duration of action potential Prolongs atrial and ventricular refractory periods Slightly slows sinus rate Slightly slows AV conduction	IV: Dilute 1 vial (1 mg/10 mL) to total volume of 50 mL (Concentration of diluted solution: 0.02 mg/mL) 1 mg over 10 mins at rate of 5 mL/min (or 300 mL/hr) May repeat dose 10 mins after completion of 1st dose Stop infusion as soon as rhythm converts For patients <60 kg, dose reduced to 0.01 mg/kg over 10 minutes	Prolongs QT interval (greater effect with higher doses) Torsades de pointes Other ventricular arrhythmias Angina Heart block Hypotension Nausea	Discontinue other antiarrhythmic agents that prolong QT intervals before administering ibutilide Electrolyte imbalances, especially potassium and magnesium, should be corrected before ibutilide is given Continuous ECG monitoring should be performed during and 4 hours after administration Increased risk of proarrhythmia if given with Class Ia, Class III antiarrhythmics, phenothiazines, tricyclic antidepressants, some antihistamines Contraindicated for patients with history of torsades de pointes Patients with fibrillation >48 hours duration should be anticoagulated before receiving ibutilide Other antiarrhythmic agents should not be started until 4 hours after ibutilide infusion is completed
Dofetilide	III	Converts atrial fibrillation, atrial flutter to NSR Maintains NSR following conversion from atrial fibrillation Blocks delayed rectifier potassium currents, thus delaying repolarization in cardiac tissue Does not affect other repolarizing potassium currents, sodium channels, adrenergic receptors	Oral dosing must be calculated individually based on QTc and creatinine clearance Continuous ECG monitoring required In patients with heart failure, QTc and serum creatinine must be obtained before initiating therapy Maximum daily dose: 500 mcg twice daily Usual dose: 125–500 mcg twice daily	Torsades de pointes Other ventricular arrhythmias Angina Hypertension Palpitations Bradycardia MI Ventricular fibrillation Abnormal conduction Headache Dizziness Nausea Diarrhea Cerebral ischemia	When effective as cardioversion, works within 1 hour Must be initiated in hospital setting Dosage must be individualized and renal function analyzed Contraindicated for patients with QTc interval >440 msec or severe renal insufficiency failure If QTc increases after initiation of therapy, dose must be reduced or stopped OD results in prolonged QT interval. To treat OD, may use isoproterenol infusion, cardiac pacing, IV magnesium (if torsades de pointes is present)

Table 6 continues on next page.

- Are the patient's serum electrolytes within normal limits? The patient's serum sodium, potassium, magnesium, and calcium levels should be assessed. Also, liver function tests, blood urea nitrogen, and creatinine levels should also be checked and be within normal limits. Hypomagnesemia and hypokalemia must be corrected before ibutilide is administered.
- What is the patient's baseline QT interval and rate corrected QT (QTc) interval? See ***Table 7*** for information about calculating corrected QT intervals.

ANTIARRHYTHMIC AGENTS USED FOR PHARMACOLOGIC CARDIOVERSION *(Continued)*

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Amiodarone[a]	III	Inhibits AV conduction Prolongs action potential Prolongs refractory period Inhibits adrenergic stimulation Can convert atrial fibrillation to NSR (unlabeled use)	Oral dosing: 1.2–1.8 g/day in divided doses to a total of 10 g Follow with 200–400 mg/day as a single maintenance dose IV: 5–7 mg/kg over 30 to 60 minutes Follow with 1.2–1.8 g/day by continuous IV infusion. Initial loading dose may be IV followed by oral administration. After target dose of 10 g total dose achieved, switch to maintenance dose of 200–400 mg/day	Bradycardia Heart block VF, incessant VT Torsades de pointes Hypotension (with IV) Pulmonary fibrosis Corneal deposits Photosensitivity Blue skin Hyper-/hypothyroid Liver dysfunction Tremor Malaise Fatigue GI upset Dizziness Poor coordination Peripheral neuropathy	Initial drug of choice for patients with CHF May be secondary drug of choice for patients with CAD May be used to slow conduction through accessory pathways Obtain baseline data before initiating: chest x-ray, thyroid function, renal tests, pulmonary function tests Patients' QTc interval should be monitored Potassium and magnesium levels should be measured
Propafenone	Ic	Slows conduction by changing ion transport across cardiac cell membranes Converts paroxysmal atrial fibrillation to NSR	Initial oral dosing: 450 mg (weight <70 kg)[b] 600 mg (weight ≥70 kg)[b] Maintenance: 150–300 mg every 8 hours[b]	Nausea Anorexia Constipation Dizziness Headache Blurred vision CHF Bradycardia AV block	Does not prolong QT interval, so less risk of torsades de pointes Should not be used in patients immediately post-MI Use in WPW under investigation
Procainamide	Ia	Increases atrial and ventricular refractory periods Converts atrial fibrillation to NSR Maintain NSR after conversion from atrial fibrillation	IV dose for conversion: Rapid loading dose: 100 mg every 5 mins until arrhythmia abolished or 1 g given. Then, wait 10 mins and administer loading infusion of 500–600 mg/30 mins. Follow with maintenance infusion at 1–4 mg/min. Stop infusion if blood pressure drops or QRS widens Oral dose: 500 mg–1 g every 4 to 6 hours (extended-release formulation)	Hypotension with IV administration Nausea and vomiting Anorexia Bradycardia Heart block Prolonged QT interval Headache Insomnia Lupus-like syndrome Rash/fever Swollen joints Agranulocytosis Pancytopenia	Serum procainamide and NAPA levels should be monitored periodically Drug of choice to treat WPW or pre-excitation syndromes During IV administration, ECG, heart rate, and blood pressure should be continuously monitored Oral sustained-release forms should not be used for initiation of therapy

Table 6 continues on next page.

Administration

Prior to administration, ensure that the patient has a good IV access. Continuous ECG monitoring should be initiated. Consider the use of equipment that can be used for monitoring, external pacing, and defibrillation. Or, have pacing/defibrillator patches readily available for use in an emergency [33]. Have emergency equipment readily available, including a defibrillator/cardioverter, external noninvasive pacing equipment, and medications such as magnesium used in the treatment of torsades de pointes/sustained ventricular tachycardia. Some experts suggest that administering IV magnesium sulfate before administering ibutilide may lower the risk of torsades de pointes [73]. Initiate continuous blood pressure monitoring. The patient's blood pressure should be checked every five minutes during the infusion.

To prepare the ibutilide infusion for an adult 60 kg or more, 1 mg of ibutilide is diluted to a total volume of 50 mL. Ibutilide is supplied in vials containing 1 mg/10 mL or 0.1 mg/mL.

ANTIARRHYTHMIC AGENTS USED FOR PHARMACOLOGIC CARDIOVERSION *(Continued)*

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Quinidine	Ia	Prolongs effective refractory period Increases conduction time Decreases vagal tone, thus facilitating conduction Converts atrial fibrillation to NSR Maintains NSR following conversion	Oral test dose: 200 mg several hours before full dosage Oral dosing: Sulfate: 300 mg every 8 to 12 hours Gluconate: 324 mg every 8 to 12 hours	Nausea, diarrhea Hypotension Bradycardia Tachycardia Torsades de pointes CHF Tinnitus Hearing loss	Range for therapeutic serum level is 2–6 mcg/mL Secondary drug of choice for patients with CAD Give medication with food to decrease GI side effects Rapid loading doses are associated with an increase in GI side effects Monitor QT interval, QRS width, and PR interval Indicated for use in rate controlled, stable atrial fibrillation with an uncontrolled ventricular rate, rate should be controlled with another agent before beginning quinidine IV use should be avoided due to risk of severe hypotension
Flecainide	Ic	Slows conduction through cardiac cells by blocking sodium channels Suppresses atrial fibrillation	Oral: Begin with 100 mg every 12 hours; may increase dose 50–100 mg twice daily every 4 days as needed Maximum: 400 mg/day If needed, medication may be administered every 8 hours	Dizziness Blurred vision Arrhythmias Chest pain CHF	Should be used with caution in patients with CHF, conduction defects, and impaired renal function Avoid use in patients immediately following myocardial infarction

AV = atrioventricular; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; NAPA = *N*-acetylprocainamide; NSR = normal sinus rhythm; OD = overdose; VF = ventricular fibrillation; VT = ventricular tachycardia.

[a] Off-label use

[b] Unlabeled dose

Source: [4; 12; 20; 28; 33; 36; 37; 56; 57; 58; 65; 70] *Table 6*

It may be mixed with either D5W or 0.9 NS. When 1 mg is diluted to a total of 50 mL, the concentration of the solution will be 0.02 mg/mL [33].

Ibutilide must be administered using a volumetric pump. The desired rate is 1 mg over 10 minutes [33]. The pump may be set at a rate of 300 mL/hour or 5 mL/minute to deliver the desired dose at the desired rate. Stop infusion immediately if the patient converts to normal sinus rhythm. If the patient develops new or worsening ventricular arrhythmias, stop the infusion immediately. Check the patient's blood pressure and assess for signs of hemodynamic instability. Following the infusion, the patient's ECG should be continuously monitored for four hours or until the patient's QTc returns to his/her baseline. Although the risk of proarrhythmias is greatest within 20 minutes of the infusion, the risk persists for several hours following administration. The administration of other antiarrhythmics (e.g., amiodarone, quinidine, procainamide, disopyramide, dronedarone) that prolong the QT interval should be avoided for four hours following ibutilide administration.

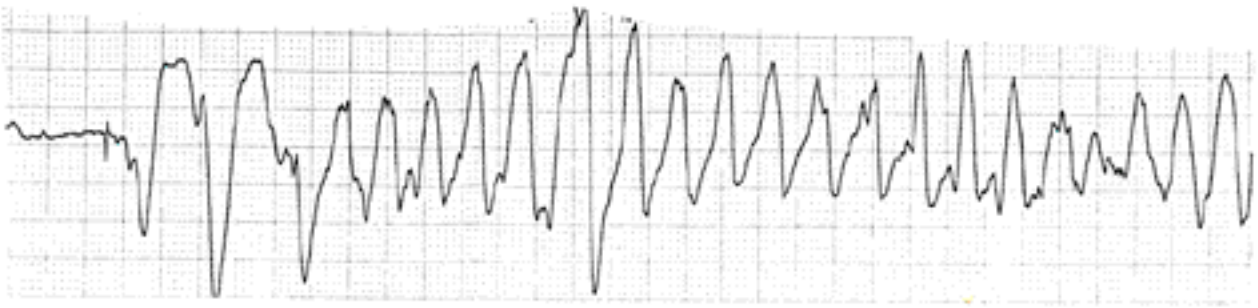
Ibutilide may be used in patients who fail to convert after treatment with propafenone. It may also be used in patients whose arrhythmia recurs during treatment with propafenone or flecainide [5; 13; 33; 53; 64].

DOFETILIDE

Dofetilide is a Class III antiarrhythmic approved for use in patients with atrial fibrillation and atrial flutter. Major clinical trials on dofetilide, including the European and Australian Multicenter Evaluation Research on Atrial Fibrillation Dofetilide (EMERALD) and Symptomatic Atrial Fibrillation Investigation and Randomized Evaluation of Dofetilide (SAFIRE) studies, have shown that dofetilide is effective in conversion of atrial fibrillation or atrial flutter to sinus rhythm, although it appears to be more effective in conversion of atrial flutter than atrial fibrillation [69]. On the cellular level, dofetilide blocks a specific potassium current, thus prolonging the duration of the cardiac action potential and effective refractory period. Prolonging the action potential and effective refractory period increases the likelihood that the entry atrial impulses will encounter a refractory period when the cardiac cells are unable

TORSADES DE POINTES

Torsades de pointes is a very rapid type of ventricular tachycardia that is characterized by "twisting" of the QRS complexes around the ECG baseline. Occurring at a rate of 250 to 350 bmp, these complexes change from upward to a downward deflection. The amplitude of each successive complex increases gradually, then decreases gradually, leading to a spindle shape pattern. See strip below:



The major risk factor for the development of torsades de pointes is excessive prolongation of the QT interval. Antiarrhythmic medications that prolong the action potential duration (and the refractory period of ventricles) may prolong the QT interval. Contributing factors to torsades de pointes also include hypomagnesemia, hypokalemia, or pre-existing bradycardia. The drug of choice for treatment of torsades de pointes is magnesium sulfate. For treatment of torsades de pointes, dosage is 1–2 grams IV over one to two minutes followed by a continuous infusion of 1–2 grams over an hour. A total dose of 4–6 grams may be needed. Other emergency measures include use of overdrive pacing to terminate the arrhythmia, electrical cardioversion, and defibrillation.

Source: [13; 28; 33; 37; 71; 72] *Figure 3*

MEASURING QT AND QTc INTERVALS

The QT interval reflects ventricular depolarization and repolarization. It is measured from the beginning of the QRS complex to the end of the T wave. The length of the QT interval is normally influenced by the heart rate, and when the rate is faster, the QT interval shortens to promote efficient depolarization, repolarization, and contraction. When the rate is slower, the QT interval is slightly longer. As a rough estimate, the QT interval is considered to be "normal" if it is less than one-half of the RR interval. When administering an antiarrhythmic medication that prolongs the QT interval, it is important to differentiate between a normally lengthened QT interval caused by a slowed heart rate and abnormally prolonged QT interval caused by side effects of the medication. This is done through a measurement known as a rate corrected QT interval or QTc. The upper limit of the QTc for women is 0.43 sec or 430 msec; for men it is 0.42 sec or 420 msec.

To calculate the QTc, follow these steps:

- Measure the QT interval. If the rhythm is irregular, measure the QT interval for 5 to 10 beats and obtain an average QT interval.
- Measure the RR interval. If the rhythm is irregular, measure the RR interval for 5 to 10 beats and obtain an average RR interval.
- Calculate the QTc by dividing the QT interval by the square root of the RR interval.

A QTc interval that increases by more than 25% from baseline (prior to medication administration) indicates that the QT interval has become dangerously prolonged.

Source: [13; 37] *Table 7*

to accept another electrical impulse, and the arrhythmia will break. Because dofetilide does not slow conduction velocity, the PR and QRS intervals remain normal. It also does not cause hypotension or bradycardia. The major proarrhythmia associated with dofetilide administration is torsades de pointes due to prolongation of the QT interval. The degree of risk is related to the dosage and serum concentration of dofetilide. The higher the dose (or the higher serum concentration), the higher the risk that proarrhythmias will develop. Other proarrhythmias seen with dofetilide administration include premature ventricular contractions, broad complex ventricular tachycardia, nonsustained ventricular tachycardia, and PSVT. Following oral administration, dofetilide is almost completely absorbed; it is primarily excreted by the kidneys [33].

Dofetilide should be initiated or re-initiated in a hospital setting so that patients can be monitored for a minimum of three days [28; 33]. This allows for creatinine clearance measurements to support individualized dose adjustments, continuous ECG monitoring, and access to cardiac resuscitation, if needed [28; 74]. Prior to administration, the patient's baseline QTc and creatinine clearance must be assessed. If the patient's baseline QTc exceeds 440 msec (or 500 msec if ventricular conduction abnormalities), dofetilide is contraindicated. The initial dose is determined by the patient's initial creatinine clearance [33]. A detailed algorithm is provided in the dispensing information to assist the physician and pharmacologist in determining the appropriate dosage. If the patient's renal function is severely impaired, dofetilide is again contraindicated.

Dosage and Administration

For persons with normal renal function, studies have shown that an oral dose of 500 mcg twice daily is effective in restoring normal sinus rhythm. In the presence of impaired renal function, the dose should be reduced. The dose may be as low as 125 mcg twice daily. The usual range for the maintenance dose (normal renal function) is 125–500 mcg twice daily. The administration protocol is as follows [33]:

- Admit the patient to an inpatient facility approved for dofetilide administration.
- Antiarrhythmic medications associated with prolonged QT interval (primarily Class I, Class III) should be discontinued; the guideline is at least three or more half-lives before initiation of dofetilide. Digoxin, beta blockers, and calcium channel blockers may be used to control ventricular rate during the withdrawal period of these drugs.
- Electrolyte imbalances, especially potassium and magnesium, should be corrected before therapy is initiated.
- QTc should be monitored periodically. Dosage should be reduced if QTc increases by more than 15% or exceeds 500 msec within two to three hours after initial dose. See the package labeling or website information for specific dosage reduction guidelines.
- After the second dose, if the QTc interval is greater than 500 msec (or 550 msec in the presence of ventricular conduction abnormalities), dofetilide should be discontinued.
- Continue ECG monitoring for a minimum of three days.

An overdose of dofetilide results in a dangerously prolonged QT interval. Emergency measures include isoproterenol infusion and external noninvasive cardiac pacing. If torsades de pointes develops, IV magnesium sulfate is the treatment of choice [74].

AMIODARONE

Amiodarone has received increasing attention for its ability to convert atrial fibrillation to normal sinus rhythm and to prevent atrial fibrillation in patients undergoing CABG surgery [54; 57; 75]. Categorized as a Class III antiarrhythmic, amiodarone has properties of all four classes. It inhibits conduction through the AV node, prolongs the action potential and refractory period, and inhibits adrenergic stimulation. It may be safely used for patients with congestive heart failure, coronary artery disease, and persons with accessory pathway conduction. The proarrhythmic effects associated with amiodarone include bradycardia, heart block, ventricular fibrillation, and ventricular tachycardias including torsades de pointes. Hypotension may occur with IV administration. Amiodarone is associated with multiple severe side effects and toxic effects. These include pulmonary fibrosis, impaired vision from corneal deposits, photosensitive skin, thyroid dysfunction, and liver dysfunction [33; 76]. Prior to beginning amiodarone therapy, the physician should obtain baseline data. Appropriate data includes a chest x-ray, pulmonary function tests, thyroid function tests, liver function tests, and renal studies. Patients receiving amiodarone therapy should be monitored for development of toxic effects. Serious toxicity, including death due to bradycardia ending in cardiac arrest, has been reported [33]. If symptoms develop, amiodarone should be discontinued. Use of the lowest effective maintenance dose is highly recommended due to the multitude and severity of side effects associated with amiodarone therapy. The FDA has issued a warning regarding concurrent use of amiodarone and simvastatin [77]. In patients who are taking both simvastatin and amiodarone, the dose of simvastatin should not exceed 20 mg/day [33; 73].

The usual initial dose of amiodarone is 150 mg over 10 minutes, then 1 mg/minute for six hours, then 0.5 mg/minute for 18 hours or 600–800 mg/day oral in divided doses up to 10 g/day [33]. When a cumulative dose of 10 g is reached, a maintenance dosage of 200–400 mg/day is begun. For elderly patients, dosing should be initiated at the lower end of the adult dosage range, and the maintenance dose is usually 100 mg/day. Elderly persons clear amiodarone more slowly [33; 54; 57].

OTHER ANTIARRHYTHMIC MEDICATIONS

Propafenone, a Class Ic antiarrhythmic, slows conduction by changing normal ion transportation across cardiac cell membranes. Studies show it may also have Class II antiarrhythmic effects [78]. It may be used for the conversion of paroxysmal atrial fibrillation to sinus rhythm. For an adult weighing 70 kg or more, an initial dose of 600 mg orally is given, followed by a maintenance oral dose of 150–300 mg every eight hours [33]. Propafenone has less risk of torsades de pointes than other antiarrhythmic agents because it does not prolong the QT interval; however, it is still associated with the development of bradycardia, heart block, and signs of congestive heart failure. For this reason, it should not be prescribed for patients immediately following acute myocardial infarction. Other common side effects include nausea, anorexia, constipation, and headache [33]. One case of a severe drug-drug interaction with mirtazapine leading to propafenone toxicity has been reported [79].

Procainamide, a Class Ia antiarrhythmic, has been used for management of atrial arrhythmias for many years, although it may be less useful than some other agents [28]. It increases both atrial and ventricular refractory periods. It can convert atrial fibrillation to normal sinus rhythm and maintain normal sinus rhythm following conversion. Depending on a patient's status, a loading dose may be administered intravenously or orally. Extended-release forms of oral therapy should not be used for initiation of therapy. Procainamide can have proarrhythmic effects including bradycardia, a prolonged QT interval, and heart block. Worsening or refractory tachyarrhythmias can develop in the presence of procainamide toxicity. Serum levels should be carefully monitored. The therapeutic serum level of procainamide is 4–10 mcg/mL. Toxicity may develop at serum levels of more than 10 mcg/mL. For some patients, especially those with impaired renal function, the combined procainamide/*N*-acetylprocainamide (NAPA) level should be monitored. NAPA is an active metabolite of procainamide that has antiarrhythmic properties. The combined procainamide/NAPA serum level should not exceed 30 mcg/mL [33].

Quinidine, another Class Ia antiarrhythmic, prolongs the effective refractory period and increases conduction time. It is effective in converting atrial fibrillation to normal sinus rhythm and in maintaining sinus rhythm following conversion. Because quinidine also decreases vagal tone, thereby facilitating conduction across the AV node, it does not slow ventricular rate. It is indicated for use in patients with controlled atrial fibrillation, usually after digoxin or verapamil has been given. Patients who are in uncontrolled atrial fibrillation should receive other antiarrhythmic agents prior to starting quinidine. Although quinidine comes in an IV form, IV administration is associated with a significant risk of severe hypotension, and use of IV quinidine is discouraged [33].

Flecainide is a Class Ic antiarrhythmic that acts by blocking sodium channels so that conduction through cardiac cells is slowed. Flecainide is only administered orally. Flecainide should not be prescribed for patients in the immediate post-myocardial infarction period. It should be used cautiously in patients with congestive heart failure, conduction defects, and impaired renal function [33]. It is a drug of choice for persons with paroxysmal atrial fibrillation [5; 12; 13; 14; 19; 20; 37; 46; 68].

ELECTRICAL CARDIOVERSION

Direct-current cardioversion involves the delivery of an electrical current that is synchronized to the QRS complexes. Synchronization is necessary to avoid inducing ventricular fibrillation that can occur when a shock is delivered during ventricular repolarization. It is important to differentiate between a cardioversion in which sinus rhythm is not restored, even transiently, and a cardioversion in which sinus rhythm is restored but atrial fibrillation recurs. When sinus rhythm is not restored, approaches that improve energy delivery and allow for successful cardioversion (e.g., increasing shock strength, delivering a biphasic rather than monophasic waveform) should be employed. When sinus rhythm is restored but atrial fibrillation returns, pretreatment with selected antiarrhythmic drugs may increase the likelihood of maintenance of sinus rhythm [28]. The success rate of electrical cardioversion exceeds 75% in patients with atrial fibrillation of relatively short duration in whom the left atrium is not significantly large [37].

INDICATIONS AND TIMING

For whom is electrical cardioversion indicated?

Electrical cardioversion has been found to be an effective and safe method for restoring normal sinus rhythm in a number of patients. It is the treatment of choice for persons with hemodynamically unstable atrial fibrillation [28]. Electrical cardioversion is also indicated for [28; 40]:

- Persons for whom there is a reasonable expectation that normal sinus rhythm can be restored and maintained
- Persons who require "atrial kick" to relieve incapacitating or unpleasant symptoms, improve exercise tolerance, and increase their ability to perform their usual daily activities
- Persons who would benefit from normal sinus rhythm but who have not been able to be successfully cardioverted pharmacologically (i.e., "failed" pharmacologic cardioversion)

Persons who have severe dyspnea or chest pain with atrial fibrillation or who have pre-excited atrial fibrillation should undergo urgent cardioversion [37].

It is not indicated for prevention of subsequent episodes [80]. Cardioversion of atrial fibrillation and subsequent maintenance of sinus rhythm are more likely to be successful when the duration of atrial fibrillation is less than six months [28]. Because electrical cardioversion carries the risk of thromboembolic complications, it generally should be performed when the patient is adequately anticoagulated. Results of observational studies suggest that thromboembolic risk after cardioversion is highest in the first 72 hours and that the majority of events occur within 10 days [28]. Cardioversion may be performed without first anticoagulating the patient only when he/she is hemodynamically unstable and requires immediate intervention, when the patient has been in atrial fibrillation less than 48 hours, or when the absence of an atrial thrombus has been confirmed by TEE [5; 20; 28; 47; 80; 81].

ANTICOAGULATION GUIDELINES

Appropriate anticoagulation management around the time of cardioversion is essential for reducing thromboembolic risk. Results of observational studies suggest that thromboembolic risk after cardioversion is highest in the first 72 hours and that the majority of events occur within 10 days [82]. As indicated, anticoagulation before cardioversion is required for most patients. Warfarin should be initiated, and the dose adjusted to reach and maintain a target goal of an international normalized ratio (INR) of 2.5 (range: 2.0 to 3.0). After the patient has been maintained for three weeks at that therapeutic goal,

cardioversion may be performed. Following cardioversion, anticoagulation should be maintained for four weeks [28; 40].

TEE guidance is an alternative to three weeks of anticoagulation before cardioversion. Therapeutic anticoagulation is achieved and followed by TEE. If no thrombus is seen, cardioversion is performed and anticoagulation is continued for four or more weeks. The absence of left arterial thrombus on TEE does not preclude the need for anticoagulation during and after cardioversion [28; 37]. Alternative strategies for achieving rapid anticoagulation include administration of low-molecular-weight heparin or a new oral anticoagulant. If a thrombus is identified on TEE, cardioversion should be postponed, followed by three to four weeks of anticoagulation. Repeat TEE to ensure thrombus resolution is an option before attempting another cardioversion. If a thrombus remains on repeat TEE, an alternative strategy (e.g., rate control plus appropriate anticoagulation) may be considered [28]. TEE is a good predictor of acute risk. If no thrombus is seen in the cardiac chambers, particularly the left atrial appendage, and dense spontaneous echo contrast is not seen, cardioversion has low acute risk of stroke. Effective anticoagulation in patients with atrial fibrillation reduces the risk of stroke three-fold after four to six weeks [37]. Data on cardioversion risks for atrial flutter are limited. However, because atrial flutter can be associated with thrombi and episodes of atrial fibrillation, it is recommended that the anticoagulation management strategy for cardioversion of atrial flutter be the same as that for atrial fibrillation [28].

PREPROCEDURE

Prior to the procedure, the patient should be carefully assessed. Serum electrolytes and serum drug levels of medications such as digoxin should be checked. Electrolyte imbalances should be corrected. The administration of IV electrolytes has been found to increase the success rate of cardioversion in patients with persistent atrial fibrillation [83]. Testing for elevated C-reactive protein levels may predict the recurrence of atrial fibrillation following cardioversion [84; 85; 86; 87]. Cardioversion should not be performed if the patient has digitalis toxicity. A baseline 12-lead ECG should be obtained. Oral antiarrhythmic medications, such as oral amiodarone or sotalol, may be started prior to the cardioversion. In some patients, this will facilitate conversion to normal sinus rhythm and maintenance of sinus rhythm following the procedure. The patient should be adequately sedated with a short-acting agent (e.g., midazolam, propofol), and an opioid analgesic, such as fentanyl, is commonly used. Reversal agents (e.g., flumazenil, naloxone) should be available [81]. The risks of the procedure should be explained to the patient and family. Common risks include the problems associated with moderate sedation, skin burns, and the development of proarrhythmias [37; 81]. The procedure should be explained briefly to patients. Consider including these points:

- An IV access will be established.
- The patient will be "nothing by mouth" (NPO) for several hours prior to the procedure.
- The patient's ECG, blood pressure, and oxygen saturation levels will be continuously monitored before, during, and following the procedure.
- The patient will be sedated or general anesthesia will be used.

Potentially life-threatening postprocedure events may occur, including the induction of ventricular tachycardia/fibrillation, asystole, and transient depression of myocardial function. Techniques to handle these situations should be readily available to prevent complications [80; 81].

PROCEDURE AND POSTPROCEDURE CARE

A variety of commercially available external cardioverters are available for external electrical cardioversion. The physician in charge of the procedure should be thoroughly familiar with the chosen device [66; 80]. ECG leads are placed on the patient. The cardioverter delivers a programmed shock in synchronization with the patient's own QRS. Synchronization decreases the risk that the patient will go into ventricular fibrillation from the electrical shock. The initial shock may be a low voltage. If unsuccessful, the voltage will be increased. Following completion of the procedure, the patient will be monitored until he/she is recovered from the anesthesia/sedation. As noted, follow-up care includes oral antiarrhythmic therapy and oral anticoagulation with warfarin sodium [80]. In patients for whom external cardioversion is unsuccessful, an internal shock with electrode catheters has been shown to be successful [80; 88; 89].

PHARMACOLOGIC THERAPY FOR MAINTENANCE OF NORMAL SINUS RHYTHM

GENERAL GUIDELINES

For patients in atrial fibrillation, restoration of normal sinus rhythm may occur spontaneously or through electrical or pharmacologic cardioversion. Regardless of the mechanism of conversion, antiarrhythmic therapy is usually indicated to maintain sinus rhythm (***Table 8***). Some reversion to atrial fibrillation is likely to occur despite optimal antiarrhythmic therapy. However, some patients may benefit from therapy that restores sinus rhythm for prolonged periods [28]. The effectiveness of antiarrhythmic therapy in maintaining normal sinus rhythm should be based on an evaluation of the severity and duration of episodes and not on their occurrence. The following are general principles for initiating drug therapy for maintenance of normal sinus rhythm [28; 54; 83]:

- Selected medications should be given initially in low doses and increased as needed. Closely monitor the patient for therapeutic effect/desired effect and side effects.
- To prevent drug interactions, closely monitor the levels and effectiveness of other agents.

ANTIARRHYTHMIC MEDICATIONS USED TO MAINTAIN SINUS RHYTHM					
Agent	**Class**	**Action**	**Dosage/Route**	**Side Effects**	**Comments**
Quinidine	Ia	Prolongs effective refractory period Increases conduction time Decreases vagal tone, thus facilitating conduction across AV node Converts atrial fibrillation to NSR Maintains NSR following conversion	Varies with preparation. Sulfate (immediate-release): 400 mg every 6 hours Sulfate (extended-release): 300–660 mg every 8 to 12 hours Gluconate (sustained-release): 324–628 mg every 8 to 12 hours	Nausea, diarrhea Hypotension Bradycardia Tachycardia Torsades de pointes CHF Tinnitus Hearing loss	Secondary drug of choice for patients with CAD Give medication with food to decrease GI side effects Monitor QT interval, QRS width, and PR interval Indicated for use in rate controlled, stable atrial fibrillation If patient is in atrial fibrillation with uncontrolled ventricular rate, rate should be controlled with another agent before beginning quinidine IV use should be avoided due to risk of severe hypotension
Disopyramide[a]	Ia	Prevents atrial fibrillation Slows conduction through accessory pathways	Usual oral dose, immediate-release: 100–200 mg every 6 hours Usual oral dose, controlled-release: 200–400 mg	Dry mouth Urinary retention Constipation Glaucoma Negative inotropic effects Increased QT interval	Monitor patient's QT interval
Flecainide	Ic	Maintains NSR Slows conduction through accessory pathways	Maintenance oral dose: 50–150 mg every 12 hours Maximum: 400 mg/day	CHF Bradycardia Heart block Blurred vision Dizziness Flushing Tinnitus Drowsiness Headache Constipation Abdominal pain Prolongs QT interval Increases risk for proarrhythmias	Drug of choice for treatment of atrial fibrillation that has no identifiable cause Recommended for use in absence of structural heart disease only Should not be used in patients with recent MI or who have abnormal LV function May take up to 5 days to achieve complete therapeutic effect
Propafenone	Ic	Slows conduction by changing ion transport across cardiac cell membranes Converts paroxysmal atrial fibrillation to NSR Maintains NSR	Maintenance oral dose: 150–300 mg three times daily	Nausea and anorexia Constipation Dizziness Headache Blurred vision CHF Bradycardia AV block	Effective for use with patients who also have hypertension Secondary drug of choice for atrial fibrillation that has no identifiable cause Does not prolong QT interval so there is less risk of torsades de pointes Should not be used in patients immediately post-MI Use in WPW under investigation

Table 8 continues on next page.

- For persons with paroxysmal atrial fibrillation, first consider the use of flecainide, propafenone, and sotalol.
- If treatment with a single medication is ineffective, combination therapy may be tried. Effective combinations include use of a beta blocker, sotalol or amiodarone, and a Class Ic medication.
- Closely monitor the patient for widening QT intervals.
- Counsel the patient to avoid the concurrent use of non-cardiac medications that can prolong the QT interval.

ANTIARRHYTHMIC MEDICATIONS USED TO MAINTAIN SINUS RHYTHM *(Continued)*

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Sotalol	II with Class III properties	Blocks beta adrenergic receptors resulting in slowed heart rate, decreased AV node conduction, and increased refractory period of AV node Prolongs cardiac action potential Maintains NSR after cardioversion	Usual oral dose: 80–160 mg twice daily May increase up to 320 mg/day in 2 to 3 divided doses	Torsades de pointes VT, VF Bradycardia Hypotension Heart block CHF Bronchospasm Fatigue Weakness GI symptoms Dizziness Dyspnea	Hypokalemia, hypomagnesemia increase risk of proarrhythmias; deficits must be corrected before therapy is initiated Effective for use in patients with concurrent CAD Use with caution in patient <2 wks post-MI Dosing should be adjusted for patients with renal impairment; see package insert for guidelines Initial drug of choice for patients with atrial fibrillation that has no identifiable cause Risk of torsades de pointes increases with doses >320 mg/day Only one sotalol preparation labeled for use in atrial fibrillation Manufacturer of labeled preparation recommends therapy be initiated in facility equipped with continuous ECG monitoring, and cardiac resuscitation Continuous ECG monitoring recommended for 3 days (when on maintenance dose)
Amiodarone[a]	III	Slows conduction through AV node Prolongs QT interval Prolongs QRS duration Maintains NSR after conversion	Oral loading dose: 800–1,600 mg/daily in divided doses for a period of 1 to 3 weeks (until control achieved or intolerable side effects occur). Follow with 600–800 mg/day in 1 to 2 doses Maintenance oral dose: 100–400 mg per day	Bradycardia Heart block Hypotension Corneal deposits Photodermatitis Paresthesias Tremor Ataxia Headache Hyper-/hypo-thyroidism Constipation Pneumonitis Pulmonary fibrosis	Initial drug of choice for patients with CHF May be secondary drug of choice for patients with CAD Obtain baseline data before initiating: chest x-ray, liver and thyroid function and renal tests, pulmonary function tests Slow-acting will take several weeks to reach therapeutic level Takes several weeks for side effects to disappear after drug stopped Patient's QTc interval should be monitored Periodic monitoring of potassium and magnesium levels should be done

Table 8 continues on next page.

ANTIARRHYTHMIC MEDICATIONS USED TO MAINTAIN SINUS RHYTHM *(Continued)*

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Dofetilide	III	Converts atrial fibrillation, atrial flutter to NSR Maintains NSR following conversion from atrial fibrillation Blocks delayed rectifier potassium currents, thus delaying repolarization in cardiac tissue Does not affect other repolarizing potassium currents, sodium channels, adrenergic receptors	Oral dosing: Must be calculated individually based on QTc and creatinine clearance. Continuous ECG monitoring required Patients' heart rate, QTc, and serum creatinine must be obtained before initiating therapy Usual dose: 125–500 mcg twice daily Maximum: 500 mcg twice daily	Torsades de pointes Other ventricular arrhythmias Hypertension Palpitations Bradycardia MI Ventricular fibrillation Abnormal conduction Headache Dizziness Nausea Diarrhea Cerebral ischemia	Must be initiated in hospital setting Dosage must be individualized based on patient's QT intervals and renal function Contraindicated for patients with prolonged QTc interval If QTc increases after initiation of therapy, dose must be reduced or stopped
Dronedarone	III	Inhibits sodium, potassium channels, thus prolonging the action potential and refractory period Similar to amiodarone, it inhibits alpha1-receptor mediated increases in blood pressure	Usual oral dose: 400 mg twice daily	Bradycardia Dermatitis Eczema Diarrhea, nausea Abdominal pain	Contraindicated in patients with severe heart failure requiring recent hospitalization Rare but severe liver injury has been reported

AV = atrioventricular; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; NSR = normal sinus rhythm; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.
[a] Off-label use

Source: [28; 33] *Table 8*

SPECIFIC MEDICATIONS

Oral antiarrhythmic medications found to be effective in maintaining normal sinus rhythm include quinidine, disopyramide, flecainide, propafenone, sotalol, amiodarone, dofetilide, and dronedarone. However, pharmacologic therapy should be abandoned if symptomatic improvement is not achieved or if the patient experiences any adverse effects [49; 90; 91]. In addition to possible adverse effects, some antiarrhythmic medications (i.e., disopyramide, quinidine, and sotalol) may increase mortality. Possible benefits on clinically relevant outcomes (e.g., stroke, embolism, heart failure) remain to be established [75].

Quinidine

Quinidine is available in different salts as quinidine sulfate or quinidine gluconate. Its use in patients with paroxysmal atrial fibrillation has not been extensively evaluated, although it appears to be as effective as Class Ic agents. It has been shown to significantly reduce the recurrence of atrial fibrillation [75]. Quinidine can be associated with severe gastrointestinal (GI) side effects, including nausea and diarrhea. Development of proarrhythmia is a concern [33]. The medication should be administered with food or milk to decrease GI effects [33]. If severe GI side effects persist, the type of preparation may be changed (i.e., from gluconate to sulfate or vice versa).

Disopyramide

Disopyramide may be administered in a short- or sustained-release form. Because it prolongs the QT interval, it is not indicated as a first drug of choice for persons who also have hypertension. The combination of left ventricular hypertrophy caused by long-standing hypertension and a prolonged QT interval greatly increases the risk of proarrhythmias such as torsades de pointes [33].

Flecainide

What is the drug of choice for treatment of atrial fibrillation that has no identifiable cause?

Flecainide is the drug of choice for the treatment of atrial fibrillation that has no identifiable cause. It is recommended for use only in the absence of structural heart disease and should not be prescribed for patients who have had a recent myocardial infarction or have abnormal left ventricular function [33].

Propafenone

Propafenone is an effective antiarrhythmic for persons who also have hypertension because it does not prolong the QT interval. Studies suggest it reduces the recurrence of atrial fibrillation [75]. It should not be prescribed for patients immediately following acute myocardial infarction [33].

Sotalol

Sotalol has been gaining popularity in the management of atrial fibrillation. It has both Class II (beta adrenergic blocking) and Class III properties. It slows the heart rate, decreases conduction through the AV node, increases AV node refractory period, and prolongs the cardiac action potential. It has been found to be effective in maintaining normal sinus rhythm. Administered orally, the initial dose for the person with normal renal function is 80 mg twice daily. This dose may be gradually increased over a period of days to a maximum of 640 mg total daily dose. The usual dose is 80–160 mg twice daily. Dosage should be reduced in the presence of renal impairment [33]. For persons undergoing electrical cardioversion, sotalol may be started prior to the procedure to facilitate cardioversion and continued maintenance of sinus rhythm. The manufacturer of the proprietary form of sotalol warns that only one preparation has been labeled for use in atrial fibrillation. See the package insert for additional information [92]. Because it prolongs the QT interval, sotalol has a proarrhythmic effect; arrhythmias associated include torsades de pointes, other forms of ventricular tachycardia, ventricular fibrillation, bradycardia, and heart block. Hypotension and signs of congestive heart failure may occur. Increased risk of all-cause mortality has been suggested [75]. Hypokalemia and hypomagnesemia increase the risk of proarrhythmic effects. Torsades de pointes has been associated with doses in excess of 320 mg/day [33]. The manufacturer recommends that sotalol be initiated in a hospital setting with continuous ECG monitoring. The facility must be equipped with cardiac resuscitation equipment/staff. ECG monitoring is recommended to continue for three days when the patient is on a maintenance dose [33].

Amiodarone

Amiodarone is a drug of choice to maintain normal sinus rhythm in patients with congestive heart failure. Studies suggest it reduces the recurrence of atrial fibrillation [75]. It has the added benefit of providing effective rate control, thus eliminating the need for other drugs to control rate. It is a secondary or last resort choice to maintain sinus rhythm in persons with coronary artery disease. Because of the multiple side effects and toxicities of amiodarone, persons receiving it should be monitored periodically, and the lowest effective maintenance dose should be used [33].

Dofetilide

Dofetilide may be used for maintenance of normal sinus rhythm. As described, dofetilide therapy must be initiated in a hospital. Evaluation for use of this drug in the elderly is imperative [12; 14; 19; 33; 34; 46; 47; 53; 54].

Dronedarone

Dronedarone received FDA approval in 2009 for the management of atrial fibrillation and atrial flutter. Dronedarone shares many antiarrhythmic properties with amiodarone but has a more favorable safety profile and fewer adverse effects. Its use is contraindicated in patients with severe heart failure requiring recent hospitalization [28; 33; 92; 93; 94; 95; 96]. Dronedarone may be considered in the management of patients with paroxysmal atrial fibrillation or after conversion of persistent atrial fibrillation [28]. It should not be used for rate control in permanent atrial fibrillation [28]. Dronedarone may be used for the prevention of recurrent atrial fibrillation [49; 75]. In addition, this medication may be initiated in the outpatient setting [28]. It is important to note that the FDA issued a drug safety announcement about cases of rare, but severe liver injury, in patients being treated with dronedarone. The risk of injury has been added to labeling for the drug [97].

PILL-IN-THE-POCKET APPROACH

The ACC/AHA/ESC Task Force for management of patients with atrial fibrillation has suggested that outpatient maintenance of sinus rhythm, the "pill-in-the-pocket" approach, shows promise. This approach allows for intermittent (rather than daily) administration of oral antiarrhythmic medication as an acceptable treatment option for patients with sporadic episodes of atrial fibrillation. It is not recommended for patients with daily episodes [28]. Self-administration of oral antiarrhythmic drugs improves the patient's quality of life, decreases overall hospital admissions, and reduces treatment costs. Class Ic drugs, such as propafenone and flecainide, are recommended for their efficacy, rapid action, and safety (i.e., no organ toxicity and low incidence of proarrhythmia). They are not recommended for patients with underlying structural heart disease [6; 28; 91].

PREVENTION OF THROMBOEMBOLIC COMPLICATIONS

What is the recommended antithrombotic therapy for persons at low risk for cerebrovascular accident?

Atrial fibrillation has been identified as the most common disorder leading to systemic embolization [5; 98; 99]. Remember that in atrial fibrillation, the atria merely "quiver." They never fully contract to expel all of the blood from the chambers into the ventricles. The blood that remains in the atria becomes stagnant, allowing clots to form. A thrombus (clot) is most likely to form in the left atrium. Soft, friable fragments of the clot may break off and flow into the ventricle, where they are ejected into the systemic or pulmonary circulation. The most common thromboembolic event linked to atrial fibrillation is the development of a CVA. The statistics are alarming. For example, atrial fibrillation is associated with a four- to fivefold increased risk of stroke and causes an estimated one in seven strokes [1]. The overall mortality rate associated with CVAs is

CHA_2DS_2-VASc SCORING SYSTEM FOR ATRIAL FIBRILLATION STROKE RISK			
Age	<65 years (0 points)	65–74 years (1 point)	≥75 years (2 points)
Sex	Female (1 point)	Male (0 points)	
CHF History	No (0 points)	Yes (1 point)	
Hypertension History	No (0 points)	Yes (1 point)	
Stroke/TIA/Thromboembolism History	No (0 points)	Yes (2 points)	
Vascular Disease History[a]	No (0 points)	Yes (1 point)	
Diabetes History	No (0 points)	Yes (1 point)	
CHF = congestive heart failure; TIA = transient ischemic attack; MI = myocardial infarction; PAD = peripheral artery disease. [a]Defined as prior MI, PAD, and/or aortic plaque.			
Source: [114]			*Table 9*

significant. Up to 20% of persons who have a CVA may die within the first year, and one-quarter to one-half of all who survive experience permanent neurologic damage resulting in partial or total loss of independence and activities of daily living [75; 100]. The associated direct and indirect costs are high [100]. Persons with atrial fibrillation are at increased risk for CVA if they have one or more of the following risk factors: advanced age, history of previous CVA, history of transient ischemic attacks (TIAs), history of previous systemic embolism, history of left ventricular dysfunction, heart failure, diabetes mellitus, or hypertension [7; 101; 102].

National recommendations are to anticoagulate persons with atrial fibrillation. Persons who should be anticoagulated include [28; 40; 45]:

- Persons who fail pharmacologic or electrical cardioversion and remain in atrial fibrillation
- Persons who experience permanent/persistent/chronic atrial fibrillation
- Persons who have converted to normal sinus rhythm but have recurrence of atrial fibrillation

Despite the existence of national recommendations to anticoagulate patients with atrial fibrillation, a systematic review revealed that less than 70% of eligible patients receive oral anticoagulation treatment, including those at highest risk [103]. Another review of anticoagulation therapy in patients with high-risk atrial fibrillation before admission for stroke revealed that 29% were not receiving any anticoagulation therapy, 31% were prescribed antiplatelet therapy, and only about one-fourth of the 39% receiving warfarin achieved therapeutic INR levels [104].

The specific type of therapy recommended depends on an assessment of the patient's level of risk to develop thromboembolic complications, irrespective of the pattern of atrial fibrillation [28; 45; 49]. Stroke-risk stratification schemes for patients with atrial fibrillation were developed in the late 1990s and later refined and validated in large population studies [105; 106; 107; 108; 109]. The $CHADS_2$ score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus,

CHA_2DS_2-VASc SCORE AND CORRESPONDING ANNUAL STROKE RISK	
CHA_2DS_2-VASc Score	**Adjusted Stroke Risk (% per year)**
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2
Source: [118]	*Table 10*

stroke [double weight]), first published in 2001, was developed to predict the risk of stroke in patients with nonrheumatic atrial fibrillation [106]. It was derived by combining risk factors from prior studies and then testing their validity in a cohort of 1,773 Medicare-aged patients over 2,121 patient years [105; 110]. The $CHADS_2$ score was found to be limited by the non-inclusion of common stroke risk factors and was subsequently expanded to include three additional independent risk factors: vascular disease, age 65 to 74 years, and female sex [111; 112; 113]. The new, more inclusive scoring system is known as the CHA_2DS_2-VASc score (***Table 9***). It has been widely used since 2010 [48; 114].

Note: Adjusted stroke rate scores (***Table 10***) are based on data from Lip and colleagues [109; 115; 116; 117]. The actual rates of stroke in contemporary cohorts may vary from these estimates.

Generally, a score of 0 indicates that no treatment is needed. A score of 1 indicates either no treatment or treatment with aspirin or an oral anticoagulant may be considered [28]. A score of 2 or greater in men or 3 or greater in women indicates

AHA/ACC/HRS CLASS I RECOMMENDATIONS FOR SELECTING AN ANTICOAGULANT REGIMEN

In patients with AF (except those with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA_2DS_2-VASc score is recommended for assessment of stroke risk.

For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, OACs are recommended. Options include warfarin and the DOACs dabigatran, rivaroxaban, apixaban, and edoxaban.

DOACs are recommended over warfarin in DOAC-eligible patients with AF (except those with moderate-to-severe mitral stenosis or a mechanical heart valve). For patients with AF who have mechanical heart valves, warfarin is recommended.

Among patients treated with warfarin, the INR should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable. For patients with AF (except those with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a DOAC is recommended.

Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent, and should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences.
Re-evaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risk.

Renal function and hepatic function should be evaluated before initiation of a DOAC and should be re-evaluated at least annually.

AF = atrial fibrillation, OACs = oral anticoagulants, DOAC = direct oral anticoagulant, INR = international normalized ratio.

Source: [40] *Table 11*

treatment with an oral anticoagulant. Anticoagulant agents routinely used for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation include warfarin, direct thrombin inhibitors (e.g., dabigatran), factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) (also referred to as direct-acting oral anticoagulants or DOACs), and antiplatelet drugs (i.e., aspirin and clopidogrel). The use of antiplatelets is a class II recommendation for patients with atrial fibrillation who are at increased risk of stroke and who are being treated for acute coronary syndrome [40]. Although anticoagulants have been effective in reducing ischemic stroke in multiple randomized controlled trials, their use is associated with an increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial hemorrhage. Platelet inhibitors (alone or in combination) are less effective than warfarin, are better tolerated by some patients, and are associated with a lower risk of intracerebral hemorrhage. However, they have similar overall rates of major bleeding in some studies. Careful consideration is required to balance the benefits and risks of bleeding in each individual patient [28; 40]. The AHA/ACC/HRS class I recommendations for risk-based anticoagulant therapy are summarized in ***Table 11*** [40].

Two medications used commonly in prevention of thromboembolic events are aspirin and warfarin. They may be used singly or in combination to prevent thromboembolic events, but the efficacy of combination therapy has not been established [119; 120; 121; 122]. Warfarin in comparison to aspirin leads to a 39% relative risk reduction in stroke [123]. Rather than adding aspirin, the AHA/ACC/HRS Task Force recommends increasing the intensity of the anticoagulant to a maximum target INR of 2.0–3.0 [28]. Aspirin acts by decreasing platelet aggregation. Because it offers only modest protection against stroke for patients with atrial fibrillation, its use may be considered for low-risk patients [28; 49]. As noted, low-risk patients include those who are younger than 65 years of age and have no underlying cardiac disease. It may also be recommended for use in patients, particularly elderly persons, who cannot safely take warfarin. The usual adult dose of aspirin is 81–325 mg oral per day [49].

WARFARIN

Warfarin is recommended for patients at high risk to develop thromboembolic events. It acts by inhibiting the synthesis of clotting factors II, VII, IX, and X that are dependent on vitamin K. Once warfarin therapy is initiated, it can take four to five days to achieve a therapeutic level. Effectiveness of warfarin therapy is evaluated by monitoring the patient's prothrombin time (PT) with the INR. The usual target level for the INR is 2.0–3.0 (target of 2.5) [20; 49]. Some clinicians recommend using the lower end of that range for elderly patients. The risk of serious bleeding complications is greater in persons older than 75 years of age. Initially the PT/INR should be monitored at least weekly. Once the therapeutic goal is achieved, the monitoring may be reduced to monthly [40]. Drug-drug and food-drug interactions may play a significant role in maintaining a stable INR level for persons taking warfarin. Drugs that may impact warfarin effectiveness and INR levels include many anti-infectives and amiodarone. Food interactions include vitamin K containing foods that can antagonize the action of warfarin. Herbal products and nutritional supplements may contain components that can increase or decrease the effectiveness of warfarin [12; 14; 124; 125].

WARFARIN PATIENT EDUCATION	
Topic	**Content**
Purpose, action of warfarin	Warfarin is used to prolong the amount of time it takes the blood to clot. This prevents clots from forming inside blood vessels and the heart; it also prevents existing clots from getting bigger. It does not dissolve an existing clot. The effectiveness of warfarin is measured by a blood test called the prothrombin time/international normalized ratio (PT/INR). The usual goal for the PT/INR for someone taking warfarin is 2.0–3.0. Your healthcare provider will determine what PT/INR numbers are best for you.
How to take warfarin	Take warfarin at the same time every day. Always take the dose prescribed by your physician. Do not take more warfarin or less warfarin unless directed to do so. If you miss a dose, take it as soon as you remember. If you do not remember until the next day, do not take two doses. Taking more medication than prescribed increases the risk of bleeding. If you miss more than one dose, call your physician for instructions. Record the date and dose in a log. Bring this to your medical appointment. Store the medication well out of the reach of children. Store the medication at room temperature, away from heat and direct light. Do not store it in damp places like the bathroom or near the kitchen sink. Discard the medication when out of date. Pregnant women should not handle crushed or broken tablets.
Follow-up care	Keep all appointments for blood tests as scheduled. These may initially be scheduled weekly, then monthly. Keep your doctor's appointments. Your physician will review your blood test and may make changes in your dose to maintain a proper balance between bleeding and clotting, weekly, then monthly. Before receiving any medical care, let the healthcare provider know that you are taking warfarin. Carry identification that states you are taking warfarin. If you become pregnant, let your doctor know right away.
Precautions: other medications	Many medications may interfere with the normal action of warfarin. These include aspirin, ibuprofen, nonsteroidal anti-inflammatory drugs, cough and cold medications, antacids, laxatives, herbal supplements, vitamins containing large amounts of vitamin K, E, or C, as well as a number of prescription drugs including antiarrhythmics. When starting warfarin, make sure that your physician knows all the medications, including prescription, over-the-counter, and herbal/dietary supplements, that you are currently taking. Do not start or stop taking any medications, including over-the-counter medications, without checking with your physician. Do not take other medicines that contain warfarin.
Precautions: diet	The effects of warfarin depend on the amount of vitamin K ingested every day. Do not make large changes in the amount of vitamin K that you consume. If you are ill and cannot eat for several days, notify your physician. Inability to eat your normal diet will change the amount of vitamin K in your body and change the effectiveness of the warfarin. If you have nausea, vomiting, diarrhea, or fever for several days, notify your physician. This too will change the amount of vitamin K in your body. It is best to limit foods high in vitamin K to ½ cup cooked or 3 oz raw serving. These foods include green tea, beef liver, soy oil, tofu, broccoli, Brussels sprouts, cabbage, cauliflower, chickpeas, kale, lettuce, turnip greens, seaweed, and spinach. Avoid drinking cranberry juice or eating cranberry products. Consumption of alcoholic beverages can affect the way warfarin acts in your body. Avoid drinking regularly (on a daily basis). Do not take more than one to two drinks at a time.

Table 12 continues on next page.

WARFARIN PATIENT EDUCATION *(Continued)*	
Topic	**Content**
Precautions: measures to reduce risk of bleeding	Taking warfarin makes it more likely that you will bleed from any type of injury. Take special care to avoid falls or other injuries. Use an electric razor or hair removing cream to avoid cuts. Use a soft toothbrush; brush and floss gently.
Signs and symptoms to report	Feeling tired or looking pale (anemia) Cuts that do not stop bleeding after applying pressure for 10 minutes Bleeding from nose, gums, or ears Blood in urine (i.e., urine that is red or rust colored) Bleeding in stools, or stools that are black and tarry Vomiting or coughing blood Unusually heavy menstrual bleeding Bruises that appear without reason Continuing, severe headache Joint pain, stiffness, or swelling Severe nausea and vomiting Numbness or tingling of hands, feet, or face Paralysis Shortness of breath Weakness Any injuries involving falls or blows to body or head
Emergency care for cuts	For small cuts, apply pressure directly over the cut until the bleeding stops. This may take up to 10 minutes. If bleeding does not stop after 10 minutes, go to the emergency room. For larger injuries, apply constant pressure and obtain immediate medical assistance.
Source: [57; 126]	*Table 12*

For patients to take warfarin safely and correctly, they should receive appropriate patient education when the medication is initiated. See ***Table 12*** for a summary of content to include.

In some cases, warfarin may be considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation. In these patients, the addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, might be considered in patients with atrial fibrillation [49]. Aspirin as monotherapy for stroke prevention is not recommended [28; 40].

ALTERNATIVES TO WARFARIN

Several DOAC alternatives to warfarin have emerged, including the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. The DOACs represent an advance in therapeutic safety and reduced intracranial bleeding as compared with warfarin, including no need for regular monitoring, faster onset of action, and potentially fewer adverse interactions [40; 127]. As an alternative to warfarin, the 2019 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation recommends oral anticoagulation with one of these newer agents over warfarin for patients with nonvalvular atrial fibrillation or atrial flutter with prior stroke, transient ischemic attack, or significant stroke risk [40].

Direct Thrombin Inhibitors

Dabigatran

Dabigatran etexilate mesylate (Pradaxa) is currently the only direct thrombin inhibitor approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [28; 33]. The usual adult dose is 150 mg twice daily [33; 131]. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial compared dabigatran (110 mg or 150 mg twice daily) with adjusted-dose warfarin in 18,113 patients over a median follow-up of two years [128]. The risk of hemorrhagic stroke was significantly (74%) lower with both doses of dabigatran compared with warfarin. Major bleeding was significantly decreased with the 110-mg dose of dabigatran but not with the 150-mg dose. Both doses had lower rates of intracranial bleeding and life-threatening bleeding but higher gastrointestinal bleeding in the 150-mg dose group. Results were similar for secondary stroke prevention [28].

Dabigatran is contraindicated in patients who have mechanical or bioprosthetic heart valves and those who have hemo-

dynamically significant valve disease, severe renal failure, or advanced liver disease [33; 129]. Dabigatran acts by inhibiting the synthesis of clotting factors V, VIII, XI, and XIII. The most common complication is bleeding; patients should be monitored for signs and symptoms of bleeding. Risk factors include concurrent use of drugs that increase the risk of bleeding (e.g., heparin). Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure [40]. Dabigatran is also associated with a significantly elevated risk of myocardial infarction or acute coronary syndrome [130].

Factor Xa Inhibitors

The factor Xa inhibitors have a unique mechanism of action compared with warfarin. Factor Xa is common to both the intrinsic and extrinsic pathways of the clotting cascade making it an excellent target for anticoagulation therapy. It plays a significant role in the formation of thrombin from prothrombin. Inhibition of Xa leads to a significant reduction in thrombin and ultimately clot formation [132]. All of the currently available factor Xa inhibitors are contraindicated for use in patients experiencing active bleeding. The most serious bleeding event is intracranial hemorrhage. Patients with atrial fibrillation should be assessed for bleeding risk using the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history, labile INR, elderly, drugs/alcohol concomitant) risk score [28; 132]. Additionally, all of the factor Xa inhibitors carry a black-box warning advising that premature discontinuation leads to increased risk for ischemic events [33; 132].

Rivaroxaban

Rivaroxaban (Xarelto) is a factor Xa inhibitor approved for prevention of stroke and systemic embolism in patients with atrial fibrillation. Rivaroxaban 20 mg once daily was compared with warfarin among 14,264 high-risk patients with atrial fibrillation [133]. Major bleeding was similar for rivaroxaban and warfarin, but fewer cases of fatal bleeding and intracranial hemorrhage were found for rivaroxaban. The risk of stroke was similar for both drugs. Bleeding is the most common complication with rivaroxaban. Major hemorrhages (e.g., intracranial, gastrointestinal, retinal, epidural, hematoma, adrenal bleeding) have been reported. Patients at increased risk of bleeding include those with congenital or acquired bleeding disorders, recent stroke, severe uncontrolled hypertension, renal impairment, advanced age, and/or concomitant use of drugs that affect hemostasis. The patient's renal function and CBC should be evaluated prior to initiation of rivaroxaban [33]. Rivaroxaban is dosed at 20 mg once daily with the evening meal [33]. Andexanet alfa (coagulation factor Xa [recombinant], inactivated-zhzo) is FDA-approved for reversal of rivaroxaban in the event of life-threatening or uncontrolled bleeding.

Apixaban

Apixaban (Eliquis) 2.5 mg twice daily was compared with warfarin in a double-blind randomized controlled trial of 18,201 patients with atrial fibrillation and two or more of the following conditions: age 80 years or older, weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL [134]. Patients were followed for a mean of 1.8 years. Apixaban was significantly better than warfarin, with fewer overall strokes, systemic emboli, and major bleeding events, but gastrointestinal bleeding complications were similar between apixaban and warfarin. Patients treated with apixaban had fewer deaths than those on warfarin. The benefit of apixaban was independent of type of atrial fibrillation, risk profile, CHA_2DS_2-VASc score, and whether the patient had a history of prior stroke [134].

Apixaban is indicated for patients with nonvalvular atrial fibrillation to reduce the risk of stroke and systemic embolism [33]. The most common complication is bleeding; patients should be monitored for signs and symptoms of bleeding. Risk factors include concurrent use of drugs that increase the risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs). Hepatic function also should be monitored [33; 40]. The usual adult dose is 5 mg twice daily [33].

Rivaroxaban or apixaban also may be used for three weeks prior to and four weeks after cardioversion in patients with atrial fibrillation or atrial flutter of 48 hours or more duration or when the duration is unknown [28; 35; 40].

Edoxaban

Edoxaban (Savaysa) is another factor Xa inhibitor approved for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation. Edoxaban was approved in 2015 on the basis of a double-blind randomized trial of 21,105 patients with nonvalvular atrial fibrillation [135]. Participants were randomized to high-dose edoxaban (60 mg daily), low-dose edoxaban (30 mg daily), or warfarin; creatinine clearance up to 30 mL/min was an exclusion criterion. Edoxaban was found to be noninferior to warfarin with regard to stroke prevention or thromboembolic complications. It also was associated with significantly lower rates of bleeding and death from cardiovascular causes [135]. In patients with upper-range creatinine clearance (greater than 95 mL/min) the efficacy of edoxaban is reduced and there is an increased rate of ischemic stroke compared with patients treated with warfarin [135]. Consequently, the FDA does not recommend edoxaban for patients with a creatinine clearance greater than 95 mL/min. Edoxaban should also be avoided in patients with renal failure or severe renal impairment, defined as a creatinine clearance less than 15 mL/min [40; 135]. The usual adult dose is 60 mg once daily [33].

RADIOFREQUENCY ABLATION AND CRYOABLATION IN THE MANAGEMENT OF ATRIAL FIBRILLATION

INDICATIONS

What is an indication for radiofrequency ablation of the AV node?

Radiofrequency ablation of the AV node is an interventional therapy commonly used in the management of atrial

ELECTROPHYSIOLOGY TESTING AND ABLATION

Electrophysiology testing is an invasive diagnostic cardiovascular procedure that can confirm and pinpoint the location of accessory conduction pathway(s) in the heart. It is performed in a specially equipped cardiac catheterization lab. Multiple catheters are introduced through the femoral vein into the right side of the heart. Each catheter contains 4 to 16 electrodes for monitoring the heart's electrical activity. The catheters are positioned in various locations in the heart; common sites include the high right atrium, the apex of the right ventricle, the AV junction/His bundle, and the coronary sinus. During the procedure, specific pacing protocols are used to determine the location and characteristics of any accessory pathways. Based on the location and characteristics of the accessory pathway(s), a treatment plan will be developed. Treatment options include medical management of the syndrome and associated arrhythmias and radiofrequency ablation of the accessory pathway(s). If the pathway is to be ablated, another catheter (the ablation catheter) is advanced to the site, and more extensive/precise mapping of the accessory pathway is done. The location of the ablation catheter is adjusted until it is close to the pathway. Radiofrequency energy waves are applied to the pathway until pre-excitation disappears and the tachyarrhythmia cannot be restarted. The procedure may last from three to five hours. Postprocedure care involves bedrest, frequent vital signs, and observing the femoral insertion sites for bleeding or hematoma formation.

Source: [17; 54; 63; 136; 137] *Table 13*

fibrillation. The relative safety of radiofrequency energy has contributed to the widespread adoption of this technique as a therapeutic modality for atrial fibrillation [136; 137]. Radiofrequency ablation has been found to be effective for persons who have significant symptoms with atrial fibrillation and/or poorly controlled ventricular rate who also [19; 40; 49; 58; 138; 139]:

- Have remained in atrial fibrillation despite attempts at electrical or pharmacologic cardioversion or who quickly revert to atrial fibrillation following cardioversion (referred to as "failed cardioversion")
- Cannot take antiarrhythmic medications because of severe side effects or the development of proarrhythmias
- Have inadequate rate control despite optimal dosing of appropriate antiarrhythmic agents

It is indicated for atrial fibrillation with lifestyle-impairing symptoms and inefficacy or intolerance of at least one antiarrhythmic agent [28; 140]. Radiofrequency ablation is performed in the electrophysiology lab. See ***Table 13*** for additional details about electrophysiology procedures. To ablate the AV node, radiofrequency waves are sent through catheters positioned at the AV node. Radiofrequency energy is electrical energy produced by a high frequency alternating current. As this current passes through cardiac tissue, it produces heat and creates a lesion in the AV node. The atria remain in atrial fibrillation, but no atrial impulses are conducted through the AV node to the ventricles. With AV node ablation, the patient's only effective ventricular rhythm is a junctional or ventricular escape rhythm. Because this rhythm is insufficient to meet the body's needs for cardiac output, a permanent pacemaker is inserted [19; 137].

Radiofrequency ablation of the AV junction is the simplest procedure performed in patients with atrial fibrillation. AV nodal modification is less effective and is not frequently performed, except in an attempt to avoid pacemaker implantation. Both approaches are used to achieve good rate control, but unlike ablation techniques in atrial tissue, neither restores normal sinus rhythm. Few absolute contraindications to radiofrequency ablation exist. Left atrial ablation and ablation for persistent atrial flutter should not be performed in the presence of known atrial thrombus [137].

Catheter-based cryoablation was developed after radiofrequency ablation. Cryoablation utilizes tissue cooling to cause tissue necrosis. Low-intensity cooling (-10° C) allows assessment of lesion efficacy and safety, prior to delivering the deeper cooling (-70° C) that causes irreversible tissue necrosis. Cryoablation is not as versatile nor as widely used as radiofrequency ablation, but it is safer for ablation near the AV node [137].

No consensus exists on the optimal ablation technique, nor is there a consensus on what constitutes a clinically successful procedure. Data reveal that it is difficult to eliminate every episode of atrial fibrillation with catheter ablation. However, catheter ablation renders 90% of patients free from symptomatic atrial fibrillation and reduces its burden by more than 99% at one year of follow-up [141]. Single-procedure ablation is successful in 60% to 80% of optimal candidates, but many patients require repeat ablation [141]. The results of a study that compared radiofrequency ablation and two regimens of cryoballoon ablation resulted in no difference in one-year efficacy (53% by time to first recurrence) but greater than 98% burden reduction, as assessed by continuous cardiac rhythm monitoring [142]. A meaningful discussion about ablation success rates must include a definition of success that includes how intensively patient rhythms are monitored [141]. Despite the lack of consensus, ablation for atrial fibrillation is generally more effective than antiarrhythmic drug therapy, especially for those patients in whom pharmacotherapy has failed [139; 143].

PRE- AND POSTPROCEDURE CARE

Prior to radiofrequency ablation of the AV node, the patient should receive information about radiofrequency ablation and permanent pacemaker insertion. Informed consent is obtained. Preprocedure evaluation should include a thorough history, physical examination, and a review ECG (12-lead if available). Laboratory studies should minimally include a complete blood cell count and an assessment of the patient's renal function and electrolyte levels. Other tests that may be indicated include exercise testing with or without cardiac imaging and cardiac catheterization [137]. The patient should be kept NPO for at least six hours prior to the procedure. Cardiac medications with electrophysiologic effects (e.g., beta-blockers, calcium channel blockers, digoxin) and Class I and III antiarrhythmic drugs should be tapered and/or discontinued. Warfarin is usually discontinued for at least a few doses preprocedure [137]. IV access should be established.

In the electrophysiology lab, the patient will be sedated, and continuous monitoring of blood pressure, heart rate and rhythm, and oxygen saturation initiated. Following the procedure, the patient's vital signs and oxygen saturation levels will be monitored closely. The patient's ECG will be monitored to evaluate proper pacemaker functioning. The sites used for insertion of the ablating catheters (usually the right and left femoral veins) will be monitored for signs of bleeding or hematoma formation. Depending on the size of catheters used, the patient may be on bed rest for four to six hours. During this time, the patient will need to keep his/her legs straight to decrease the risk of the bleeding from the catheter insertion sites. The pacemaker insertion pocket (often in the subclavian area) is monitored for signs of bleeding or excessive swelling. The head of the patient's bed is often elevated 30 degrees for 24 hours to maintain stable placement of the pacemaker leads.

DISCHARGE INSTRUCTIONS

Patients who have received pacemakers frequently have many questions and concerns. Careful discharge teaching and provision of written information can help to alleviate anxiety. General measures to cover in discharge teaching include [53; 137]:

- Check the incision daily for signs of infection or redness, tenderness, or drainage. Notify your physician if these develop.
- Do not apply lotion or powder to the incision.
- Do not lift more than 10 pounds (or as specified by your physician) for the first four weeks following implantation. Avoid excessive pushing or pulling.
- Limit activity involving the affected arm for the length of time directed by your physician.
- Always carry your pacemaker identification card with you.

Patients and their family members often have many questions about operating home, office, or industrial equipment. Pacemaker manufacturers provide detailed information in written booklets that should be given to the patient at the time the pacemaker is implanted.

ELECTROPHYSIOLOGIC MAPPING AND ABLATION

Because the ectopic beats of atrial fibrillation can occur in various portions of the atrium, electrophysiology studies have been performed on many patients to determine the site or sites of the abnormal foci. The most common area of abnormal activity has been found to be in the vicinity of the pulmonary veins in the left atrium. This discovery led to the use of radiofrequency ablation of the pulmonary vein region as a cure for atrial fibrillation. It has even been suggested that the procedure could be used as a first-line approach to cure atrial fibrillation, because there is no need for long-term antiarrhythmic drug use. However, there is not yet a consensus on this approach as curative [137; 144; 145; 146].

Pulmonary vein isolation is achieved in the electrophysiology lab, and a dose of radiofrequency energy is delivered to ablate the desired region. New energy sources such as laser, ultrasound, and cryothermia have also been used [147; 148]. Multidimensional computed tomography (CT) and magnetic resonance angiography help visualize the anatomic landmarks necessary for ablation procedures and may also help prevent procedure-related complications [144; 147; 149]. Increasing evidence suggests that comprehensive evaluation of the left atrium using cardiac magnetic resonance imaging or CT has significant prognostic value for long-term outcomes [149; 150]. Complications include fistulas, pseudoaneurysms, TIA, and cardiac tamponade. Pulmonary vein stenosis and stroke are rare, but serious, complications [80; 144]. As with other ablation techniques, anticoagulation is initiated at the time of the procedure and continued for at least three months.

This procedure is suggested only for patients who have not responded to pharmacologic therapy with multiple antiarrhythmic medications, patients with paroxysmal atrial fibrillation, and patients with ECG evidence of an underlying electrophysiologic disorder (e.g., WPW syndrome) [70; 151]. In 2013, the recommendations for catheter ablation were expanded to include patients with symptomatic persistent atrial fibrillation and symptomatic paroxysmal atrial fibrillation in patients with significant left atrial dilation or with significant left ventricular dysfunction [49].

MANAGEMENT OF ATRIAL FIBRILLATION FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY

SCOPE OF THE PROBLEM AND RISK FACTORS

A common complication of CABG surgery is atrial fibrillation. Although reported rates vary, it is estimated that 15% to 50% of persons undergoing CABG surgery will develop atrial fibrillation postoperatively [152; 153]. If a patient undergoes CABG surgery combined with valve repair, the likelihood of developing atrial fibrillation increases markedly. This represents a serious problem, as it increases the length of a patient's stay and cost of care, increases the risk of CVA and of

hemodynamic compromise in the postoperative patient, and causes discomfort for the patient from palpitations, dyspnea, and other signs and symptoms. Postoperative atrial fibrillation has also been found to be an independent predictor of poor long-term prognosis and long-term mortality [153; 154]. Atrial fibrillation generally occurs within five days following surgery and is most likely to occur within two to three days [155]. However, it can develop as late as three weeks postoperatively [154]. Risk factors associated with development of atrial fibrillation include [46; 47; 80; 153; 156; 157]:

- Increasing age; the risk increases in patients older than 60 years of age
- COPD
- Abrupt discontinuation of beta blocking agents prior to surgery. Research has shown that after CABG surgery, catecholamine levels may be elevated and normal beta adrenergic receptor function can be altered. These changes have been linked to the development of atrial fibrillation. Pre-operative use of beta blockers may provide some protection from these changes.
- Length of aortic cross-clamp time during the procedure. Longer cross-clamp times have been linked with an increased incidence of atrial fibrillation following surgery.
- Postoperative pericarditis

Less common risk factors include chronic renal failure, an enlarged left atrium, cardiomegaly, and a history of rheumatic heart disease.

RECOMMENDED MEDICAL THERAPIES

For prevention of postoperative atrial fibrillation following CABG, many sources recommend that beta-blocker therapy be initiated (or resumed) as soon as reasonably possible following surgery [156; 158]. Use of a beta blocker to prevent the development of atrial fibrillation following cardiac surgery is a class I recommendation in AHA/ACC/HRS guidelines [28]. Prophylactic use of other antiarrhythmic agents has not been recommended. Use of digoxin has been found to have little effect and is not recommended [28]. Preoperative administration of statins may reduce postoperative atrial fibrillation and shorten the patient's stay on the ICU and in the hospital [28; 159]. Studies have found that the postoperative prophylactic use of amiodarone reduces the risk of atrial fibrillation and decreases the total cost of care [158; 160; 161]. However, the use of amiodarone and other antiarrhythmic medications, such as calcium channel blockers and procainamide has been linked to the unacceptable side effects of bradycardia and hypotension [75]. Early intervention for patients who develop increasingly frequent premature atrial contractions (PACs) has been recommended by some clinicians. However, there is no consensus regarding the best treatment. Immediate intervention is indicated for persons who develop atrial fibrillation in the postoperative period. Based on an assessment of the patient's symptoms and hemodynamic status, medical treatment may involve intravenous medications for rate control, pharmacologic cardioversion, or electrical cardioversion along with identification and correction of factors that may contribute to the development of arrhythmias such as hypokalemia and hypomagnesemia. If atrial fibrillation persists despite appropriate therapy, anticoagulation therapy should be started as soon as the surgeon decides it is feasible. Four to six weeks following surgery, the patient's status should be re-evaluated [162; 163]. In some persons, postoperative atrial fibrillation is a relatively transient arrhythmia that may spontaneously resolve. However, for others, the arrhythmia may persist and require medical management as previously described for persons with coronary artery disease [28; 40].

ATRIAL FIBRILLATION IN WOLFF-PARKINSON-WHITE SYNDROME

Atrial fibrillation is an arrhythmia that may develop in persons with WPW syndrome. Management of atrial fibrillation in WPW is very different than management of atrial fibrillation caused by other cardiac and noncardiac causes. To understand the seriousness of this arrhythmia and rationale for treatment, let's look briefly at the WPW syndrome itself.

PATHOPHYSIOLOGY OF WPW

Which ECG characteristics are associated with Wolff-Parkinson-White syndrome?

During early fetal development, a number of bundles of fibers exist that connect the atria and ventricles. As fetal development progresses, these connections disappear until the AV node is left as the only functional electrical connection between atria and ventricles. In persons with WPW, one or more of these fibrous connecting bundles has persisted into adulthood. The connecting bundle, called an accessory pathway, provides an alternative route for the conduction of an electrical impulse through the heart. Depending on a number of factors, an electrical impulse may travel only through the normal conducting pathway, through both the normal and the accessory pathways, or only through the accessory pathway. When the impulse travels through the accessory pathway, it bypasses the normal delay in the AV node and reaches the ventricles early. It initiates ventricular depolarization before the impulse traveling down the normal conduction pathway can reach the ventricles. The ventricles depolarize abnormally. The abnormal conduction through the accessory pathway alters the normal ECG waveform. The changes include [164]:

- A shortened PR interval (less than 0.12 sec). The PR interval is shortened because the impulse from the atria reaches the ventricles through the accessory pathway more rapidly than normal.
- The presence of a delta wave. A delta wave is a slurring of the initial deflection (either positive or negative) of the QRS complex. It reflects the early, abnormal depolarization of the ventricles that occurs when the impulse travels through the accessory pathway.

- An abnormally widened QRS complex (greater than 0.12 sec). The widened, abnormal QRS occurs when most of the ventricular depolarization is stimulated by an impulse traveling down the accessory pathway. In normal conduction, both ventricles depolarize almost simultaneously. With accessory pathway conduction, one ventricle is stimulated to depolarize before the other.
- Abnormal ST waves. An ST wave represents repolarization. When depolarization is abnormal, the pattern of repolarization will also be abnormal.

These ECG characteristics are often very subtle and may be confused with ECG changes associated with other conditions, such as acute myocardial infarction, bundle branch block, and left ventricular hypertrophy. The early depolarization of ventricles through accessory pathway conduction is called pre-excitation. The degree of pre-excitation (i.e., the extent to which the ventricles depolarize from accessory pathway conduction) can vary. Factors that increase conduction across the AV node decrease conduction through the accessory pathway. These factors include exertion, intense emotion that increases adrenergic stimulation, and certain medications, such as procainamide, beta agonists (e.g., epinephrine, albuterol, terbutaline), and atropine. Factors that inhibit or slow conduction across the AV node increase the extent of pre-excitation. These factors may include a normal increase in vagal tone associated with sleep, and medications such as digoxin, adenosine, beta blockers, and calcium channel blockers. Medications known to slow conduction through the AV node should be not used for persons with WPW [165; 166].

The presence of multiple conduction pathways (normal and one or more abnormal) often leads to development of tachyarrhythmias, including atrial fibrillation. Patients with WPW who develop atrial flutter or atrial fibrillation are at increased risk of dangerous ventricular arrhythmias due to the extremely fast conduction across the bypass tract [164]. Atrial fibrillation develops in approximately one-third of persons with WPW. Approximately 80% of patients with WPW syndrome will develop atrial fibrillation and 5% will have atrial flutter [164]. Atrial fibrillation seen in WPW is characterized by [17; 19; 164; 165; 166]:

- Irregularly irregular rhythm
- QRS that may appear different and reflect varying degrees of pre-excitation. Some impulses will be conducted through the normal pathway, others through the accessory pathway.
- A higher than usual ventricular rate. In "normal" atrial fibrillation, the AV node blocks conduction of most of the fib waves and keeps the ventricular rate from exceeding 150 to 250 bpm. Because impulses in atrial fibrillation associated with WPW can bypass the AV node, the ventricular rate may approach 350 bpm. At this rate, the risk that the atrial fibrillation will degenerate into ventricular fibrillation is high.

DIAGNOSIS

WPW should be suspected in any person who shows the following signs and symptoms:

- Shortened PR interval and delta wave associated with accessory pathway conduction present on ECG
- Subjective complaint of palpitations
- History of syncope, presyncope, or sudden cardiac arrest episodes

Definitive diagnosis can be done through electrophysiology testing [164].

MANAGEMENT OF ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE IN WPW

When a patient with WPW presents with atrial fibrillation with rapid ventricular response, the patient's hemodynamic status should be immediately assessed. If there are signs of hemodynamic instability, such as hypotension, signs of congestive heart failure, or ischemic chest pain, the patient should be immediately cardioverted [28; 164]. If the patient is not hemodynamically unstable, rate control is the high priority. Appropriate medication selection is critical. Use of medications such as verapamil and digoxin that slow or block conduction through the AV node will aggravate atrial fibrillation in WPW and run the risk of accelerating the ventricular rate to the point that ventricular fibrillation can occur [33; 164]. The treatment of choice for hemodynamically stable patients with atrial fibrillation and WPW is IV procainamide or ibutilide [28]. Verapamil, diltiazem, adenosine, digoxin (oral or intravenous), and intravenous amiodarone can precipitate ventricular fibrillation and should not be used [28].

SIMULATED CASE STUDY: THE PATIENT WITH ACUTE-ONSET ATRIAL FIBRILLATION

Patient D is a man, 68 years of age, who presents to the emergency department late one evening complaining of increasing shortness of breath, dizziness, and the sensation of his "heart racing." On admission, his heart rate is 160 bpm, blood pressure 100/50 mm Hg, respirations 26 breaths per minute, and oxygen saturation 88% on room air. Patient D says that his symptoms started abruptly earlier that day and have steadily become worse. He reports a history of long-standing hypertension, coronary artery disease, and a recent percutaneous transluminal angioplasty with placement of two stents.

Comments and rationale: *Symptoms such as those Patient D presents are common indications of acute onset atrial fibrillation with rapid ventricular response. His past medical history is positive for risk factors for the development of atrial fibrillation. These include a positive cardiac history, with hypertension and coronary artery disease, as well as increasing age.*

A 12-lead ECG is obtained. It shows a narrow QRS complex tachycardia with an irregularly irregular rhythm. A diagnosis of atrial fibrillation with rapid ventricular response is made. Oxygen via nasal cannula at 2 liters is started. Patient D is attached to continuous telemetry, oxygen saturation, and noninvasive blood pressure monitoring. Telemetry monitoring shows a variable heart rate ranging from 120 to 160 bpm. At lower rates, fibrillatory waves are present. Crackles are present in the bases of both lungs. Peripheral pulses are diminished and irregular. Patient D's skin is cool but dry. A peripheral IV access is established. After determining that Patient D has no known allergies to medications, 20 mg of diltiazem is prescribed to be given by IV push.

Comments and rationale: *ECG characteristics associated with atrial fibrillation with rapid ventricular rate include a QRS complex within normal limits (sometimes called "narrow complex") and an irregularly irregular ventricular rhythm. Sinus P waves are absent. At rapid rates, the irregular rhythm and absence of P waves may be difficult to determine. Fibrillatory waves are present but are often not seen at rapid rates. Because of the variable filling time associated with atrial fibrillation, pulse pressure may be intermittent and some beats may not perfuse well to the periphery. Loss of normal atrial contraction coupled with tachycardic heart rates may precipitate signs of heart failure, such as dyspnea, rales, and hypotension. Patient D is symptomatic with his atrial fibrillation but not dangerously unstable (with rapidly falling blood pressure, rapidly increasing signs of heart failure, or increasing chest pain). Therefore, the initial goal of treatment is to slow his heart rate. Diltiazem, a calcium channel blocker, slows conduction through the AV node and prolongs the AV node refractory period, thus slowing the ventricular rate in atrial fibrillation. It has a rapid onset of action. Because IV diltiazem administration is associated with development of bradycardia, heart block, increased signs of congestive heart failure, and hypotension, the patient should be continuously monitored during and after its administration. If the diagnosis of atrial fibrillation with rapid ventricular response cannot be made, adenosine may be used to establish a diagnosis. Oxygen by nasal cannula is used to increase oxygen saturation and decrease the subjective sensation of dyspnea.*

In response to the IV diltiazem, Patient D's heart rate initially slowed to a rate of 110 to 120 bpm but rapidly returned to a high rate. After 15 minutes, another bolus was ordered, followed by a continuous infusion of diltiazem at 5 mg/hour. The orders indicated that the drip could be titrated up to a maximum of 15 mg/hour to achieve the desired rate (as long as Patient D's blood pressure remained within ordered parameters). Additional laboratory and diagnostic tests are ordered to rule out or identify any precipitating causes for the arrhythmia. The tests included a complete blood count, serum electrolytes, thyroid function studies, renal and liver function studies, and cardiac enzymes. A portable chest x-ray is performed. Patient D is questioned about his use of over-the-counter medications, alcoholic beverages, illicit drugs, and dietary supplements or herbal medicines. He is then transferred to an inpatient telemetry unit for further monitoring and clinical management.

Comments and rationale: *A diltiazem bolus may be repeated after 15 minutes if the desired rate control is not achieved from the initial bolus. The patient should be monitored for the development of side effects, such as hypotension and bradyarrhythmias. Following a bolus, a continuous infusion may then be started to achieve rate control. Blood pressure, ECG, and oxygen saturation monitoring should be done continuously during continuous intravenous infusion. Signs, such as falling blood pressure, decreasing oxygen saturation, and failure to control rate, should be noted and handled immediately. If intolerable side effects develop, the diltiazem will be discontinued and another medication prescribed. If side effects do not develop but rate control is not achieved, additional medications may be prescribed. Other medications used for rate control include procainamide, esmolol, metoprolol, and propranolol. Patients receiving multiple antiarrhythmics should be monitored closely as combination therapy may result in a cumulative effect on heart rate and rhythm, blood pressure, and the patient's risk of developing congestive heart failure. To effectively manage atrial fibrillation, any underlying or precipitating causes should be identified and corrected. Precipitating causes may include anemia, consumption of alcohol, use of cocaine or other similar substance, hyperthyroidism, and electrolyte imbalances (especially potassium and magnesium). Atrial arrhythmias may also develop during acute stages of myocardial infarction.*

Patient D is transferred to an appropriate inpatient unit. Continuous ECG, blood pressure, and oxygen saturation monitoring are maintained. After one to two hours on the diltiazem drip, the patient's heart rate drops and stabilizes at 80 to 90 bpm. Fibrillatory waves and an irregularly irregular ventricular response are clearly present on ECG. His laboratory data comes back showing normal serum electrolytes, renal function studies, thyroid function tests, and liver function tests. His hematocrit and hemoglobin are within normal limits. His cardiac enzymes and troponin are negative for myocardial infarction. His chest x-ray shows some congestion in his lower lobes consistent with mild congestive heart failure. Intravenous furosemide is ordered at a low dose to relieve the pulmonary congestion. Patient D's vital signs improve. His blood pressure increases to 118/70 mm Hg, his respiratory rate slows to 18 breaths per minute, and he reports a decreased sensation of dyspnea and palpitations. After he stabilizes, the process of weaning the IV drip and starting the patient on oral diltiazem is initiated. Low-dose oral diltiazem is effective in maintaining rate control for Patient D when his activity is limited; however, when his activity level is increased, he begins to experience increasing episodes of an uncontrolled rate. The dose is increased, and rate control during activity improves. Evaluation of Patient D's medical therapy shows his heart rate controlled at 70 to 80 bpm, his blood pressure is stable, and his symptoms relieved. Because of the high risk of thromboembolic events and serious consequences of CVA, Patient D is started on anticoagulation therapy. It is determined that he is at high risk for a CVA, and a heparin drip is started. Oral anticoagulation with warfarin also begins at this time. Routine monitoring of his partial thromboplastin time and PT/INR is ordered.

Comments and rationale: *Once rate control is achieved and maintained, the patient's vital signs are stable, and other signs (e.g., signs of congestive heart failure, angina) have resolved, the patient may be changed to an oral dose for maintenance therapy. Short periods of a rapid rate may still occur, especially with exertion. If these episodes are intermittent and nonsustained, they may be effectively managed by adjusting the medication dose or adding additional antiarrhythmic medications. Rate control is considered successful if it alleviates troublesome symptoms, relieves dyspnea, increases activity tolerance, and improves the patient's ability to perform activities of daily living. Anticoagulation is indicated for persons who remain in atrial fibrillation. Because the atria never fully contract in atrial fibrillation, stasis of blood can occur, which may lead to the development of clots. To prevent thromboembolic events such as CVA, anticoagulation should be started. For high-risk patients, warfarin is the drug of choice. In an inpatient setting, intravenous heparin may be used to provide adequate anticoagulation until warfarin reaches a therapeutic serum level.*

With careful questioning, it is determined that Patient D's subjective symptoms of atrial fibrillation actually began a week or more prior to his admission. Patient D admits to feeling some palpitations and shortness of breath intermittently but did not seek medical care until the symptoms became severe. Current assessment of Patient D's status shows normal breath sounds with absence of rales, the chest x-ray shows resolution of pulmonary congestion, vital signs are stable, and he is able to participate in activities of daily living and ambulate without trouble. It is decided to send Patient D home on oral medication to maintain rate control, on warfarin for anticoagulation, and monitoring his status over the next several weeks to evaluate the effectiveness of this therapy.

Comments and rationale: *Options for long-term management of the patient with atrial fibrillation include restoration of normal sinus rhythm through pharmacologic or electrical cardioversion or rate control through use of oral antiarrhythmic medications. For patients known (or suspected) to be in atrial fibrillation for more than 48 hours, national standards recommend adequate anticoagulation for three weeks prior to either pharmacologic or electrical cardioversion. Or, a transesophageal echo may be performed to rule out a left atrial thrombus. If no thrombus exists, the patient may be safely cardioverted. For patients whose symptoms are controlled by rate control, oral therapy/antiarrhythmics coupled with oral anticoagulation often is sufficient treatment. If the patient develops recurrent episodes of rapid atrial fibrillation, or experiences troublesome symptoms at home despite optimal antiarrhythmic therapy, he/she may benefit from restoration of normal sinus rhythm by more aggressive methods.*

Patient D receives verbal and written instructions on how to take his warfarin and his antiarrhythmic medications. Appointments with the outpatient laboratory for PT/INR monitoring are set up, and a follow-up appointment with his physician is scheduled. Patient D is instructed on signs and symptoms to report to the doctor, including signs of bleeding and recurrence of his signs of rapid atrial fibrillation. Indications that medical therapy is effective in managing his atrial fibrillation include: ability to perform normal activities without symptoms of fatigue, dyspnea, dizziness, or palpitations; vital signs within desired parameters; absence of annoying or problematic side effects from medications; and absence of signs of thromboembolic events.

SIMULATED CASE STUDY: CLINICAL MANAGEMENT OF THE PATIENT WITH PERSISTENT ATRIAL FIBRILLATION

Patient W is a woman, 58 years of age, who is admitted to the unit with bradycardia and near syncope. She says that this morning she had been grocery shopping, became very dizzy, and nearly passed out. On admission assessment, her blood pressure is 116/74 mm Hg, and her heart rate is 48 bpm and irregular. Her respirations are even and easy at a rate of 20 breaths per minute. Her oxygen saturation on room air is 99%. Peripheral pulses are slightly diminished. Lung fields are clear to auscultation. Patient W is placed on continuous telemetry monitoring, and a 12-lead ECG is obtained. The ECG shows that her underlying rhythm is atrial fibrillation with a slow ventricular response. Patient W says that she has had atrial fibrillation for several months. Initially, her heart rate had been controlled on oral antiarrhythmic medications. However, over the last month, she has been experiencing increasing episodes of palpitations and a rapid heart rate. Her medication had been increased, but she developed hypotension and a slow heart rate on the increased dose. A few days prior to her admission, her oral antiarrhythmic medication was changed. On the new medication, she has not had any prolonged episodes of a rapid heart rate but experienced some "dizzy spells."

Comments and rationale: *Lack of adequate rate control coupled with development of serious side effects such as bradycardia, hypotension, and syncope with multiple oral agents are indications that oral antiarrhythmic therapy is not effective in managing the patient's atrial fibrillation. Other options include pharmacologic cardioversion, electrical cardioversion, radiofrequency ablation with or without pacemaker insertion, or continuation of oral medications with insertion of a demand pacemaker to treat symptomatic bradycardia.*

Laboratory tests are ordered, including a complete blood count, serum electrolytes, renal and hepatic function tests, chest x-ray, urinalysis, and PT/INR. A peripheral IV access is established. Continuous telemetry monitoring is maintained, and Patient W's vital signs are monitored every four hours. Her heart rate remains between 48 and 52 bpm. Patient W's oral antiarrhythmic medication is discontinued. Analysis of Patient W's ECG shows that her QTc is 580 msec. The therapeutic options of electrical cardioversion, radiofrequency ablation, and continued oral antiarrhythmic therapy with insertion of a demand pacemaker are discussed with the patient. The patient expresses reluctance to undergo pacemaker insertion at this time. With the patient's agreement, she is scheduled for electrical cardioversion. Patient W expresses the understanding that pacemaker insertion or ablation with pacemaker insertion might still be required if cardioversion is unsuccessful or if she becomes symptomatic on therapy to maintain sinus rhythm following successful cardioversion.

Comments and rationale: *Laboratory tests such as a complete blood count and serum electrolytes are ordered to rule out any abnormal findings (e.g., anemia, hypokalemia, hypomagnesemia) that may make management of atrial fibrillation more difficult. Due to Patient W's continued bradycardia, her oral antiarrhythmic medication is discontinued. Her QTc interval is significantly prolonged. Because Patient W has developed bradycardia and a prolonged QTc interval, she is not a candidate for pharmacologic cardioversion.*

Patient W's complete blood count, renal and hepatic function studies, and urinalysis come back within normal limits. Her serum electrolytes show hypokalemia but a normal serum magnesium level. IV potassium replacement is given, and a repeat potassium level returns within normal limits. Patient W's INR comes back at 2.7. Her usual warfarin dose is continued. A review of her outpatient laboratory results shows that her INR has been maintained between 2.6 and 3.1 for more than six weeks.

Comments and rationale: *Hypokalemia may contribute to the continuation of atrial fibrillation. It should be corrected prior to electrical cardioversion or other intervention. Because of the risk of thromboembolic complications caused by left atrial thrombi for persons with atrial fibrillation of more than 48 hours duration, anticoagulation with warfarin is indicated. National standards require anticoagulation for at least three weeks prior to cardioversion. The therapeutic target for warfarin is an INR of 2.0–3.0.*

Patient W is kept NPO for six hours prior to the cardioversion. She is taken to the preoperative area prior to the procedure and sedated with IV medications. Continuous ECG, blood pressure, and oxygen saturation monitoring is initiated. The cardioverter/defibrillator is set for a low-energy, synchronized shock. The initial shock is ineffective in restoring sinus rhythm. A second, slightly higher energy shock is effective. ECG monitoring shows Patient W is now in normal sinus rhythm at a rate of 62 bpm. Her vital signs are monitored closely until she wakes up from the sedation. Patient W is returned to her room. Continuous telemetry monitoring is continued.

Comments and rationale: *Electrical cardioversion is a painful procedure; sedation or general anesthesia is required. Because of the risks associated with sedation/anesthesia, and the risk that the patient may go into ventricular fibrillation from an electrical shock, cardioversion should be performed in a setting where emergency equipment for intubation and management of cardiac arrest is readily available.*

Patient W remains in normal sinus rhythm at an acceptable rate in the immediate period postcardioversion. Her blood pressure is stable, and her dizzy spells do not recur. She is discharged on a low-dose oral antiarrhythmic and warfarin. Patient W is instructed to notify a physician if she experiences palpitations, dizziness, or near-fainting spells.

Comments and rationale: *Oral antiarrhythmic therapy is generally required to maintain normal sinus rhythm following successful cardioversion. Although Patient W had been unable to take higher dose oral antiarrhythmics, she was able to tolerate low-dose therapy. It is likely that Patient W will experience short episodes of atrial fibrillation. However, therapy is considered successful if these episodes are brief, do not cause debilitating symptoms, and resolve without additional treatment. National standards recommend that anticoagulation therapy be continued for at least four weeks following cardioversion.*

CONCLUSION

Atrial fibrillation is an increasingly common health problem in the United States. As the American population continues to age, the number of older adults who require clinical management of atrial fibrillation will also increase. Appropriate clinical management involves careful assessment of the patient's symptoms and status, correction of any underlying or contributing causes, and identification of realistic medical goals. Therapies available for the management of atrial fibrillation include a wide variety of antiarrhythmic medications, pharmacologic cardioversion, electrical cardioversion, and radiofrequency ablation with or without pacemaker insertion. Because the risk of CVA is high for persons with atrial fibrillation, anticoagulation therapy should be considered and initiated when appropriate. Ongoing monitoring of the patent's response to antiarrhythmic and anticoagulation therapy is crucial to the effective management of atrial fibrillation and the prevention of serious complications.

RESOURCES

American Heart Association
1-800-242-8721
https://www.heart.org

Heart Rhythm Society
202-464-3400
https://www.hrsonline.org

National Heart, Lung, and Blood Institute
1-877-645-2448
https://www.nhlbi.nih.gov

Customer Information and Evaluation are located on pages 103–104.

Prescription Opioids: Risk Management and Strategies for Safe Use

Includes 15 Advanced Pharmacotherapeutic/Pharmacology Hours

Audience

This course is designed for nurses, physicians, physician assistants, and pharmacy professionals involved in the care of patients prescribed opioids to treat pain.

Course Objective

The purpose of this course is to provide the information necessary for clinicians to make informed decisions regarding prescribed opioids in order to minimize adverse events, substance abuse, and drug diversion.

Learning Objectives

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

1. Define terms associated with opioid therapy and aberrant drug use.
2. Analyze behavioral responses to prescribed opioids and signs of emerging opioid misuse.
3. Outline the impact of clinical and professional society attitudes toward opioid prescribing.
4. Review the role of OxyContin in the rise of prescribed opioids for chronic noncancer pain.
5. Evaluate the basic epidemiology of prescription opioid use, misuse, and dependence in the United States.
6. Identify factors that influence opioid prescribing decisions.
7. Describe the morbidity and mortality associated with the use of prescription opioids.
8. Discuss characteristics of appropriate and inappropriate opioid prescribing and contributory factors to both.
9. Compare opioid abuse risk assessment tools and the utility of risk stratification.
10. Outline the appropriate periodic review and monitoring of patients prescribed opioid analgesics, including the role of urine drug testing.
11. Describe necessary components of patient/caregiver education for prescribed opioid analgesics, including guidance on the safe use and disposal of medications.
12. Compare available opioid abuse-deterrent formulations.
13. Evaluate government and industry efforts to address problems arising from prescription opioid analgesic misuse.
14. Review the unintended negative consequences of efforts to reduce prescribed opioid analgesic misuse, diversion, and overdose.
15. Discuss treatment considerations for patients with active or remitted substance use disorder who require prescribed opioid analgesics for chronic pain.

Faculty

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

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

Division Planner
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NetCE designates this continuing education activity for 15 pharmacotherapeutic/pharmacology contact hours.

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

INTRODUCTION

In the United States, the use of prescription opioids for the treatment of pain is challenging and complex. There exists a prevailing tendency to inappropriate patterns of underprescribing (because of fear of adverse effects and addiction) or overprescribing (because of failure to select properly or frustration over a poor therapeutic response). These practice patterns are especially prevalent in the management of patients with chronic noncancer pain and have resulted in or contributed to unnecessary patient suffering from inadequately treated pain and increasing rates of opioid abuse, addiction, diversion, and overdose.

Morphine was synthesized close to 200 years ago and entered clinical use more than 150 years ago. To this day, morphine and its opioid analogs remain the most powerful analgesics for severe acute pain and effective therapies for many chronic pain conditions. Opioid analgesic prescribing for pain control has risen dramatically since the late 1990s, and although opioid analgesic use in moderate-to-severe acute pain, cancer pain, and terminal pain is widely accepted, its use in chronic noncancer pain remains controversial [1]. Opioids can pro-

vide effective pain control, but problematic side effects are common, long-term outcomes vary, and escalating rates of addiction, diversion, and fatal overdose involving opioids have occurred in tandem with their increasing clinical use for pain control. These negative outcomes from increasingly widespread prescribing have heightened awareness of the need for prescribers to mitigate the inherent risks that come with opioid analgesics in order to minimize their abuse, addiction, diversion, and fatal toxicity [2].

There is a shortage of pain specialist physicians in the United States that is expected to worsen, and this has resulted in most of the medical care for patients with chronic pain being delivered by primary care physicians [3]. The current problems involving prescription opioid analgesics are primarily the result of prescriber factors and the undue influence of stakeholders over pain medicine practice [4; 5]. Prescriber factors include inappropriate opioid prescribing and inadequate patient counseling and monitoring, reflecting deficits in knowledge, competence, and performance [6]. Many primary care providers lack sufficient knowledge or training in pain medicine and in appropriate opioid use, and the majority report they do not feel confident managing chronic pain [7; 8]. A clinical skills assessment by the American Academy of Family Physicians found significant and widespread knowledge deficits among family practice physicians in the medical skills necessary for providing optimal pain management, managing drug abuse and addiction, and utilizing risk evaluation and mitigation strategies when prescribing opioids [9].

The goal of this course is provide clinicians with an understanding of the essential components of appropriate opioid prescribing. This objective will be achieved through discussion of behavioral responses in patients receiving opioids for pain; the antecedents, catalysts, manifestations, and consequences of the dramatic and widespread increase in clinical and illicit use of prescription opioids; the assessment and management of pain; patient risk of developing problems with their prescribed opioid analgesic; governmental, law enforcement, and industry strategies and tactics to reduce prescription opioid abuse; and treatment approaches for patients with comorbid chronic pain and substance use disorders. Among primary care providers, there is great variability in the understanding of opioid use and misuse and in the confidence with which opioids are used for management of chronic pain. Often, there is confusion or difficulty distinguishing physiological tolerance and dependence or uncontrolled pain behaviors from symptoms and signs of opioid use disorder. In addition to substantial differences in patient tolerability and analgesia with opioid analgesics, patients can also exhibit a range of psychological, emotional, and behavioral responses to prescribed opioids, the result of inadequate pain control, an emerging opioid use problem, or both. An appreciation for the complexities of opioid prescribing, and the dual risks of litigation due to inadequate pain control and drug diversion or misuse, is necessary for all clinicians in order to provide the best possible patient care and to prevent a growing social problem.

There is also considerable evidence that, in the past, major stakeholders have negatively influenced the delivery of safe, effective, and appropriate analgesic care to patients with chronic pain. This has occurred, in part, through bias of the information provided to clinicians to guide their practice and prescribing behavior with respect to opioid analgesics. Effective practice is based on training, clinical judgment, and ongoing study of advances in practice areas. Careful clinicians pay attention to published research and other mediums of knowledge transfer that are relevant to their particular practice, with a trained eye toward the quality of evidence. Unfortunately, much of what has been published on chronic pain management, especially as regards opioid drug use, has uncertain validity because of various forms of bias and nonrigorous statistical analysis. This has had an adverse impact on the consistency and quality of care, on clinician confidence in how to render care, and on the public health cost of opioid analgesic care. For these reasons, an ***Appendix*** to this course has been included to provide some historical perspective on opioid prescribing practices and to address sources of bias in clinical (therapeutic) research.

DEFINITIONS

Definitions and use of terms describing opioid analgesic misuse, abuse, and addiction have changed over time, and their current correct use is inconsistent not only among healthcare providers, but also among federal agencies reporting epidemiological data such as prevalence of opioid analgesic misuse, abuse, or addiction. Misuse and misunderstanding of these concepts and their correct definitions has resulted in misinformation and represents an impediment to proper patient care.

OPIOID ABUSE, DEPENDENCE, AND ADDICTION

How is inappropriate opioid prescribing defined?

Inappropriate opioid analgesic prescribing for pain is defined as the nonprescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness [10]. Appropriate opioid prescribing is essential to achieve pain control, to minimize societal harms from diversion, and to minimize patient risk of abuse, addiction, and fatal toxicity. The foundation of appropriate opioid prescribing is based on thorough patient assessment, treatment planning, and follow-up and monitoring. Essential for proper patient assessment and treatment planning is comprehension of the clinical concepts of opioid abuse and addiction, their behavioral manifestations in patients with pain, and how these potentially problematic behavioral responses to opioids both resemble and differ from physical dependence and pseudodependence. Prescriber knowledge deficit has been identified as a key obstacle to appropriate opioid prescribing and, along with gaps in policy, treatment, attitudes, and research, contributes to widespread inadequate treatment of pain [7]. A 2013 survey measured primary care physician understanding of opioids and addiction. Of the 200 participants, [11]:

OPIOID USE TERMINOLOGY	
Term	**Definition**
Misuse, nonmedical use	Use of the opioid that departs from intended prescribing by the provider
Abuse	A maladaptive pattern of opioid use with the primary intent of achieving euphoria or getting high
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Characterized by behavior including impaired control over drug use, compulsive drug use, continued use despite harm, and drug craving.
Physical dependence	The expected response to chronic administration of many drug classes such as opioids, anabolic steroids, and beta-blockers, manifesting in neurologic adaptation whereby a drug class-specific withdrawal syndrome is produced by abrupt cessation, rapid dose reduction, decreased blood concentration, or antagonist administration
Tolerance	A state of adaptation in which the physiologic changes from drug exposure over time lead to diminished drug effect
Pseudoaddiction	An iatrogenic condition whereby patients display aberrant drug-seeking behaviors mimicking opioid use disorder but driven by intense need for pain relief. Resolves with adequate pain relief.
Diversion	Transfer of a controlled substance from authorized to unauthorized possession or distribution
Opioid	Any compound that binds to an opioid receptor in the CNS, including naturally occurring, synthetic, and semi-synthetic opioid drugs and endogenous opioid peptides
Iatrogenic	A response, usually unfavorable, to a medical or surgical treatment induced by the treatment itself
CNS = central nervous system.	
Source: [10; 20; 21]	*Table 1*

- 35% admitted knowing little about opioid addiction.
- 66% and 57% viewed low levels of education and income, respectively, as causal or highly contributory to opioid addiction.
- 30% believed opioid addiction "is more of a psychological problem," akin to poor lifestyle choices rather than a chronic illness or disease.
- 92% associated prescription analgesics with opioid addiction, but only 69% associated heroin with opioid addiction.
- 43% regarded opioid dependence and addiction as synonymous.

This last point is very important because confusion and conflation of the clinical concepts of dependence and addiction has led to accusations of many nonaddicted patients with chronic pain misusing or abusing prescribed opioids and to failure to detect treatment-emergent opioid problems [12]. Knowledge gaps concerning opioid analgesics, addiction, and pain may be related to attitude gaps, and negative attitudes may interfere with appropriate prescribing of opioid analgesics. For example, when 248 primary care physician survey participants were questioned regarding their prescribing approach in patients with headache pain and either a past or current history of substance abuse, 16% and 42% of physicians, respectively, would not prescribe opioids under any circumstance [13]. Possibly contributing to this knowledge deficit is the extent of educational exposure to concepts central in pain management.

A 2018 systematic review evaluated pain medicine curricula in 383 medical schools in Australia, New Zealand, the United States, Canada, the United Kingdom, and Europe [14]. Pain medicine was primarily incorporated into anesthesia or pharmacology courses, rather than offered as a dedicated pain medicine module. Ninety-six percent of medical schools in the United Kingdom and the United States and nearly 80% of medical schools in Europe had no compulsory dedicated pain medicine education. The median number of hours of pain content in the entire medical school curriculum was 20 in Canada, 20 in Australia and New Zealand, 13 in the United Kingdom, 12 in Europe, and 11 in the United States [14].

The nomenclature related to addiction is often inconsistent, inaccurate, and confusing, partially reflecting the diverse perspectives of those working in the related fields of health care, law enforcement, regulatory agencies, and reimbursement/payer organizations. Changes over time in the fundamental understanding of addiction have also contributed to the persistent misuse of obsolete terminology [15]. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association, is perhaps the most influential reference for the diagnosis of addiction and all other psychiatric disorders. Prior to the 2013 release of the DSM-5, previous versions eschewed the term "addiction" in favor of "substance dependence," with a separate diagnostic entity of "substance abuse" representing a lower-grade, less severe version of substance dependence [16]. Also in earlier DSM versions, physiological dependence, manifesting as substance tolerance and withdrawal, was considered a diagnostic criterion of substance dependence. The result was the perpetuation of patient and healthcare professional confusion between physical and psychological dependence and the belief that tolerance and withdrawal meant addiction. This confusion enhanced provider and patient fears over addiction developing from opi-

COMMON MISCONCEPTIONS OF PAIN THERAPY WITH OPIOID ANALGESICS AND ADDICTION	
Misconception or Belief	**Correction**
The tolerance and withdrawal of opioid dependence equates to opioid addiction.	Tolerance, withdrawal, and physiologic dependence are expected responses to opioids and other controlled substances when given in sufficient doses over time and are not, by themselves, indicative of addiction.
Addiction can be accurately predicted and diagnosed in the initial assessment of patients with pain.	Addiction is not an entirely predictable response to reward-producing drugs but may occur in biologically and psychologically susceptible individuals; it is diagnosed over time based on established criteria.
Medications for pain or anxiety should not be used in patients with a substance use disorder history.	Uncontrolled pain or anxiety and other psychiatric illnesses may trigger a relapse to substance use or exacerbate an existing disorder. Treatment should be tailored to patient need and may include alternative treatment modalities, monitored prescriptions, or other measures as needed.
Behaviors such as "clock-watching," preoccupation with obtaining opioid analgesics, deception, stockpiling unused medication, and illicit substance use indicate addiction.	Patients with undertreated pain may engage in problematic behaviors that mimic opioid abuse but are driven by intense need for relief and resolve with adequate pain control.
Substance misuse is the same as substance abuse, dependence, or addiction; all require cessation of opioid prescribing.	Many factors can underlie substance misuse, including varying cultural values, lack of education, misunderstandings, and poor judgment, that do not meet the criteria for a substance use disorder. Misuse does require evaluation for patient education and possible treatment modifications but does not mandate discontinuation of opioids.
Opioid therapy always leads to addiction.	This has been proven false; the rate of iatrogenic opioid use disorder is low.
Some opioids are worse than others in terms of addiction potential.	Addiction is the result of individual susceptibility, and any opioid analgesic can be abused by predisposed individuals.
If morphine is used now, there will not be options when the pain worsens.	An increase in pain severity can be countered by dose increase, switching to another opioid, or adding a non-opioid analgesic.
If I start taking an opioid, I will have to keep increasing the dose to control my pain.	After an effective dose is reached, many patients with chronic pain are able to maintain analgesia on the same dose.
Morphine and opioids cause heavy sedation and probably hasten death.	The initial sedation goes away within the first two weeks of initiation. Opioids have conclusively been shown to not hasten death in hospice patients; pain undertreatment is a far greater concern in hastening death.
Source: [15; 21]	*Table 2*

oid analgesics and contributed to the undertreatment of pain [16]. The DSM-5 has eliminated the categories of substance dependence and substance abuse by combining them into the single diagnostic entity of substance use disorder. The disorder is measured on a continuum from mild to severe [16].

In 2011, the American Society of Addiction Medicine (ASAM) published their latest revision in defining the disease of addiction. Since that time, the public understanding and acceptance of addiction as a chronic brain disease and the possibility of remission and recovery have increased. Additionally, there is growing acknowledgment of the roles of prevention and harm reduction along the spectrum of addiction and recovery. Consequently, ASAM updated its definition of addiction and adopted the following revised definition in 2019 [17]:

> Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

According to the ASAM, the five characteristics of addiction are [18]:

- Inability to consistently abstain
- Impairment in behavioral control
- Craving or increased "hunger" for drug or reward experiences

TERMS TO AVOID OR LIMIT THE USE OF	
Term	**Rationale for not using**
Addicted/addiction	Frequently misused by those untrained to make the diagnosis. Not all who abuse are addicted.
Addictive	Patently false when describing a substance. Addiction resides within the person and not in the substance used. Some drugs do have high abuse liability, but most persons do not respond to exposure with addictive behavior.
Chemical coping	Overused in the literature and by clinicians. Not very helpful, especially if a better treatment or coping strategy is not immediately available.
Drug-seeking	Used when a patient is assumed to lack legitimate need for medication. Should be replaced with relief-seeking, if appropriate.
Hooked	Slang for addicted. Assumes the absence of medical need for the substance and suggests an off-hand, bad attitude.
Inebriated/intoxicated	A snap conclusion when a patient suspected of taking medication or other substance displays an altered sensorium. Better to objectively describe observations.
Malingering	Overcalled and best not expressed unless there is legally valid proof of deception for illicit purposes.
Narcotic	A term formerly referring to opium, morphine, and heroin and still used in the area of law and misused by media in reference to all opioids. Should never be used in a clinical or education context due to strong emotional association with crime, addiction, and death. Best replaced with opioid.
Painkiller	Negative use by media in reports of opioid addiction and overdose. Best replaced with pain reliever.

Source: [19] *Table 3*

- Diminished recognition of significant problems with one's behaviors and interpersonal relationships
- A dysfunctional emotional response

This summary of addiction should not be used as diagnostic criteria for addiction because the core symptoms vary substantially among addicted persons, with some features more prominent than others [17].

Many terms used in discussions of opioid use and misuse may have ambiguous meanings (***Table 1***). The absence of consensus in the terminology and definitions of substance use, substance use disorders, and addiction has led to considerable confusion and misconceptions (***Table 2***). These misconceptions may be harbored by clinicians, patients, family members, and the public and can negatively impact patient interaction, assessment, treatment, and outcomes. Correction of these erroneous beliefs and attitudes is important, as is the use of nonpejorative and nonstigmatizing language when describing opioid analgesics, the patients who need them, and patients who develop aberrant behaviors or addiction involving opioids (***Table 3***). Pejorative terminology has a strong negative effect on patients and serves to reinforce their sense of shame and stigma over using opioid analgesics. These terms signal a negative attitude and judgment to patients [15; 19].

BEHAVIORAL RESPONSES TO PRESCRIBED OPIOIDS

Which behaviors are most suggestive of an emerging opioid use disorder?

Patients with pain display a continuum of behavioral responses to prescribed opioids. Some develop aberrant behaviors, which are defined as unintended behaviors involving the acquisition or use of prescribed opioids [22]. Depending on the study, researchers have reported that as many as 40% of patients with pain receiving opioid therapy exhibit aberrant behavior; however, in only a minority of these patients does the aberrant behavior reflect an emerging opioid use disorder. It is important to distinguish the underlying basis and the level of risk for opioid use disorder represented in the aberrant behavior. This is accomplished by differential diagnosis (***Table 4***). To capture the perspective of pain practitioner viewpoints in associating aberrant behaviors and risk of patient opioid problems, 100 pain physicians were instructed to rank a list of 13 aberrant drug-use behaviors from least to most suggestive of emergent opioid use disorder. Selling the prescribed opioid and prescription forgery received highest ranking as most aberrant, and altered route of administration was given the third highest ranking. Lowest ranked were unkempt patient appearance, sporadic unsanctioned dose escalation, and prescribed opioid hoarding [23].

CONSIDERATIONS FOR DIFFERENTIAL DIAGNOSES
• Inadequate pain management: – Stable condition but inadequate pain control – Progressive condition/pathology – Tolerance to opioids • Inability to comply with treatment due to: – Cognitive impairment – Psychiatric condition • Self-medication of mood, anxiety, sleep, post-traumatic stress disorder, etc. • Diversion
Source: [19] *Table 4*

There are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [24; 25; 26]:

- Selling medications
- Prescription forgery or alteration
- Injecting medications meant for oral use
- Obtaining medications from nonmedical sources
- Resisting medication change despite worsening function or significant negative effects
- Loss of control over alcohol use
- Using illegal drugs or non-prescribed controlled substances
- Recurrent episodes of:
  - Prescription loss or theft
  - Obtaining opioids from other providers in violation of a treatment agreement
  - Unsanctioned dose escalation
  - Running out of medication and requesting early refills

Behaviors with a lower level of evidence for their association with opioid misuse include [23; 24; 25]:

- Aggressive demands for more drug
- Asking for specific medications
- Stockpiling medications during times when pain is less severe
- Using pain medications to treat other symptoms
- Reluctance to decrease opioid dosing once stable
- In the earlier stages of treatment:
  - Increasing medication dosing without provider permission
  - Obtaining prescriptions from sources other than the pain provider
  - Sharing or borrowing similar medications from friends/family

It is essential for clinicians to consider poorly managed pain or poor coping skills as the basis for aberrant behavior. Even aberrant behaviors highly suggesting opioid abuse may reflect a patient's attempt to feel normal or alleviate emotional or physical distress. This is termed chemical coping and refers to the inappropriate use of a prescribed opioid to treat emotional or psychiatric conditions, commonly depression, anxiety, and insomnia. In these cases, the patient is not technically addicted to the opioid, but he or she fears withdrawal from the opioid and losing the ability to function without the drug and, as a result, may abuse opioids, engage in illegal behavior to obtain opioids, or doctor-shop. Aberrant behavior can also be driven by undertreated pain or a failure of treatment management [27]. Importantly, no single behavioral marker clearly identifies addiction in patients with pain who are prescribed opioids, and while all addicts are abusers, not all abusers are opioid-addicted [27].

For the purposes of this course, the term opioid addiction is used to indicate a severe opioid use problem, consistent with the definition of addiction provided earlier in this course and in place of the now-discarded DSM-IV term of opioid dependence. Opioid use disorder is used to encompass the range of problematic opioid use.

CLINICIAN AND PROFESSIONAL SOCIETY ATTITUDES TOWARD OPIOID PRESCRIPTION DRUG USE

BACKGROUND

What factors contributed to broad expansion and indications for opioid prescribing for pain in the 1990s to early 2000s?

Opium and its alkaloids have been used for thousands of years as analgesics. From the end of the 19th century into the early 20th century, heroin was sold as a cough suppressant and briefly promoted as more effective and less addictive than morphine. It was legally marketed in pill form and became widely abused for the intense euphoria by crushing the heroin pills into powder for inhalation or injection [1]. Heroin addiction skyrocketed, and Congress banned the drug in 1924. Wariness of prescribing opioids persisted through the 1980s and 1990s [28].

The United States has a long history of pain undertreatment as a standard medical practice. This was a consequence of the long-standing emphasis on treating the underlying primary illness, minimizing the importance of addressing pain, and viewing pain as an endurable consequence [1]. Another primary factor historically responsible for pain undertreatment has been a resistance to prescribing opioids, driven by fears of patient addiction and the threat of prosecution and potential loss of licensure if opioid prescribing was deemed inappropriate by the state medical board. The widespread practice of

including non-professional lay members on medical boards intensified physician concerns over prejudicial interpretation by board members, even when legitimate medical necessity merited long-term, high-dose opioid prescribing to patients with severe, chronic noncancer pain [28].

These physician concerns were confirmed by the results of a 1992 survey that captured medical board member perception and opinion of legality and appropriateness in opioid prescribing for different pain conditions. A total of 304 members of 49 state medical boards were surveyed; 85% were physicians (MDs and DOs) and 15% were lay public members [29]. Physician members were asked to rank 12 opioids by their order of recommendation for chronic, moderate-to-severe cancer pain. The top selection was codeine with aspirin/acetaminophen (47%), despite codeine being widely accepted as too weak for chronic moderate-to-severe pain. When asked of the general incidence of psychological dependence (as compulsive non-medical use) from opioid pain treatment, 39% did not know. When asked to define "addiction" by selecting one or more of several common definitions, 85% chose physical dependence, 71% chose psychological dependence, 41% chose tolerance, 21% chose physical dependence alone, 10% chose psychological dependence alone, and 1% chose tolerance alone [29].

Respondents were also asked for their opinion, as state medical board members, of the legality and medical legitimacy of opioid prescribing longer than three months for several patient scenarios. Approximately 10% of board members described opioid prescribing as illegal under medical practice, controlled substances law, or both, and requiring investigation in patients with cancer pain alone, 26% in cancer pain with patient history of opioid abuse, 59% in chronic noncancer pain alone, and more than 90% in patients with chronic noncancer pain and history of opioid abuse [29]. Underscoring the gravity of these findings was that 80% of respondents stated their medical board was the agency most likely to investigate improper controlled substance prescribing in their state [29].

Against this backdrop, some pain physicians began to re-examine and challenge the intense physician reluctance to prescribe opioids. Observing the extent that suffering was relieved by opioids in cancer patients with severe pain and the apparent lack of euphoria that differed from the responses of opioid abusers, it was suggested that opioids could also be used to relieve suffering in many patients with intense, persistent noncancer pain, with little risk of addiction. This was followed by an effort to destigmatize the use of opioids, with the objective of easing access to opioids by the large number of patients with severe, persistent noncancer pain. While widely viewed as driven by good intentions, this crusade for acceptance of opioid use in noncancer pain was also accompanied by the regular tendency to minimize the inherent potential risks that accompany opioid prescription drug use, despite the absence of valid evidence to support the assumption [30].

Results from a 1986 chart review study of 38 patients with chronic noncancer pain receiving long-term opioid therapy were cited to support the assertion that long-term opioid use in patients with intractable nonmalignant pain was effective and safe with little risk of addiction. Of the 38 patients in the study, the 2 who developed opioid problems had histories of drug abuse [31]. This paper was followed by several other publications on opioids for chronic noncancer pain [32; 33; 34; 35]. Each paper cited the prevalence rates of iatrogenic opioid addiction reported by three earlier pain studies [36; 37; 38]:

- Of 11,882 hospitalized patients with a negative substance abuse history who received ≥1 opioid dose, 4 developed addiction.
- A national survey of roughly 10,000 patients treated for burn pain found no cases of addiction.
- Of 2,369 patients treated at a headache center who had access to opioid analgesics, 3 developed problems with their prescribed opioid.

These iatrogenic addiction figures were disseminated through communications to specialists, general practitioners, other providers, administrators, regulators, and the lay public. "Less than 1%" became the message that opioids posed little risk of addiction in patient with pain without substance abuse histories. Substantial support for compassion-based efforts to broaden opioid use for pain control also came from the 1990 opinion paper by the co-author of the landmark paper describing gate control theory that revolutionized the concept of pain [39]. In 1988, the Federation of State Medical Boards (FSMB) released a policy explicitly reassuring physicians they would not face regulatory action for prescribing even large amounts of opioids, assuming it was medically warranted [30]. Physician awareness of the new FSMB policy was promoted by widely circulated publications. For example, the Joint Commission published a guide, supported by Purdue Pharma, stating, "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance, and risk of death," and "This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control" [30].

During the 1990s, the American Pain Foundation endorsed more aggressive treatment of chronic pain, while the American Pain Society (APS) promoted the position that pain should be considered a fifth vital sign. The APS and the American Academy of Pain Medicine (AAPM) published a landmark consensus statement in 1997 that stated long-term opioid analgesic use for chronic noncancer pain posed minimal risk of overdose or addiction [30; 40]. The pharmaceutical industry was also instrumental in the movement toward loosening opioid prescribing constraints and broadening the indications for opioid use in managing chronic pain [30; 41]. Professional pain societies wrote consensus statements claiming little risk of addiction or overdose in patients with pain and that long-term opioids were easy to discontinue. In 1997, Congress

RETAIL PURCHASES[a] OF PRESCRIPTION OPIOIDS (GRAMS OF DRUG)—UNITED STATES, 2019–2021			
Opioid	**2019**	**2021**	**Change**
Methadone	15,080,444 g	13,866,600 g	-8.01%
Oxycodone	35,929,260 g	31,190,066 g	-13.2%
Fentanyl base	193,531 g	154,574 g	-20.1%
Hydromorphone	987,221 g	1,013,929 g	+2.71%
Hydrocodone	20,040,962 g	17,399,719 g	-13.2%
Morphine	11,966,623 g	9,728,577 g	-18.7%
Codeine	12,105,985 g	9,942,219 g	-17.9%
Meperidine	292,694 g	153,171 g	-47.7%
Total	96,596,720 g	83,448,855 g	-13.6%
[a]Purchasers include pharmacies, hospitals, practitioners, teaching institutions, and treatment programs.			
Source: [50]			*Table 5*

passed SB402, also known as The Pain Patient's Bill of Rights [42]. In 2001, the Joint Commission issued new standards requiring hospitals to make pain assessment routine and pain treatment a priority. The now familiar pain scale was introduced, with patients asked to rate their pain from 1 to 10 and circle a smiling or frowning face, and pain became the fifth vital sign [43]. Immediately following the release of the new standards, concern was raised that the standards would lead to the inappropriate use of opioids. By 2002, pain as a "fifth vital sign" in the standards was changed to "pain used to be considered the fifth vital sign," and by 2004, this phrase no longer appeared in the Joint Commission's Accreditation Standards manual [44]. The standard that pain be assessed in all patients also remained controversial for two reasons: It seemed inappropriate for some patients due to the nature of their medical condition; and no similar standard existed requiring the universal assessment of other symptoms [44]. Thus, in early 2016, the Joint Commission began revising its pain assessment and management standards, with a focus on acute pain in the hospital setting. Draft standards were published in 2017, implemented in 2018, and revised in 2019 [45; 46].

The financial support supplied to professional societies by drug companies helped influence members to change prescribing practices. Patient advocacy groups, often guided by physicians who felt constrained by the prohibition of opioid prescribing and pain specialist organization consensus that chronic pain had been previously undertreated, worked to elevate awareness that pain was untreated and unrecognized [28; 40]. During this time, opioid prescribing for chronic noncancer pain dramatically increased across the country. The movement for more aggressive pain treatment culminated in 2000, when Congress proclaimed 2000–2010 as the Decade of Pain Control and Research [47]. Shifting demographics also contributed to the changing attitudes toward opioid prescribing. With painful chronic illness rates increasing with the overall population age, there came growing awareness of the importance in providing effective pain relief [43].

Pharmaceutical companies began introducing new opioid formulations, and existing opioid products became more widely prescribed (***Table 5***). The theme of minimal abuse liability was widely used in the marketing materials distributed to prescribers and pharmacists [48]. When the escalating rates of addiction, diversion, and fatal overdose involving prescribed opioids became apparent, the same pain specialists and organizations, pain advocacy groups, drug companies, and media reinforced the perception of opioid legitimacy by primarily attributing the growing individual and public health hazard to improper Internet availability, illicit diversion, and the prevalence of societal drug addiction tendencies [49].

THE OXYCONTIN STORY: A CASE STUDY

How has the story of extended-release oxycodone proliferation in the United States affected pain management and substance use disorder trends?

The story of extended-release oxycodone, marketed as OxyContin, is informative and unique. Although the United States has experienced several waves of widespread prescription drug abuse over the past 150 years, the rapid ascent of OxyContin from market entry to miracle drug for chronic pain to a demonized substance of abuse and diversion on a vast scale is without precedent. Multiple factors facilitated this phenomenon. OxyContin contains a larger amount of high-potency opioid than short-acting opioid formulations. The delayed-release mechanism was easy to circumvent by chewing and swallowing or by crushing the pill and then injecting or snorting the powder. This produced a rapid, powerful opioid effect on par with heroin. Large profits were also possible from illicit sales of OxyContin, which generally commanded a black-market value of $1 per milligram (with higher prices in more rural areas) [51]. In addition, the original product labeling warned against crushing the tablets because rapid release of a potentially toxic amount of oxycodone would ensue, alerting abusers on how to best achieve maximum drug effect. The original labeling also included the FDA-condoned statement

OXYCONTIN SALES AND PRESCRIBING, 1996–2002				
Year	**Sales**	**Increase from Previous Year**	**Number of Prescriptions**	**Increase from Previous Year**
1996	$44,790,000	N/A	316,786	N/A
1997	$125,464,000	180%	924,375	192%
1998	$286,486,000	128%	1,910,944	107%
1999	$555,239,000	94%	3,504,827	83%
2000	$981,643,000	77%	5,932,981	69%
2001	$1,354,717,000	13%	7,183,327	21%
2002	$1,536,816,000	13%	7,234,204	7%

Source: [43] *Table 6*

that the extended-release (ER) mechanism of OxyContin presented a lower abuse potential than other oxycodone products. Perhaps most importantly, its release coincided with the growing acceptance of opioids in pain treatment and the aggressive sale and marketing tactics of its producer, Purdue Pharma [43].

The timing of product launch was fortuitous. Until the 1990s, Schedule II opioids were primarily limited to use in operating rooms and inpatient settings because they required intravenous or intramuscular administration. This posed a serious obstacle to patients with chronic pain who required high-potency opioids. In response to the increasingly permissive climate and by genuine unmet patient need, several high-dose ER formulations of pre-existing opioids were introduced to market. MS Contin, an ER version of morphine sulfate, was introduced in 1985 but was primarily limited to use in cancer pain, partially a result of the stigma surrounding morphine. OxyContin was introduced in late 1995, at the point in time when prescriber attitudes were shifting from fearing iatrogenic addiction to developing a sense of security with prescribing opioid analgesics [43].

To help ensure product success, innovative approaches were employed to elevate visibility and encourage OxyContin prescribing, as well as highly aggressive marketing and sales tactics. The amount of money spent in promotion, marketing, and sales was unprecedented for an opioid, exceeding $200 million in 2001 alone [52]. Marketing and promotion efforts and the timing of the product launch resulted in a tenfold increase in OxyContin prescribing and sales revenue in just three years' time (***Table 6***).

In addition to the usual doctor-directed ads in medical journals, a novel indirect marketing campaign involving "non-branded education" was implemented. Direct-to-consumer advertising of opioid drugs was prohibited, so the concept of pain relief from opioids was promoted to consumers without explicit mention of OxyContin. The public-education program Partners Against Pain (PAP) was launched, with videos, patient pain journals, and an elaborate website that marketed (to prescribers and patients) the message that pain was widespread and treatable with opioid analgesics [43; 53]. The FDA later stated that the PAP website did provide information about OxyContin specifically and also contained a "Find a Doctor" feature to link consumers to physicians in their geographic area known to be willing to prescribe OxyContin [43].

More than 40 national pain-management and speaker-training conferences were conducted between 1996 and 2001. Thousands of prescribers attended the all-expenses-paid symposia held in resort locations [52]. From 1996 to July 2002, more than 20,000 pain-related educational programs and continuing medical education offerings for prescribers were funded by pharmaceutical sponsorship or financial contribution. This included a program that educated hospital physicians and staff on hospital and postoperative pain treatment compliance with Joint Commission pain standards. Pharmaceutical funding was used to underwrite the cost of the Joint Commission pain management educational programs, including the distribution of educational videos and a book on pain management (sold on the Joint Commission's website) [52]. Pharmaceutical funding has also paid for websites that provided free continuing medical educational on pain management; numerous pain management websites; groups such as the American Chronic Pain Association, the AAPM, and the APS; and a youth-focused website [43].

In 1999, pharmaceutical sales representatives were reportedly given 14,000 copies of a promotional video for physician distribution. Physicians were instructed to encourage patient viewing in their waiting rooms or as a "check-out" item and to use the video as an educational tool for office or hospital staff. The FDA later stated they were not provided the video before distribution for detection of inaccurate or unfounded claims, of which they later found several examples [43]. A patient starter coupon program was initiated that provided patients with a free limited-time prescription. Roughly 34,000 coupons had been redeemed when the program ended in 2001 [43; 52].

Between 1996 and 2000, the internal sales force of the pharmaceutical firm that produces OxyContin grew from 318 representatives to 671, and a bonus system was implemented to encourage OxyContin sales [52]. The company is said to have maintained an active database containing nationwide profiles

of individual physicians and their prescribing patterns, allowing for the identification of high-end and low-end OxyContin prescribers by zip code, county, and state; practices with large numbers of patients with chronic pain; and high prescribers of the company's older product MS Contin [52]. Sales representatives were reportedly directed to high opioid prescribers in their sales territories, with the goal of expanding the primary care OxyContin prescribing base. Sales representatives were also directed to call on oncology nurses, consultant pharmacists, hospices, hospitals, and nursing homes [43].

In 1996, the majority of ER opioid prescriptions went to cancer patients, but by 2000, only 3% of OxyContin prescriptions came from oncologists [54; 55]. Opioid medications, and OxyContin in particular, had been successfully promoted as the first-line therapy for an increasingly wide range of moderate-to-severe pain conditions. Family practice physicians became the largest group of OxyContin prescribers, accounting for 21% of prescriptions in 2000 and close to 50% in 2003 [52; 53]. This was followed by the growing concern that, in a managed care system, time constraints imposed on primary care physicians did not allow sufficient time to evaluate and follow patients with complex chronic pain [52].

The most critical issue and source of greatest prescriber concern was the risk of iatrogenic addiction. To help counter this perception, promotion and marketing to healthcare professionals and patients alike emphasized that OxyContin prescribing carried little risk of addiction. Misrepresenting this risk proved costly. In 2007, the pharmaceutical company paid $634 million in fines following guilty pleas from three of its executives to criminal charges for promoting false claims that OxyContin was less addictive and less subject to abuse and diversion than other opioids [52].

The escalating rates of OxyContin misuse were integral to the growing nationwide problem of prescription opioid abuse, diversion, addiction, and overdose. By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States. Predictably, this public health epidemic created a backlash from regulatory and law enforcement agencies [56].

THE PAIN MANAGEMENT MOVEMENT

By the mid-2000s, professional and law enforcement efforts had emerged to curtail OxyContin abuse, including the pain management movement and creation of the pain management subspecialty. However, these efforts had some unintended negative consequences. Pharmacists were tasked with evaluating legal prescription appropriateness through a "drug use review." Encouraged by drug enforcement authorities, some became adversaries of physicians and patients by reporting any out-of-the-ordinary prescribing to the police [56].

Legitimate OxyContin use was also tarnished by negative media coverage suggesting that drug diversion was the result of irresponsible prescribing practices. A 2011 study of OxyContin coverage content in lay media and professional publications found that abuse, addiction, crime, and death were emphasized, typically from law enforcement and the criminal justice system perspectives. The majority of patients with legitimate medical need who benefited from the drug were rarely mentioned. An unfortunate outcome is the stigma sometimes experienced by patients who require OxyContin for long-term pain control [57].

EPIDEMIOLOGY OF CHRONIC PAIN AND OPIOID USE

What factors contribute to the increasing prevalence of chronic pain?

Chronic pain costs the nation up to $635 billion each year in medical treatment and lost productivity. It also affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined [7]. The lifetime prevalence of chronic pain ranges from 54% to 80%, and among adults 21 years of age and older, 14% report pain lasting 3 to 12 months and 42% report pain persisting longer than 1 year [7]. An estimated 41% of patients with chronic pain report their pain is uncontrolled, and 10% of all adults with pain suffer from severe, disabling chronic pain.

The increasing prevalence of chronic pain is the result of multiple factors, including the aging population; rising rates of obesity and obesity-related pain conditions, such as joint deterioration; advances in lifesaving trauma interventions; poorly managed post-surgical pain; and greater public awareness of pain as a condition warranting medical attention [7]. In addition, many armed forces veterans have been returning from military action in Afghanistan and Iraq with traumatic injuries and chronic pain, and veterans' care clinicians have been reporting the perception that long-term pain management is lacking support in the veteran healthcare infrastructure [58].

The extent of opioid analgesic use in the United States today is unprecedented in the country's history and unparalleled anywhere in the world. Before 1990, prescribers in the United States were skeptical of prescribing opioids for chronic non-cancer pain. But as of 2017, nearly 58 opioid prescriptions were written for every 100 Americans, and more than 17% of Americans had at least one opioid prescription filled, with an average of 3.4 opioid prescriptions dispensed per patient [59]. Sales of opioid analgesics was an estimated $22.66 billion in 2021. Market size is expected to expand at an annual rate of 1.2% between 2022 and 2030 [60].

Worldwide consumption of opioid analgesics has increased dramatically in the past few decades, with the United States driving a substantial proportion of this increase. For example, the 1990 global consumption of hydrocodone was 4 tons (3,628 kg), compared with the 2021 consumption of 26.6 tons (24,131 kg); the majority (26.3 tons) of this were consumed in the United States. Similarly, 3 tons (2,722 kg) of oxycodone were consumed globally in 1990, versus 62 tons (56,246 kg)

AGENCIES INVOLVED IN COLLECTING AND REPORTING DATA ON NONMEDICAL OPIOID ANALGESIC USE	
Agency [Sponsor]	**Activities**
National Institute on Drug Abuse [NIH, DHHS]	Conducts research involving drug abuse and addiction, tracks trends, disseminates results to improve drug abuse and addiction prevention, treatment, and policy
Monitoring the Future Survey [NIDA, ISR]	Collects data related to drug, alcohol, and cigarette use and attitudes in public and private secondary school students in 8th, 10th, and 12th grade
Drug Abuse Warning Network [SAMHSA]	Monitors drug-related hospital emergency visits and deaths to track the impact of drug use, misuse, and abuse; conducts retrospective review of medical records and case files
Drug Evaluation Network System [TRI, ONDCP]	Generates reports to assist in treatment planning, tracks changes in patient function over time, tracks trends in drug usage, monitors program performance and prepares mandated reports to government and elected officials, maintains an electronic data collection system
The National Epidemiologic Survey on Alcohol and Related Conditions [DHHS/NIH/NIAAA]	Provides information on alcohol use and nonmedical use of prescription opioids (excluding methadone and heroin), sedatives, tranquilizers, and amphetamines in non-institutionalized populations 18 years of age and older
The National Survey on Drug Use and Health [SAMHSA's OAS, DHHS, RTI]	Obtains statistical information related to illicit drug use, administers population-level questionnaires to non-institutionalized residents 12 years of age and older through in-person interviews to obtain data on illicit and prescription drug use
The National Center on Addiction and Substance Abuse at Columbia University [private funding]	Studies and combats substance abuse, surveys children, teens, college students, parents, other adults, prisoners, and women receiving temporary assistance
Researched Abuse, Diversion, and Addiction-Related System [Purdue Pharma, Rocky Mountain Poison Control Center]	Collects product- and locality-specific data; measures rates of abuse, misuse, and diversion to help understand trends; helps develop interventions; assists pharmaceutical companies in regulatory adherence; operates a prescription drug abuse, misuse, and diversion surveillance system
The Arrestee Drug Abuse Monitoring Program [NIJ]	Collects data related to newly booked arrestees regarding drug use, drug and alcohol dependence, treatment, and drug market participation
The National Poison Data System [AAPCC]	Provides a real-time comprehensive poisoning surveillance and toxicovigilance database, operates a uniform data set from the AAPCC
Office of the Medical Investigator (OMI) [city, county, and state governments]	Investigates deaths that come under the jurisdiction of the OMI, including poisoning and drug-related fatalities
AAPCC = American Association of Poison Control Centers, DHHS = U.S. Department of Health and Human Services, ISR = Institute for Social Research, NIAAA = National Institute on Alcohol Abuse and Alcoholism, NIDA = National Institute on Drug Abuse, NIH = National Institutes of Health, NIJ = National Institute on Justice, ONDCP = White House Office of National Drug Control Policy, SAMHSA's OAS = Substance Abuse and Mental Health Services Administration, TRI = Treatment Research Institute.	
Source: [62]	*Table 7*

in 2021, of which 42.3 tons (38,374 kg or 68.2%) were consumed in the United States [61]. With only 4.9% of the world's population, the United States annually consumes more than 85% of all opioid supplies, including [61]:

- 99% of all hydrocodone
- 68% of all oxycodone
- 52% of all methadone
- 40% of all hydromorphone
- 19% of all fentanyl

This disproportionate rate of opioid consumption reflects sociocultural and economic factors and standards of clinical medicine.

Between 1992 and 2003, the U.S. population increased 14%, while persons abusing opioid analgesics increased 94% and first-time nonmedical opioid analgesic users 12 to 17 years of age increased 542% [47]. To assist in monitoring the public health problem associated with prescribed opioids, numerous governmental, nonprofit, and private sector agencies and organizations are involved in collecting, reporting, and analyzing data on the abuse, addiction, fatal overdose, and treatment admissions related to opioid analgesics (***Table 7***) [62].

As of April 2020, 40 states have passed laws that address opioid analgesic prescribing. State-specific legislation, medical and pharmacy boards, Medicaid programs, department of workforce services, and workers' compensation programs have adopted policies, guidelines, and regulations that place limits

on prescribing opioid analgesic medications and/or require monitoring of opioid prescriptions. Many insurance companies and managed healthcare organizations have also implemented policies related to limitations on opioid analgesic prescriptions. This has led to a general downward trend in total daily doses of opioids used, use of ER/LA opioid analgesics, and use of high-dose opioids. This trend began even before the release of the 2016 CDC guidelines for opioid prescribing. The use of ER/LA opioid analgesics for chronic pain continues to decline year-over-year. As of 2023, more than 90% of opioid prescriptions have been for immediate-release opioids or short-acting opioids [63].

In 2020, the Drug Enforcement Agency's Automation of Reports and Consolidated Orders System (ARCOS) reported that the number of dosage units distributed nationwide at the retail level (i.e., hospitals, pharmacies, practitioners, treatment programs, and teaching institutions) was down from 2018. However, opioids continued to rank as fifth out of the seventh most distributed controlled prescription drugs. Hydrocodone and oxycodone products were dispensed at more than twice the rate of any other controlled prescription drug, which remains a steady trend [64]. Although the amount of prescription opioids available on the legitimate market has declined each year since peaking in 2011, the number of prescription opioids available in 2020 remained significant. ARCOS indicated that 9.7 billion dosage units of opioid controlled prescription drugs were manufactured and distributed in 2019. Of that number, approximately 78% were oxycodone and hydrocodone products [64].

Prescribing rates are down overall, but they vary widely between states, particularly at the county level. The nationwide prescribing rate for 2018 was 51.4 prescriptions per 100 persons, yet some counties had rates that were seven times higher than the national average. For example, Alabama and Arkansas had the highest prescription rates (just under 100 prescriptions for 100 people), while New York and Hawaii had the lowest rates at 34.0 and 33.4 prescriptions per 100 people, respectively [64].

FACTORS THAT INFLUENCE OPIOID ANALGESIC PRESCRIBING

What factors influence the decision to prescribe an opioid analgesic?

A decision to prescribe opioids is based on clinician knowledge and judgment and also on patient preference, availability of non-opioid pain treatment approaches, the complexities and bias in third-party reimbursement, aggressive pharmaceutical marketing, and medico-legal concerns. These and other factors have tended to skew the standard of care toward reliance on opioids for long-term chronic pain management in the past few decades [8].

The use of patient satisfaction as a barometer of clinician skill may also influence opioid analgesic prescribing. Satisfaction with clinical care can be obtained from patient surveys, commonly including questions about how adequately their pain was addressed by the provider. Numerous for-profit provider-grading websites offer patients a forum to broadcast their opinions of care received from physicians. Healthcare professionals are likely to get a poor rating from patients who were refused opioids over abuse concerns, and reimbursement and job security can be adversely impacted by negative patient survey ratings in some institutions [65].

The financial structure of many managed care firms and third-party carriers incentivizes pain treatment and discourages substance abuse or addiction treatment. From a financial reimbursement perspective, the time spent providing patient education and counseling related to addiction issues has become one of health care's least valued commodities. This is especially the case in emergency department (ED) settings, where evaluation is often based on patient volume and not on time spent with individual patients. As such, it is faster and pays better to diagnose pain and prescribe an opioid than to diagnose and treat addiction [65].

Increasing Population Rates of Chronic Pain

Any discussion of the rising rates of opioid analgesic prescribing should also acknowledge the increasing prevalence of chronic pain in the United States, with data showing increasing rates over the past several decades that are projected to continue in the future. Musculoskeletal conditions are the most common type of chronic pain, with back pain the most common type of chronic musculoskeletal pain [66]. Increases in low back pain prevalence and associated disability have been quantified in several studies. For example, an investigation of low back pain rates over a 40-year period found increases in prevalence from 8.1% in 1956–1958 to 17.8% in 1994–1995 in men, and 9.1% to 18.2% in women [67]. A comparison of back pain prevalence in North Carolina between 1992 and 2006 found an increase in chronic, impairing low back pain, from 3.9% in 1992 to 10.2% in 2006, and an 11.6% annual increase in healthcare utilization and disability [68]. Data from the National Center for Health Statistics estimate that in 2021 20.9% (51.6 million) of adults in the United States had chronic pain and 6.9% (17.1 million) had high-impact chronic pain (defined as pain that limits life or work activities on most days or every day in the past six months), with higher prevalences of both types of pain reported among women, older adults, previously but not currently employed adults, adults living in poverty, adults with public health insurance, and rural residents [69].

OPIOID ANALGESIC-RELATED MORBIDITY

There are a number of ways that the larger picture of opioid analgesic-related morbidity may be examined. Because the effects of opioid analgesic misuse can manifest in many ways in a variety of settings, it is important to examine data from different sources in order to get an accurate picture of opioid-related morbidity in the United States.

Emergency Department Admissions

The legacy Drug Abuse Warning Network (DAWN) was established in 1972 by the Drug Enforcement Administration to track and publish data collected from participating states on ED visits resulting from substance misuse or abuse, adverse reactions, drug-related suicide attempts, and substance abuse treatment [70]. By its final year in 2011, legacy DAWN had collected data from metropolitan areas in 37 states, with complete coverage in 13 states. Although their total figures did not capture all 50 states, the population rates were representative and able to be extrapolated to the United States as a whole [71].

In 2011, the overall admission rate for misuse or abuse of opioid analgesics (excluding adverse reactions) was 134.8 per 100,000, an increase of 153% compared with 2004. In the 13 states involved in the legacy DAWN network, the top four opioid analgesics involved in drug-related ED visits for 2011 were various formulations of oxycodone (175,229), hydrocodone (97,183), methadone (75,693), and morphine (38,416). Between 2004 and 2011, ED admissions increased 74% for methadone, 220% for oxycodone, 96% for hydrocodone, and 144% for morphine. Importantly, there was no meaningful change in ED admission rates involving opioid analgesics between 2009 and 2011. If this is also borne out by subsequent data, it strongly suggests a plateau in the misuse and abuse rates of these agents [71].

As of 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) re-established DAWN and will retain the important aspects of legacy DAWN. In comparison to legacy DAWN, the re-established DAWN functions as a smaller-scale sentinel surveillance system, or an early-warning system. The new DAWN will focus on detecting "outbreaks" (i.e., sudden increases in ED visits for specific drugs), identifying new and novel psychoactive substances, monitoring the magnitude of the health effects from substance use (as reflected in ED visits), and documenting the geographic, temporal, and demographic distribution of the problems to inform planning and policy at the local, state, and national levels [72].

Nonmedical Use of Prescription Opioids

In 2021, 9.2 million people reported nonmedical use of opioid analgesics (i.e., use without a prescription or for the non-analgesic effect) and 1.4 million were first-time nonmedical users that year [73]. An estimated 2.6 million people misused oxycodone products (including OxyContin) in the past year (1.2% of the population) [73]. The most frequent initial (past year) drug used was cannabis (52.5 million), followed by nonmedical use of prescription opioids (9.2 million), hallucinogens (7.4 million), nonmedical use of tranquilizers (4.9 million), stimulants (4.9 million), cocaine (4.8 million), methamphetamine (2.5 million), inhalants (2.2 million), and heroin (1.1 million) [73].

Among people 12 years of age or older in 2021, 3.3% (9.2 million) reported opioid misuse in the past year. The percentage was lowest among adolescents 12 to 17 years of age (1.9% or 497,000 people). Percentages were similar among young adults 18 to 25 years of age (3.1% or 1.0 million people) and adults 26 years of age or older (3.5% or 7.7 million people) [73].

Rates of Prescription Opioid Abuse and Addiction

The vast majority of people who misused opioids in the past year misused prescription pain relievers. Specifically, 8.7 million people 12 years of age or older misused prescription pain relievers in the past year, compared with 1.1 million people who used heroin [73]. In 2021, the majority (8.1 million) of the 8.7 million misusers of prescription pain relievers misused only prescription pain relievers in the past year—they had not used heroin. An estimated 574,000 people misused prescription pain relievers and used heroin in the past year, and 525,000 people used heroin in the past year but had not misused prescription pain relievers [73].

Widespread opioid analgesic prescribing and nonmedical use, abuse, and dependence are not unique to the United States. Canadian estimates for 2009 indicated that of the total population, 19.2% used prescription opioid analgesics, including nonmedical use by 4.8%, and that 0.4% used the drugs nonmedically to get high. The past-year nonmedical use prevalence of 1 in 20 adults was comparable to U.S. rates. Although the study found high rates of prescribed opioid analgesic use and nonmedical use, most noteworthy was the conclusion that opioid analgesic prescribed use, nonmedical use, and nonmedical use to get high was not associated with the level of prescription opioid dispensing. This finding stands in contrast to the stream of reports over the past decade from the CDC, the DEA, and other governmental agencies in the United States [74].

SAMHSA data do differentiate the underlying basis of misuse. For instance, a person who took or received a prescription opioid from a relative or friend for a headache is recorded as a nonmedical user (abuser); although placed in the same category as someone who stole prescription opioids from a medicine cabinet to get high, the motivations and possible interventions for the respective problems are entirely different. The importance of this distinction is clear in a large 2008 survey of high school seniors, which found that 12.3% had used opioid analgesics for nonmedical reasons at some point [75]. This is similar to a 2012 study of 7,374 high school seniors, which found that 12.9% reported lifetime nonmedical use of prescription opioids [76]. A multi-cohort national study of more than 8,000 high school seniors found that 36.9% of past-year nonmedical users of prescription opioids obtained the medications from their own previous prescriptions. Analyses indicated that these users were primarily motivated by a desire to relieve physical pain [77]. This should lead to exploration of important public health questions, such as why so many young people suffering from untreated (or mistreated) physical pain resort to self-medication [76; 77].

Opioid Use Disorders in Patients with Pain Receiving Long-Term Opioid Analgesics

The literature examining opioid use disorder incidence in patients with chronic pain receiving opioid analgesic therapy have reported rates of addiction developing during opioid therapy ranging from 0.03% to 50% [78; 79]. These vast differences are mainly the result of widely varying criteria to define opioid addiction. Many of the studies used diagnostic criteria according to the DSM-IV, or the DSM-III in studies that began before 1994. The DSM-III and IV criteria include tolerance and withdrawal as diagnostic criteria, which can reflect physical dependence that is an expected development of long-term opioid therapy. Other DSM diagnostic criteria may also describe common non-addiction based experiences of patients with pain who are receiving long-term opioid therapy, such as using the medication in higher amounts or for a longer term than intended and a persistent desire or unsuccessful attempts to cut down, control, or halt the use of the opioids [80]. Also, DSM criteria require the patient experience of impaired function or distress resulting from their opioid use. Many of those with chronic pain report clinically significant dysfunction and distress from their chronic pain; some studies do not clarify whether pain or the opioid is causing the reported dysfunction and distress. For these reasons, more recent pain researchers have concluded that DSM criteria are not applicable and may be misleading as a diagnostic basis in patients with chronic pain [78; 81].

One study that controlled for the improper fit of DSM opioid addiction criteria in patients receiving long-term opioid therapy followed a group of patients with sickle cell anemia [82]. Researchers found that 31% of patients receiving opioids developed opioid dependence according to the DSM-IV criteria. When pain-related symptoms that actually accounted for positive diagnostic criteria were removed, the addiction incidence fell to 2% [82]. In a review of 24 studies enrolling 2,507 patients with chronic pain with a 26.2-month average duration of opioid therapy, the overall opioid addiction rate was 3.27% [79]. A 2013 study evaluated the rate of drug misuse and illicit use in 1,350 patients with a pain duration greater than one year who were currently prescribed opioids for three months or longer and enrolled in an interventional pain program. The study found that 1.3% were using non-prescribed prescription drugs and 7.9% were using illicit drugs (primarily cannabis; substantially fewer for cocaine and methamphetamine). The authors concluded the rates they found in patients receiving opioids were comparable to those of the general population [83].

Treatment Admissions for Opioid Use Disorders

Among persons 12 years of age or older with a past-year opioid use disorder due to their use of heroin or misuse of prescription pain relievers, 22.1% (533,000 people) received medication-assisted treatment in the past year [73].

Diversion of Prescription Opioids

Research has more closely defined the location of prescribed opioid diversion into illicit use in the supply chain from the manufacturer to the distributor, retailer, and the end user. This information carries with it substantial public policy and regulatory implications. The 2021 NSDUH data asked non-medical users of prescription opioids how they obtained their most recently used drugs [73]. Among persons 12 years of age or older, 33.9% obtained their prescription opioids from a friend or relative for free, 39.3% got them through a prescription from one doctor (vs. 34.7% in 2018), 7.3% bought them from a friend or relative, and 7.9% bought them from a drug dealer or other stranger. Less frequent sources included stealing from a friend or relative (3.7%); multiple doctors (3.2%); theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.7% in 2018); and some other way (4.0%) [73].

Neonatal Abstinence Syndrome (NAS)

Rates of opioid misuse may also be tracked by unintended effects of use during pregnancy on newborns. Cases of neonatal abstinence syndrome (NAS)—a group of problems that can occur in newborns exposed to prescription opioids or other drugs while in the womb—grew by 83% in the United States between 2010 and 2017 [84].

OPIOID ANALGESIC-RELATED MORTALITY

Opioid analgesics may result in deaths due to unintentional or intentional overdose or intoxication-related accidents. However, the majority of data focus on unintentional overdose. The rates of fatal toxicity involving prescription opioid analgesics have escalated in tandem with the increasing rates in opioid analgesic prescribing, abuse, addiction, and diversion. Unfortunately, additional valuable information is not revealed by the mortality data, such as whether the potential cause of the fatality was opioid ingestion for intoxication or for pain control, or whether the decedent was taking the medication as prescribed, using the opioid nonmedically (e.g., for insomnia control), using the medication plus someone else's prescribed opioid for poorly managed pain, or taking someone else's prescribed opioid to get high. Also unknown is the relative contribution of the opioid to the fatality. In one postmortem study of fatalities involving prescription opioids, 79% of decedents also tested positive for alcohol and other drugs [85]. In the absence of more details surrounding opioid fatalities, crafting preventive measures is difficult, and estimates of the true fatality rate from prescription opioids remain elusive.

Regional differences have been found in fatal drug overdose involving opioids, with the highest rates occurring in the Southwest and Appalachian regions. Differences between states have also been found. Data from 2021 indicate the highest fatal drug overdose rates occurred in West Virginia (90.9 per 100,000), Tennessee (56.6 per 100,000), Louisiana (55.9 per 100,000), Kentucky (55.6 per 100,000), New Mexico (51.6 per 100,000), and Ohio (48.1 per 100,000. In 2020, 91,799 drug overdose deaths occurred in the United States. The age-adjusted rate of overdose deaths increased by 31% from 2019

(21.6 per 100,000) to 2020 (28.3 per 100,000). Opioids were involved in 68,630 overdose deaths in 2020 (74.8% of all drug overdose deaths) [86]. Significant increases in drug overdose death rates during this period were primarily seen in California, Mississippi, Virginia, and South Carolina [87].

According to one analysis, nearly one in four people on Medicaid received prescription opioids in 2015 [88]. The report analyzed 1.8 million opioid prescriptions written for 3.1 million Medicaid members across 14 states. According to the CDC, Medicaid patients are prescribed opioids at twice the rate of non-Medicaid patients and are at six times the risk of overdose [89]. However, essential information was omitted in this CDC report but uncovered by an investigation into Washington state opioid fatalities [90]. Left out of the CDC publication was the policy decision in early 2004 by the State of Washington to list methadone as a preferred opioid analgesic, as a cost-cutting measure. Morphine was the only other long-acting opioid placed on the preferred analgesics list. Methadone fatalities increased from 140 in 2002 to 256 in 2004. Many of these fatalities involved the combination of methadone and other prescribed medication, particularly benzodiazepines and antidepressants; of the 274 methadone-related fatalities in 2009, prescribed medications for anxiety or other mental-health concerns were found in 43% of decedents. The number of methadone fatalities in 2006 was 300% greater than the number attributed to any other long-acting pain reliever. Although the escalation in methadone fatalities had become obvious, the cost-cutting objectives were significant and state officials maintained the stance that methadone was safe and effective [91].

Gender Differences

The opioid overdose rate among women has increased faster than it has in men. From 1999 to 2010, overdose fatality increased by more than 400% in women, compared to 265% for men; during this period, nearly 48,000 women died of opioid analgesic overdose. In aggregate, women tend to possess background characteristics and opioid analgesic use patterns that may contribute to overdose vulnerability. Women are more likely to experience chronic pain, receive prescriptions for opioid analgesics, receive higher doses of opioids, and use opioids for longer periods than men. Substance use disorders involving opioid analgesics are thought to develop more rapidly in women, and women may be more likely to obtain opioid prescriptions from multiple prescribers than men [92].

Women 25 to 54 years of age have the highest rate of ED admission for opioid misuse or abuse, and the greatest risk of prescription opioid fatality occurs in women 45 to 54 years of age. Non-Hispanic white and American Indian or Alaska Native women have the highest mortality risk from prescription opioids, and opioid analgesics are involved in 1 in 10 suicides among women [92].

Overdose Fatality and Prescribed Opioid Dosage

Several studies have reported a positive association between high-dose opioid prescribing and overdose risk. However, these studies utilized methods in design and data analysis that cast doubt on the results, such as failure to control for the possible effect of opioid abuse on overdose outcomes and differences in the indications, formulations, and opioid products in patients prescribed high versus low dosing [93].

A study was conducted to re-examine the relationship between opioid dose and overdose risk while controlling or eliminating the methodological shortcomings in previous studies. The records of 38,861 patients prescribed morphine ER, transdermal (patch) fentanyl, or buprenorphine patch between 2005 and 2010 were evaluated. High-dose was defined as 120 mg morphine equivalent dose (MED) or more; low-dose included 30 mg MED or less. The rates of overdose were 0.7% with morphine ER, 0.4% with fentanyl patch, and 0.3% with buprenorphine patch. The relative risk of overdose among patients prescribed high doses was 1.44 for morphine ER, 1.51 for fentanyl patch, 0.78 for buprenorphine patch, and 1.18 when all three opioids were combined. These results indicate a roughly 1.5 times greater overdose risk with high-dose morphine and fentanyl than with low-dose, no difference in overdose risk between high- and low-dose buprenorphine, and an overall overdose risk markedly lower than previous reports [93].

This data should be considered tentative as it was presented at a conference and, as of 2023, has not yet been published in a peer-reviewed journal. As with the previous research, this study was performed retrospectively and not prospectively, which can lessen the validity of the results. However, in light of these limitations, the results provide a credible counterbalance to previously published figures.

Contributory and Risk Factors for Overdose

What are known risk factors for fatal opioid toxicity?

The reasons for opioid analgesic overdose fatalities are multifactorial and include prescriber behaviors, patient contributory factors, nonmedical use patterns, and systemic failures. Risk factors identified for fatal opioid toxicity include [6]:

- Prescriber error due to knowledge deficits
- Patient nonadherence to medication regimen
- Unanticipated medical and mental health comorbidities, including substance use disorders
- Co-administration of other CNS-depressant drugs, including alcohol, benzodiazepines, and antidepressants
- Sleep-disordered breathing (e.g., sleep apnea)
- Body mass index of 30 or greater

Additional factors specifically contributing to methadone fatality include [94]:

- Payer policies that encourage or mandate methadone as first-line therapy

- Methadone prescribing in opioid-naïve patients
- Lack of prescriber knowledge of methadone pharmacology

A population-based study examined patterns and characteristics of opioid users in Ontario, Canada, whose cause of death involved opioid toxicity [95]. Between 2006 and 2008, 2,330 drug-related deaths were identified, of which 58% were partially or entirely attributed to opioids. The manner of death was classified by a coroner as accidental (68%), undetermined (16.3%), or suicide (15.7%). Among decedents, at least 7% ingested opioids that were prescribed to friends or a family member; 19% altered the route of administration through injection, inhalation, or chewing a transdermal patch; 3% had been released from incarceration just before their death; and 5% had switched from one opioid to another near the time of death [95]. Differences were found between decedents who died accidentally versus suicide. A personal history of substance abuse, enrollment in a methadone maintenance program, cirrhosis, hepatitis, and cocaine use were significantly associated with accidental death. Mental illness, previous suicide attempts, chronic pain, and a history of cancer were significantly associated with death by suicide.

Methadone

Historically, methadone was used primarily as pharmacotherapy for heroin addiction. During the 1990s, however, methadone gained increased acceptance for use as an analgesic, and methadone began to be prescribed to outpatients with moderate-to-severe noncancer pain. Prescribing rates soared over the next decade; comparison of methadone sales quantity between 1997 and 2007 shows an increase of 1293% [96; 97]. This rising use of methadone occurred simultaneously with concerns over the abuse potential of OxyContin and the search for a relatively inexpensive long-acting opioid analgesic alternative [98].

By 2008, two-thirds of methadone prescriptions were for pain treatment. The unique pharmacologic properties of methadone make its use in pain management complex, with greater potential for hazard than other prescribed opioids. Prescribers familiar with using methadone as opioid addiction treatment may be unaware that suppression of opioid withdrawal symptoms lasts 24 or more hours, while the analgesic duration is 4 to 8 hours, despite a half-life exceeding 60 hours in some patients. Accidental overdose fatalities can occur when patients re-administer methadone when the analgesia wears off and pain returns, potentially elevating plasma concentrations to life-threatening levels. These same pharmacological properties also imperil those who use it illicitly. Opioid abusers often co-administer benzodiazepines, which greatly elevates lethality risk with methadone. Concurrent use of alcohol poses the same risk [98].

Since the mid-2000s, methadone has become disproportionately represented in cases of opioid analgesic fatality. Based on data showing that 70% of fatalities among those prescribed methadone occurred in the first seven days of treatment, the FDA changed the methadone labeling in 2006 to lengthen dosing intervals from every 3 to 4 hours to every 8 to 12 hours; the initial recommended dose of 2.5–10 mg was unchanged [6; 99]. In 2008, use of the highest oral dose preparations, 40 mg, was prohibited from use in pain treatment and restricted to addiction therapy [94].

Mortality Risk in Highly Controlled Inpatient Settings

In addition to the well-publicized risk of overdose fatality with prescribed and diverted opioid analgesics, it is worth mentioning that use of opioid analgesics carries risk even under the most tightly controlled conditions. In 2012, the Joint Commission released a *Sentinel Event Alert* entitled "Safe Use of Opioids in Hospitals," which referenced database reports of death or serious morbidity between 2004 and 2011. Of all events resulting in serious morbidity or mortality, 47% resulted from wrong medication dose errors, 29% resulted from inadequate patient monitoring, and 11% were due to other factors, including excessive dosing, medication interactions, and adverse drug reactions. Prescriber knowledge deficits in opioid pharmacology and optimum opioid route of administration (e.g., oral, parenteral, transdermal patches) accounted for some of the serious adverse patient outcomes [100]. The Joint Commission findings of serious opioid-related morbidity and mortality even when administered under highly controlled conditions and correlational data that show increased prescription opioid abuse and overdose fatality with increased opioid prescribing suggest that adverse outcomes occur at a fixed ratio to overall use [100].

Chronic Pain and Suicide by Overdose

Prolonged intense pain can destroy quality of life and the will to live, driving some patients to suicide [39]. The growing concern over opioid addiction and fatal overdose have obscured the relevant problem of intentional overdose. For many individuals, committing suicide is a way out of a situation or problem causing extreme suffering. According to DAWN, an estimated 228,366 ED visits for drug-related suicide attempts occurred in 2011 [101]. This was a 51% increase in these types of visits in individuals older than 11 years of age compared with 2005 [102]. There was a 58% increase in individuals 18 to 29 years of age, and a 104% increase in those 45 to 64 years of age [102]. Approximately 39% involved alcohol and 11% involved illicit drugs [101; 102].

Although an accurate estimate of the number of suicide attempts and completions is unknown because intent is often misclassified or not classified, risk factors for suicidal ideation are very high in the chronic pain population. Many patients with pain experience concurrent depression, and some have histories of alcohol and substance abuse. Multiple studies have shown rates of suicidal ideation and suicide attempts as high as 50% in patients suffering from chronic pain [103]. An estimated 50% of patients with chronic pain have had serious thoughts of committing suicide due to their pain disorder, and drug overdose is the most commonly reported plan for committing suicide (75%) in these patients [104; 105].

The Canadian Community Health Survey found that, after adjusting for sociodemographics and acute mental disorders and comorbidities, the presence of one or more chronic pain conditions significantly elevated the risk of suicidal ideation and suicide attempts [106]. A literature review found that risk of suicide completion was doubled in patients with chronic pain relative to non-pain controls [107].

UNTREATED/UNCONTROLLED PAIN AND MORBIDITY/MORTALITY

Mortality Risk

A link between chronic uncontrolled pain and adverse health outcomes has been identified in previous research, and the results of a 2010 study reaffirmed this association and uncovered a significant mortality risk not previously identified. Over a 10-year period, a prospective longitudinal study collected annual mortality information from a cohort of 6,940 primary care patients [108]. Survival among those reporting moderate-to-severe interference from chronic pain was significantly worse than survival among those reporting mild or no chronic pain or interference. After adjusting for sociodemographic factors and long-term disabling illness, moderate-to-severe chronic pain inflicted a 68% greater mortality risk than cardiovascular disease [108]. While considerable attention has been given to the risk of fatal toxicity and overdose involving opioid analgesics, these data suggest the mortality risk of uncontrolled, severe, chronic pain surpasses that of accidental death from toxicity or overdose with prescribed opioid analgesics.

Alterations in Brain Structure and Function

Substantial evidence indicates that poorly controlled acute pain can induce neuroplastic changes that underlie the development and perpetuation of chronic pain. Evidence from studies of uncontrolled chronic pain are now documenting changes in brain morphology, such as decreased prefrontal cortex gray matter volume in patients with chronic back pain or fibromyalgia [109]. Diminished prefrontal cortex gray matter volume is associated with adverse functional changes and decreased patient ability to engage in behaviors that can inhibit pain experience [109]. One study compared the brain morphologies of patients with chronic back pain to control subjects, and found 5% to 11% less neocortical gray matter volume among patients with back pain, an association between pain duration and volume reduction, and a loss in gray matter volume equivalent to the effects from aging 10 to 20 years [110].

ARRESTEE DATA

Researchers have found a distinctive pattern in the lifespans of drug abuse epidemics. This pattern reflects the escalating and declining prevalence in the use of a substance, the projected course into the near future, and prevalence rate variation across localities. The phases common to all drug epidemics are incubation, expansion, plateau, and decline in use of the drug. Arrestee data are a valuable source of information for tracking drug use trends and are consistent or slightly ahead of drug use data collected from general population studies in measuring drug epidemic phenomenon. To better understand the problem of prescription opioid abuse, information was obtained from 41,501 adult male arrestees in nine geographic locations. Arrestees provided data on their past three-day opioid analgesic use. Data from 2000–2003 were compared with data from 2007–2010. By location, the prescription opioid epidemic phase and the 2010 rate of past three-day opioid analgesic use by arrestees were [111]:

- Atlanta: 4% (never became an epidemic)
- Charlotte: 8% (plateau, possibly declining)
- Chicago: 3% (never became an epidemic)
- Denver: 7% (never became widespread, now declining)
- Indianapolis: 16% (plateau)
- Manhattan: 6% (plateau)
- Minneapolis: 8% (plateau)
- Portland: 15% (plateau, possibly declining)
- Sacramento: 12% (plateau)

These results illustrate the uneven geographic distribution of the prescription opioid use epidemic. It is also clear that prevalence rates are stabilizing or declining in all localities. These arrestee data indicate the epidemic has likely peaked and predict the decline in first-time and past-year use and an increase in prescription opioid addiction and treatment-seeking rates. In susceptible persons, progression in severity of a substance use disorder to addiction often occurs over many years. Persons who now meet diagnostic criteria for opioid analgesic addiction, and may be seeking help, probably began their use during an earlier phase of the epidemic.

MITIGATING RISK IN OPIOID PRESCRIBING PRACTICE

BACKGROUND

What are characteristics of appropriate opioid prescribing?

As discussed, pain treatment, especially in the context of opioid prescribing, is defined as inappropriate by its non-treatment, inadequate treatment, overtreatment, or continued use of ineffective treatment [10]. Inappropriate pain treatment with opioid analgesics elevates the risk of uncontrolled pain, possibly serious adverse side effects, and abuse and diversion. Therefore, clinicians who treat patients with chronic pain are required to use strategies that assess and mitigate the risk of abuse liability inherent in opioids. Although risk assessment and mitigation strategies have been developed to decrease the problem of prescribed opioid abuse, diversion, and overdose, their use can also reduce the development of serious side effects and help ensure the treatment selected is benefiting the patient [112].

CHARACTERISTICS OF APPROPRIATE AND INAPPROPRIATE OPIOID PRESCRIBING	
Medically Legitimate Pain Management and Prescribing	**Inappropriate Pain Management and Prescribing**
Based on sound clinical judgment and current best clinical practices	Inadequate attention in initial assessment to clinical indication or patient risk of opioid problems
Appropriately documented	Inadequate monitoring
Demonstrable patient benefit	Inadequate patient education and informed consent
Occurs during the usual course of professional practice	Unjustified dose escalation without sufficient attention to risks or alternative treatments
A legitimate physician-patient relationship exists	Excessive reliance on opioids, especially high-dose opioids, for chronic pain
Prescribing or administration appropriate to diagnosis	Failure to use risk assessment tools
Careful follow-up monitoring of patient response and safe patient use	
Demonstration of adjustment to therapy, as needed	
Documentation of appropriate referrals, as necessary	
Source: [10]	*Table 8*

The 2011 Institute of Medicine report *Relieving Pain in America* reinforced the importance of framing chronic pain as a unique chronic disease state with complex neurophysiological, emotional, and social components, making its management distinct from that of acute pain [7]. Treating chronic pain differs from acute pain by the duration, multimodal approach, and risk mitigation of the therapy. Clinicians may fear that managing the issues surrounding opioid analgesic prescribing render the practice too difficult or complex [112]. To assist in the dual need of protecting one's clinical practice while reducing opioid abuse, the FSMB released a model policy for opioid analgesic prescribing in 2013. This policy was the result of identification of harmful but remediable factors contributing to pain undertreatment and inappropriate opioid prescribing, including [10]:

- Knowledge gaps in medical standards, current evidence-based outcomes, guidelines for appropriate pain treatment, and regulatory policies
- Prescriber concerns that legitimate opioid prescribing will lead to unnecessary scrutiny by regulatory authorities
- Conflicting information in existing clinical guidelines
- Prescriber concerns of patient deception to obtain drugs for abuse and fears of precipitating addiction

Prescribers were held to a standard of safe and best clinical practice, the general points of which include [10]:

- Prescribers should know best clinical practices in opioid prescribing, associated risks of opioids, assessment of pain and function, and pain management approaches. Pharmacologic and nonpharmacologic modalities should be used on the basis of current knowledge in the evidence base or best clinical practices.
- Pain should be assessed and treated promptly, with therapy selection based on the nature of the pain, treatment response, and patient risk level for developing opioid problems.
- Prescribers should use safeguards to minimize misuse and diversion risk of opioid analgesics.
- In allegations of inappropriate pain management, the Board will not take disciplinary action for deviation from "best practices" when medical records show reasonable cause for deviation.

The model policy additionally stated that physicians would not be sanctioned on the sole basis of medically legitimate opioid prescribing **(*Table 8*).**

In 2015, the FSMB appointed a workgroup to review and analyze the original policy document as well as other state and federal policies on the prescribing of opioids in pain treatment, including advisories issued by the CDC and the FDA [113]. In April 2017, the FSMB adopted the *Guidelines for the Chronic Use of Opioid Analgesics*, an update to the original model policy that includes recommendations identified by the workgroup. The stated goal of this document is to provide state medical and osteopathic boards with an updated guideline for assessing physician management of pain, so as to determine whether opioid analgesics are used in a manner that is both medically appropriate and in compliance with applicable state and federal laws and regulations [113].

The FSMB 2017 Guidelines communicate the message that pain management is an important area of patient care, integral to medical practice; and that opioid analgesics may be necessary for pain control. In order to implement best practices for responsible opioid prescribing, clinicians should understand the relevant pharmacologic and clinical issues in the use of opioid analgesics and should obtain sufficient targeted continuing education and training on the safe prescribing of opioids and other analgesics as well as training in multimodal treatments. The Guidelines focus on the general overall safe and evidence-based prescribing of opioids and treatment of chronic, non-cancer pain, with the specific limitation and restriction that they do not operate to create any specific standard of care. A variety of strategies may be used to achieve the

goals of the Guidelines, including the patient's level of pain, preferences of the clinician and the patient, available resources, and other concurrent issues. The Guidelines do not encourage the prescribing of opioids over other pharmacological and nonpharmacological means of treatment. Pain management should be viewed as essential to both the quality of medical practice and to the quality of life for patients who suffer from pain. The Guidelines are not intended for the treatment of acute pain, acute pain management in the perioperative setting, emergency care, cancer-related pain, palliative care, or end-of-life care. They apply most directly to the treatment of chronic pain lasting more than three months in duration or past the time of normal tissue healing [113].

ASSESSING OPIOID BENEFIT AND RISK OF MISUSE

In deciding whether to prescribe an opioid analgesic for chronic pain, clinicians should perform, and document in the record, an assessment of the potential benefits and risks to the patient. The elements of such an assessment include [113]:

- Pain indications for opioid therapy
- Nature and intensity of pain
- Past and current pain treatments and patient response
- Comorbid conditions
- Pain impact on physical and psychological function
- Social support, housing, and employment
- Home environment (i.e., stressful or supportive)
- Pain impact on sleep, mood, work, relationships, leisure, and substance use
- Patient history of physical, emotional, or sexual abuse

If there is a history of substance abuse, active or in remission, consult an addiction specialist before starting opioids [113]. In active substance abuse, do not prescribe opioids until the patient is engaged in a treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly ER or LA types), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental ingestion by children [114].

RISK ASSESSMENT TOOLS

Risk assessment involves a determination of whether potential opioid benefits outweigh the potential risks. The individual and public health consequences of prescription opioid abuse, addiction, diversion, and overdose justify assessment and risk stratification in every patient considered for long-term opioid therapy [115]. Patients with chronic pain and past or current alcohol or drug abuse, psychiatric illness, or serious aberrant drug-related behaviors should still be considered for opioid therapy, but with tighter monitoring conditions and consultation from mental health or addiction specialists. Pain management outcomes are negatively affected by untreated psychiatric comorbidity, and proper assessment can identify and lead to the treatment of these conditions [116]. Periodic reassessment is necessary because patient circumstances and the benefit/risk balance of opioid therapy can change, due to alterations in the primary pain condition, comorbid disease, or psychological or social circumstances [115].

Before Opioid Therapy Initiation

Screening and assessment tools can help guide patient stratification according to risk level and inform the appropriate degree of structure and monitoring in the treatment plan. It should be noted that despite widespread endorsement of screening tool use to help determine patient risk level, most screening tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [97]. In addition to screening and assessment tools, urine drug testing, monitoring of prescribing practices, prescription monitoring programs, opioid treatment agreements, and utilization of universal precautions are essential. Presently, a combination of strategies is recommended to stratify risk, to identify and understand aberrant drug-related behaviors, and to tailor treatments accordingly [117].

Opioid Risk Tool

The Opioid Risk Tool (ORT) is a five-item assessment to help predict aberrant drug-related behavior. It is also used to establish patient risk level through patient categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychological disorders, and other risk factors [27].

Screener and Opioid Assessment for Patients with Pain—Revised

The Screener and Opioid Assessment for Patients with Pain–Revised (SOAPP-R) is a patient-administered, 24-item screen with questions addressing history of alcohol/substance use, psychologic status, mood, cravings, and stress. Like the ORT, the SOAPP-R helps assess risk level of aberrant drug-related behaviors and the appropriate extent of monitoring [118].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consists of four questions designed to help clinicians determine the likelihood that a patient is misusing or abusing alcohol. These same four questions were adapted to include drugs (CAGE-AID), and this tool may be used to assess the likelihood of current substance abuse [119].

Diagnosis, Intractability, Risk, Efficacy Tool

The Diagnosis, Intractability, Risk, Efficacy (DIRE) tool is a clinician-rated questionnaire used to predict patient compliance with long-term opioid therapy [120]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

Mental Health Screening Tool

The Mental Health Screening Tool is a five-item screen that asks about a patient's feelings of happiness, calmness, peacefulness, nervousness, and depression in the past month [121]. A

PATIENT RISK STRATIFICATION
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing including magnetic resonance imaging, physical examination, and interventional diagnostic techniques
With or without mild psychological comorbidity
With or without minor medical comorbidity
None or well-defined and controlled personal or family history of alcoholism or substance abuse
Age 45 years or older
High levels of pain acceptance and active coping strategies
High motivation, willingness to participate in multimodal therapy and attempting to function at normal levels
Medium Risk
Significant pain problems with objective signs and symptoms confirmed by radiological evaluation, physical examination, or diagnostic interventions
Moderate psychological problems, well-controlled by therapy
Moderate coexisting medical disorders well controlled by medical therapy and which are not affected by chronic opioid therapy such as central sleep apnea
Those who develop mild tolerance but not hyperalgesia without physical dependence or addiction
Past history of personal or family history of alcoholism or substance abuse
Pain involving more than three regions of the body
Defined pathology with moderate levels of pain acceptance and coping strategies
Willing to participate in multimodal therapy, attempting to function in their normal daily lives
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of misuse, abuse, addiction, diversion, dependency, tolerance, and hyperalgesia
History of alcoholism
Major psychological disorders
Age younger than 45 years
HIV-related pain
High levels of pain exacerbation and low levels of coping strategies
Unwilling to participate in multimodal therapy; not functioning close to a near normal lifestyle
Source: [97] *Table 9*

lower score on this tool is an indicator that the patient should be referred to a specialist for pain management.

PATIENT RISK STRATIFICATION

What characterizes a patient at high risk for developing problematic opioid behavioral responses?

Common to most clinical practice guidelines, and discussed in the FSMB 2017 Guidelines, is patient stratification by level of risk [113]. All practice guidelines for opioid analgesic prescribing recommend assessing the risk of misuse, abuse, or addiction in all patients before initiating long-term (≥90 days) opioid therapy and in high-risk patients prior to acute pain therapy. Patient risk level is designated as low, medium, or high based on background and clinical characteristics (***Table 9***) [97].

Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations [21].

SAFETY PRECAUTIONS

A simplified approach to opioid prescribing safety, based on the core concept of universal precautions but designed with high specificity for opioid analgesics, was presented at the 2013 annual conference of the AAPM. The eight principles are specifically intended to reduce fatalities with opioid analgesic prescribing and are now incorporated in the AAPM Safe

Opioid Prescribing Initiative [122]. They may be recalled using the acronym RELIABLE:

- **R**espiratory: If a patient on long-term opioids develops a respiratory condition (e.g., asthma, pneumonia, flu), reduce the opioid dose by 20% to 30%.
- **E**xperience: Assess the patient before prescribing opioids to explore biologic, social, and psychiatric risk factors.
- **L**ong-term: Extended-release opioids should not be used for acute pain.
- **I**nitiating methadone: Never start methadone at a dose ≥15 mg/day.
- **A**pnea: Screen for hypoxemia and obstructive or central sleep apnea, especially in patients who are taking 150 mg/day MED or who are obese, infirm, or elderly.
- **B**enzodiazepines: Avoid these agents if possible because they enhance opioid toxicity.
- **L**ook for comorbidities: Patients often misuse opioid analgesics for their mental health disorder instead of their pain, so assess patients for a history of bipolar disorder, post-traumatic stress disorder, depression, stress, and general anxiety disorder.
- **E**xercise caution with rotation: Conversion tables and equal analgesic tables should not be used to determine opioid starting doses. Assume everyone is opioid naïve, start on a low dose, and titrate slowly to the maximum dose one can safely prescribe.

DEVELOPING A SAFE OPIOID TREATMENT PLAN FOR MANAGING CHRONIC PAIN

What are the ten essential steps of opioid prescribing for chronic pain that can help mitigate any potential problems?

As discussed, healthcare professionals should know best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with non-opioid pharmacologic or nonpharmacologic pain therapy without adequate pain relief are considered to be candidates for a trial of opioid therapy. The treatment plan should always be individualized for the patient and begun as an "initial therapeutic trial" before embarking on a definitive course of treatment [113].

All patients with pain have a level of risk that can only be roughly estimated initially and modified over time as more information is obtained. There are ten essential steps of opioid prescribing for chronic pain to help mitigate any potential problems [113]:

- Diagnosis with an appropriate differential
- Psychologic assessment, including risk of substance use disorders
- Informed consent
- Treatment agreement
- Pre- and post-treatment assessments of pain level and function
- Appropriate trial of opioid therapy with or without adjunctive medication
- Reassessment of patient levels of pain and functioning
- Regular assessment with the 5 A's (i.e., analgesia, activity, adverse effects, aberrant behaviors, and affect)
- Periodically review pain diagnosis and comorbid conditions, including substance use disorders
- Documentation

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [113]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications [113].

The treatment agreement also outlines joint prescriber and patient responsibilities [113]. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug tests (UDTs). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed [113]. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

Considerations for Non-English-Proficient Patients

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of opioids 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.

INITIATING A TRIAL OF OPIOID THERAPY

Opioid therapy should be presented as a trial for a pre-defined period (usually no more than 30 days). The goals of treatment should be reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [113]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In opioid-naïve patients, start at the lowest possible dose and titrate to effect. Dosages for opioid-tolerant patients should always be individualized and titrated by efficacy and tolerability [113]. The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression.

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over ER/LA opioids. Taper opioid dose when no longer needed [114].

PERIODIC REVIEW AND MONITORING

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [113]. This can include input from family members and/or the state prescription drug monitoring program (PDMP) [113]. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the 5 A's [10]:

- Analgesia
- Activities of daily living
- Adverse or side effects
- Aberrant drug-related behaviors
- Affect (i.e., patient mood)

Assessment During Ongoing Opioid Therapy

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [123]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Inability to concentrate or short attention span
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [113]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

VIGIL

VIGIL is the acronym for a five-step risk management strategy designed to empower clinicians to appropriately prescribe opioids for pain by reducing regulatory concerns and to give pharmacists a framework for resolving ambiguous opioid analgesic prescriptions in a manner that preserves legitimate patient need while potentially deterring diverters. The components of VIGIL are [124; 125]:

- **V**erification: Is this a responsible opioid user?
- **I**dentification: Is the identity of this patient verifiable?
- **G**eneralization: Do we agree on mutual responsibilities and expectations?
- **I**nterpretation: Do I feel comfortable allowing this person to have controlled substances?
- **L**egalization: Am I acting legally and responsibly?

The foundation of VIGIL is a collaborative prescriber/pharmacist relationship [125; 126].

Current Opioid Misuse Measure

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients with chronic pain. Unlike the ORT and the SOAPP-R, the COMM identifies aberrant behaviors associated with opioid misuse in patients already receiving long-term opioid therapy [21]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

Pain Assessment and Documentation Tool

Guidelines by the FSMB and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation with patients with chronic pain receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [127]. The PADT is a

MONITORING FREQUENCY ACCORDING TO PATIENT RISK			
Monitoring Tool	**Patient Risk Level**		
	Low	**Medium**	**High**
Urine drug test	Every 1 to 2 years	Every 6 to 12 months	Every 3 to 6 months
State prescription drug monitoring program	Twice per year	3 times per year	4 times per year
Source: [128]			*Table 10*

clinician-directed interview, with most sections (e.g., analgesia, activities of daily living, adverse events) consisting of questions asked of the patient. However, the potential aberrant drug-related behavior section must be completed by the physician based on his or her observations of the patient.

The Brief Intervention Tool

The Brief Intervention Tool is a 26-item, "yes-no," patient-administered questionnaire used to identify early signs of opioid abuse or addiction. The items assess the extent of problems related to drug use in several areas, including drug use-related functional impairment [121].

Involvement of Family Members

Family members of the patient can provide valuable information that better informs decision making regarding continuing opioid therapy. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [123]:

- Is the person's day centered around taking the opioid medication? Response can help clarify long-term risks and benefits of the medication and identify other treatment options.
- Does the person take pain medication only on occasion, perhaps three or four times per week? If yes, the likelihood of addiction is low.
- Have there been any other substance (alcohol or drug) abuse problems in the person's life? An affirmative response should be taken into consideration when prescribing.
- Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed? If so, this suggests the pain medication is failing to promote rehabilitation. Daily activity is essential, and the patient may be considered for enrollment in a graduated exercise program.
- Is the person in pain able to function (e.g., work, do household chores, play) with pain medication in a way that is clearly better than without? If yes, this suggests the pain medication is contributing to wellness.
- Does the person smoke? Smoking increases pain and reduces the effectiveness of opioids. Smoking itself is an addictive behavior and, therefore, a clear risk for opioid addiction. If possible, opioids should be avoided persons who smoke.

Urine Drug Testing

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use [113]. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 10***) [128]. High-quality evidence supporting the benefits of UDTs in improving patient care are lacking, as much of the existing evidence comes from industry-sponsored studies that can portray a biased perspective, usually by stressing the prevalence of aberrant behaviors in patients who then require more frequent UDT monitoring [129].

Initially, testing involves the use of class-specific immunoassay drug panels [10]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions unless liquid chromatography is coupled with mass spectrometry confirmation.

Urine test results suggesting opioid misuse should be discussed with the patient using a positive, supportive approach. The test results and the patient discussion should be documented.

Ethical Concerns with UDTs

It is important to appreciate the limitations of UDTs. Healthcare providers are increasingly relying on UDTs as a means to reduce abuse and diversion of prescribed opioids. This has led to a proliferation in diagnostic laboratories that offer urine testing. With this increase have come questions of whether these business interests benefit or hinder patient care, what

prescribers should do with the information they obtain, the accuracy of urine screens, and whether some companies and clinicians are financially exploiting the UDT boom [129]. A random sample of UDT results from 800 patients with pain treated at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid and 19.5% were positive for an illicit drug/unreported opioid [130]. However, a negative UDT result for the prescribed opioid does not necessarily indicate diversion; it may indicate the patient halted its use due to side effects, lack of efficacy, or pain remission. The increasingly stringent climate surrounding clinical decision-making regarding aberrant UDTs is concerning. In many cases, a negative result for the prescribed opioid or a positive UDT serves as the pretense to terminate a patient rather than an impetus to guide him or her into addiction treatment or an alternative pain management program [129].

In principle, and ideally in practice, UDTs are a worthwhile element of effective pain management and pharmacovigilance when used to enhance the diagnostic and therapeutic objectives of pain therapy. However, when UDT use is motivated by fear, coercion, or profiteering, patients may be offended or feel intimidated by the practice [129].

As a side note, cannabis use by patients with chronic pain receiving opioid therapy has traditionally been viewed as a treatment agreement violation that is grounds for termination of opioid therapy. However, some now argue against cannabis use as a rationale for termination or substantial treatment and monitoring changes, especially considering the increasing legalization of medical use at the state level [24].

PATIENT AND CAREGIVER EDUCATION

Safe Use of Opioids

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids, the FDA has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unless prescribed [114]. A copy of this form may be accessed online at https://www.fda.gov/media/86281/download.

When prescribing opioids, clinicians should provide patients with the following information and instructions [114]:

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled
- Warning and rationale to never break or chew/crush tablets or cut or tear patches prior to use
- Warning and rationale to avoid other central nervous system (CNS) depressants, such as sedative-hypnotics, anxiolytics, alcohol, or illicit drugs
- Warning not to abruptly halt or reduce the opioid without physician oversight of safe tapering when discontinuing
- The potential of serious side effects or death
- Risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions
- The risks of falls, using heavy machinery, and driving
- Warning and rationale to never share an opioid analgesic
- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

Disposal of Opioids

What are best practices for disposal of unused opioids?

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [131]. According to the Office of National Drug Control Policy, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [132]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [132]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established the following best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [131]:

- Consider writing prescriptions in smaller amounts.
- Educate patients about safe storing and disposal practices.
- Give drug-specific information to patients about the temperature at which they should store their medications. Generally, the bathroom is not the best storage place. It is damp and moist, potentially resulting in potency decrements, and accessible to many people, including children and teens, resulting in potential theft or safety issues.
- Ask patients not to advertise that they are taking these types of medications and to keep their medications secure.

- Refer patients to community "take back" services overseen by law enforcement that collect controlled substances, seal them in plastic bags, and store them in a secure location until they can be incinerated. Contact your state law enforcement agency or visit https://www.dea.gov to determine if a program is available in your area.

In April 2023, the FDA announced it will require manufacturers of opioid analgesics dispensed in outpatient settings to make prepaid mail-back envelopes available to outpatient pharmacies and other dispensers as an additional opioid analgesic disposal option for patients. The REMS modification also requires manufacturers to develop educational materials for patients on safe disposal of opioid analgesics, which outpatient pharmacies and other dispensers may provide to patients. The agency anticipates approval of the modified REMS in 2024 [133].

CONSULTATION AND REFERRAL

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [113].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [113]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [24].

MEDICAL RECORDS

Documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [113]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a joint discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [113]. Clinicians should provide physically dependent patients with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

COMPLIANCE WITH FEDERAL AND STATE LAWS

OPIOID RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. Another element of opioid risk mitigation is FDA partnership with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [123].

FDA AMENDMENTS ACT OF 2007

The FDA Amendments Act (FDAAA) of 2007 gave the FDA authority to require REMS from manufacturers to ensure that benefits of a drug or biological product outweigh risks. REMS replaced the previously existing risk management programs, termed Risk Minimization Action Plans (RiskMAPs). An important distinction between the two programs is that the FDA did not have authority to require or enforce a RiskMAP after product approval. The FDA now has the authority to require REMS as part of the approval process for a new medication or post-approval if the agency becomes aware of new safety information pertaining to serious medication-associated risks following approval for marketing [114].

As defined by the FDAAA, REMS may include a medication guide, a patient education package insert, a communication plan, and other elements to assure safe use (ETASUs). ETASUs must address the goals to mitigate a specific serious risk listed in the labeling of the drug and may include [114]:

- Prescriber training, experience, or certification
- Distributor or dispenser training or certification
- Restricted distribution or dispensing
- Dispensing limited to patients with evidence of safe use conditions, such as laboratory test results
- Patient monitoring
- Patient enrollment in a registry
- Physician and/or pharmacist enrollment in a registry

The FDA maintains a list of current opioid analgesic REMS at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm [134].

SPECIFIC OPIOIDS WITH A REMS REQUIREMENT

In 2011, the FDA announced the components of REMS that would apply to all ER/LA opioid formulations. The decision to not include short-acting formulations was based on the substantially greater opioid amount in ER/LA formulations and the corresponding greater risk of serious adverse outcomes, including fatality, when taken by someone for whom they were not prescribed, by patients who succeed in defeating the delayed-release mechanism, or by any user co-ingesting alcohol, benzodiazepines, or other respiratory suppressant substances. Primary elements of the ER/LA REMS include changes in product labeling and the requirement that all ER/LA opioid formulation manufacturers provide specific information to prescribers and patients [135]. For example, there is a new indication for all ER/LA opioids that the pain must be severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The original indication for the treatment of "moderate" pain was eliminated. In addition, the distinctions between cancer pain and chronic noncancer pain were removed. Prescriber education regarding ER/LA opioids is provided through accredited continuing education activities supported by independent educational grants from ER/LA opioid analgesic companies. This includes guidance regarding patient education on the risks and benefits of ER/LA opioid analgesics [135].

In 2012, the FDA issued a class-specific REMS for all transmucosal immediate-release fentanyl (TIRF) opioid products. Training was required for all prescribers, pharmacies, distributors, and outpatients who prescribed, dispensed, or received TIRF products [136]. In December 2020, the FDA approved modifications to this REMS. The modified TIRF REMS consists of a restricted distribution program to ensure the safe use of TIRF medicines, including use only in opioid-tolerant patients [136]. The modified REMS requires that prescribers document a patient's opioid tolerance; that outpatient pharmacies dispensing TIRF medicines document and verify a patient's opioid tolerance prior to dispensing; that inpatient pharmacies develop internal policies to verify opioid tolerance in patients who require TIRF medicines while hospitalized; and that a new patient registry be established to monitor accidental exposure, misuse, abuse, addiction, and overdose [136].

ABUSE-DETERRENT OPIOID FORMULATIONS

Drug developers, manufacturers, and regulatory bodies face daunting challenges in formulating and implementing strategies to reduce the abuse, addiction, diversion, and overdose of prescription opioids. One challenge has been to identify and manufacture analgesics effective in the treatment of severe pain that also possess minimal abuse liability. These products must provide full analgesia with low "opioid attractiveness" to persons intent on abusing or diverting the drug; this strategy is consistent with the opioid REMS principle of drug benefit outweighing risk [137]. The development of abuse-deterrent formulations (ADFs) was also an approach to help avoid the unintended harms to patients with legitimate pain observed in Washington and Florida, where imposition of opioid prescribing restrictions were found to discourage legitimate treatment of chronic pain while making little or no impact on opioid analgesic abuse and diversion [138]. Although ADF opioids retain some abuse liability if used inappropriately or combined with other substances, most ADFs are now being developed to prevent defeat of the delayed-release mechanism or use through illicit routes of administration [139; 140].

Helping to prompt the development of ADF opioids were reports that as many as 80% of prescription opioid abusers in drug rehabilitation tampered with ER opioid formulations [141]. Strategies used by opioid abusers to disable the delayed-release mechanism to accelerate drug release include crushing and swallowing; crushing and snorting; crushing and smoking; or crushing, dissolving, and injecting. The FDA states that ADFs should target known or expected routes of abuse for the opioid constituent in the given formulation [142].

ADVANTAGES AND DISADVANTAGES OF DIFFERENT ADF STRATEGIES

What is an advantage of abuse-deterrent opioid formulations utilizing aversive components?

Several ADF opioids have received approval for marketing in the United States; others are in the process of evaluation, and one ADF was released for marketing and subsequently recalled by the manufacturer [138; 143]. These formulations use different strategies to prevent misuse, with varying advantages and disadvantages (***Table 11***) [138].

While all ADF strategies may potentially deter tampering, physical barriers to crushing or chewing appear to be the only strategy that benefits nonabusers and abusers alike by preventing accidental crushing or chewing and not inducing adverse events. This contrasts with strategies that precipitate adverse events to deter inappropriate use, such as ADFs that use sequestered aversive agents that will induce adverse events in patients who chew or crush the tablets, accidentally or without intent of abuse. The extent of deterrence from these formulations is unclear because some persons are willing to endure discomfort from the aversive agent in order to obtain the more intense high from tampering. Sequestered opioid antagonists may offer a more effective approach in pharmacologic abuse deterrence by rendering the opioid ineffective, but they can induce sudden and severe opioid withdrawal in physically dependent patients who accidentally chew the tablet [138].

ADF OUTCOME DATA

Although opioid ADFs have been introduced into widespread clinical use relatively recently, several studies of their efficacy have already been published. These reports have documented significantly reduced abuse rates of ADF opioids after they have fully replaced the original formulations, but no effect on the overall rates of opioid abuse. For example, data were obtained on 140,496 persons assessed for substance abuse treatment,

ADVANTAGES AND DISADVANTAGES OF ADF STRATEGIES		
ADF Strategy	**Advantages**	**Disadvantages**
Physical barriers	Prevents crushing or chewing to block rapid high-dose opioid release into the system Prevents accidental crushing or chewing in compliant patients No adverse events in compliant patients FDA-approved formulation available	Does not deter abuse of intact tablets Only one FDA-approved product available
Aversive components (e.g., niacin)	May prevent abuse by chewing or crushing the product May limit abuse of intact tablets because taking too much will amplify adverse events	Potential adverse events in compliant patients taking product as intended Adverse events with intact tablets may prevent legitimate dose increase if pain increases or efficacy decreases over time Adverse events may not be sufficient to deter a motivated abuser No FDA-approved formulations
Sequestered antagonist (e.g., naloxone, naltrexone)	Prevents abuse by chewing or crushing opioids FDA-approved formulation available	Does not deter abuse of intact tablets Chewing or crushing the tablet may trigger severe withdrawal symptoms
New molecular entities/ prodrugs	Prevents abuse by providing a chemical barrier to the in vitro conversion to the parent opioid.	—

Source: [138; 144] *Table 11*

spanning from one year before ADF OxyContin (Oxy ADF) introduction to two years post-Oxy ADF introduction. Abuse of OxyContin was 41% lower with the ADF versus the original formulation, including a 17% decrease in oral abuse and a 66% decrease in abuse through non-oral routes. Meaningful reductions in ER morphine and ER oxymorphone abuse rates were not found. The authors concluded that conversion of OxyContin to an ADF formulation was successful in reducing non-oral administration that requires tampering [145]. Another study found that following OxyContin ADF introduction, poison center exposures for oxycodone ER abuse declined 38% per population and 32% per unique recipients of dispensed drug. Therapeutic error exposures declined 24% per population and 15% per unique recipients of dispensed drug, and diversion reports declined 53% per population and 50% per unique recipients of dispensed drug. The declines were greater than those observed for other prescription opioids in aggregate [146]. However, several published reports have documented the abandonment of opioid analgesics and a migration to heroin use by previous OxyContin abusers following the introduction of ADF OxyContin [147; 148].

REGULATORY MANDATES

The FDA has prohibited labeling or marketing claims of abuse resistance or abuse deterrence to be used in any ADF opioid product because supportive epidemiologic data have not yet been published [149]. Any future label claim of abuse deterrence must be supported by post-marketing data [138].

In 2013, Purdue Pharma and Endo Pharma, the makers of OxyContin and Opana ER, respectively, requested a ruling from the FDA that the original formulations were removed from market and replaced by ADFs because of safety or efficacy concerns. Such a ruling would render the original formulations ineligible for generic replication, thus protecting ADF OxyContin and Opana ER market share from generic non-ADF competition [150]. The FDA ruled in favor of this request for Purdue but not for Endo. The basis for the decision was the extent of abuse liability with the original OxyContin preparation and insufficiency in the abuse deterrence with the ADF formulation to block future applications to produce generic versions of the non-ADF Opana ER [151]. Interestingly, this favorable ruling for Purdue Pharma was made on April 16, 2013, the exact date of patent expiration for OxyContin [150].

In 2013, the FDA issued a draft document to guide pharmaceutical companies in developing ADF opioid products. Although the FDA strongly encourages industry to employ ADFs in new opioid products, the guidance document fell short of a mandate [142]. Later that year, the FDA approved an ER formulation of hydrocodone (Zohydro) that lacks abuse-deterrent properties, which seemed contradictory to the FDA stance on ADF product development [152].

In June 2017, the FDA requested that Endo Pharma remove the reformulated Opana ER from the market based on concerns that the benefits of the drug may no longer outweigh the risks [153]. This is the first time the FDA has taken steps to remove a currently marketed opioid pain medication.

The agency's decision was based on a review of available postmarketing data, which demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following release of the ADF formulation. Injection abuse of reformulated Opana ER has been associated with a serious outbreak of HIV and hepatitis C and with cases of thrombotic microangiopathy [153].

OTHER GOVERNMENT AND INDUSTRY EFFORTS

Which government agency is responsible for formulating federal standards for the handling of controlled substances?

In response to increasing rates of opioid analgesic abuse, addiction, diversion, and overdose, the National Drug Control Policy created a multiagency Drug Abuse Prevention Plan in 2011 to reduce prescription drug abuse. The four key elements of the plan are expansion of PDMPs; responsible disposal of unused medications; reduction of pill mills through enhanced law enforcement efforts; and support for provider and patient education. Regarding provider education, several state medical boards (e.g., California, West Virginia) require prescribers to obtain continuing education credit in pain management and prescription opioid use [154].

As noted, emerging trends and patterns of prescription opioid abuse, addiction, and overdose are monitored by several industry and government agencies through data collection from a variety of sources, including health insurance claims; the Automation of Reports and Consolidated Orders System (ARCOS), a DEA-run program that monitors the flow of controlled substances from manufacturing through distribution to retail sale or dispensing; the Treatment Episode Data Set (TEDS), which monitors treatment admissions; National Center for Health Statistics state mortality data; and the Researched, Abuse, Diversion and Addiction-Related Surveillance (RADARS) System, which monitors prescription drug abuse, misuse, and diversion [155].

The DEA is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [156].

Almost all states have enacted PDMPs to facilitate the collection, analysis, and reporting of information on controlled substances prescribing and dispensing. Most PDMPs employ electronic data transfer systems that transmit prescription information from the dispensing pharmacy to a state agency [113].

The General Accounting Office evaluated the efficacy of PDMPs and concluded that such programs have the potential to help law enforcement and regulatory agencies rapidly identify and investigate activities that may involve illegal prescribing, dispensing, or consumption of controlled substances. In states that have made real-time data available, PDMPs can help reduce prescription drug abuse and diversion by allowing prescribers to access and detect whether a patient has been receiving multiple prescriptions for controlled substances or whether a patient has filled or refilled an order for a prescribed opioid [113]. However, several concerns over PDMPs were voiced around the time of their widespread introduction, including the risk that PDMPs may negatively affect patients with legitimate opioid need by reducing opioid prescribing, potential privacy issues, and more frequent physician visits [156].

REGULATIONS AND PROGRAMS AT THE STATE LEVEL

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [157]:

- Physical examination required prior to prescribing
- Tamper-resistant prescription forms
- Pain clinic regulatory oversight
- Prescription limits
- Prohibition from obtaining controlled substance prescriptions from multiple providers
- Patient identification required before dispensing
- Immunity from prosecution or mitigation at sentencing for individuals seeking assistance during an overdose

UNINTENDED NEGATIVE CONSEQUENCES OF EFFORTS TO REDUCE PRESCRIBED OPIOID MISUSE, DIVERSION, AND OVERDOSE

The United States is unquestionably experiencing serious substance abuse problems involving prescription opioids. Although efforts to curtail opioid analgesic prescribing and distribution have been well intentioned, several of the approaches have resulted in unintended consequences.

DIFFICULTY OBTAINING LEGITIMATE OPIOID ANALGESICS

Enactments of restrictive mandates to govern opioid analgesic prescribing and dispensing have created difficulty for patients in accessing legitimate opioid therapeutics. This has been especially well documented in the state of Washington, but it is highly prevalent in general. Concerns have been voiced by numerous key opinion leaders and prominent individuals in the pain treatment profession and community in an effort to draw attention to regulatory and law enforcement overreach at the expense of patients suffering in pain who require access to opioid analgesics.

One example is Jan Chambers, president of the National Fibromyalgia and Chronic Pain Association (NFMCPA). For incorporation into a position paper on patient rights to access pain medication, Chambers sought input from members requiring prescribed opioids for their pain condition. In the open letter encouraging member input, Chambers expressed concern over federal law enforcement and regulatory overreach involving heightened scrutiny of prescription filing and dispensing. Mandates cited as especially harmful were patient-prescriber opioid contracts required to specify a single pharmacy, a 30-day maximum supply of opioids and no refills, and prohibition of faxing or phoning opioid prescriptions to a pharmacy. Also mentioned was the increasing rate of pharmacy refusal to dispense opioids, the result of greater pressures imposed by the DEA on pharmacy networks to obtain additional patient information to verify legitimacy. These pharmacy networks, in turn, have transferred this burden to individual pharmacists, who, similar to prescribers, have become fearful of attracting DEA scrutiny over opioid prescription dispensing. The end result has been difficulty finding a pharmacy to fill opioid prescriptions [158].

Similar concerns over negative unintended patient impact were communicated by Amy Abernethy, president of the American Academy of Hospice and Palliative Medicine (AAHPM) to the National Conference of Insurance Legislators (NCOIL). NCOIL is an organization of state legislators involved in insurance legislation and regulation, and her response concerned several recommendations in a proposed set of best practices guidelines to reduce opioid abuse that were released by NCOIL in 2013. Strategies included in the NCOIL draft were those already implemented at the state level that led to measurable reductions in abuse and overdose. Abernethy countered by arguing that the narrow measure of success came at the expense of patients and providers [159].

With a shortage of pain medicine specialists in the United States, most chronic pain care is provided at the primary care level, and in some states (e.g., Washington), many primary care practices display signs in offices stating they no longer prescribe opioids. Interestingly, a small number of primary care physicians have chosen to transform their practices into cash-only entities and charge very high fees for what amounts to the sole prescribing of opioid analgesics. Patients requiring opioids to maintain pain control and quality of life are forced to seek treatment from these physicians because many others have become intimidated by the new legislation [5].

PATIENTS WHO REQUIRE ULTRA-HIGH-DOSE OPIOIDS

Patient who require ultra-high-dose opioids to control chronic pain should be restricted from the coadministration of what agents?

An element of the backlash against escalating opioid prescribing and associated problems has been intense lobbying by some pain professionals to impose pre-established dose ceiling on opioid prescribing, such that a maximum daily dosage cannot be exceeded. Prominent among these groups has been Physicians for Responsible Opioid Prescribing (PROP) and the advocacy group Public Citizen. The imposition of a 100-mg MED maximum daily ceiling and a maximum prescribing duration of 90 consecutive days was requested for noncancer pain. The groups cited observational study findings of a correlational relationship between prescribed opioid dose and overdose risk as evidence, but these recommendations were rejected by the FDA [160].

Despite FDA rejection of a mandate for daily dose ceilings, many practitioners believe that high-dose prescribing is irresponsible and without medical legitimacy. This view was disseminated and seemingly legitimized by the 2009 opioid prescribing guidelines published by the APS and the AAPM, which stated that no existing evidence supports daily opioid doses ≥200 mg MED [115]. The validity of these assertions has been undermined by several findings of differences between patients in the opioid dose necessary to achieve sufficient pain control, which can vary 40-fold for the same clinical condition [161]. While ultra-high-dose opioid prescribing remains controversial, a small subset of patients do require massive doses of opioids for chronic pain. Authors and guidelines statements of the contrary are based on opinion without empirical support [162].

Patients with chronic pain who require ultra-high-dose opioids, in some cases more than 2,000 mg/day MED, are likely to be labeled as addicts or abusers by healthcare professionals and family members alike. In general, these patients are profoundly ill, impaired, and/or bed- or house-bound due to severe unremitting pain refractory to analgesic efforts using lower-dose opioids. The reason some patients require ultra-high opioid doses remains unclear, but it is very likely that some, and perhaps the majority, possess a cytochrome P450 polymorphism or other genetic abnormality [163].

Patients with chronic pain who legitimately require ultra-high-dose opioids also require supplemental management considerations in addition to those applied to all patients with chronic pain prescribed opioids. Patients and their caregivers should receive education on recognizing overmedication and overdose and what to do if these occur, especially before tolerance has developed. Patients should be restricted from use of benzodiazepines, muscle relaxants, sedatives, and any other potential respiratory depressant medication. While not used in most pain medicine settings, blood levels of opioids have value when a significant discrepancy is observed between prescribed dose and apparent drug effect; serum level results can suggest metabolic variation that impacts opioid dose-response. Serum opioid level testing in these patients can also establish baseline for comparison against future tests. In the unfortunate event of patient death while receiving ultra-high-dose opioids, documenting high serum opioid level while the patient was ambulatory and functional can defend the prescriber against accusation of responsibility for the patient's overdose death when coroner findings reveal high serum opioid levels in the absence of other explanatory findings [162].

Some complications are highly probable with ultra-high-dose opioid therapy that may not occur with lower doses. Endocrine suppression is likely to occur, with testosterone suppression possible in men and some women. Sudden suppression of adrenal corticoids in an opioid-maintained patient manifests in nausea, weakness, and a drop in blood pressure. For these patients, hormone replacement is necessary if opioids remain essential for pain control. Movement and physical exercises are strongly recommended. Almost without exception, patients who require ultra-high opioid dosages have been too ill to engage in normal social or family functions and usually require resocialization counseling for guidance and motivation to resocialize and begin a new quality of life [162].

LAW ENFORCEMENT TACTICS

Activities by the DEA to curb prescription opioid abuse and diversion have been identified in particular as potentially excessive and inappropriate. The U.S. Congress has pressured the DEA to reduce the diversion of prescribed opioids, which the DEA initially achieved through the successful raiding and closure of many pill mills and rogue Internet pharmacies. The focus of the agency has now shifted to reducing opioid supply by targeting wholesalers and pharmacies within the legitimate supply chain. Many complaints have centered on DEA use of tactics identical to those use in combating illegal drug cartels, such as wiretaps, undercover operations, and informants. Retail and wholesale pharmacies raided by DEA tactical squads have complained of being treated as if they were armed criminal organizations [164].

The DEA has accelerated the use of audits and inspections to identify and sanction drug wholesalers, levying millions of dollars in fines for what it has claimed were violations of the law. In 2012, the DEA suspended the license of drug wholesaler Cardinal Health, Inc., prohibiting opioid analgesic sales from its central Florida center. The DEA rationale was failure to detect suspicious order volume from several of Cardinal Health's pharmacy customers. Numerous Walgreens and CVS pharmacies and distribution centers were also raided [164].

The DEA has justified their tactics on the basis of Congressional pressure to contain opioid diversion, with agency success measured by disruption and destruction of organizations and networks feeding the problem. However, John Burke, president of the nonprofit National Association of Drug Diversion Investigators (NADDI), stated that DEA behavior reflects a mindset that retail and wholesale pharmacies comprise an enemy requiring containment. Concerns have been raised over the potential of DEA activity to adversely and negatively impact legitimate medical practice. This has led several congressional members to request that the Government Accountability Office investigate the effect of DEA conduct on medication shortages for patients with pain [164].

Actions of the DEA have produced widespread fear among prescribers and retail pharmacists regarding the prescribing or dispensing of opioids. In some localities, pharmacists greatly restrict dispensing opioids by refusing to fill prescriptions paid for in cash, from customers not well known to them, or from customers from certain geographic areas. Other pharmacy chains have stopped filling opioid prescriptions from higher-volume opioid prescribers. Prescribers report feeling burdened by mandates to tighten patient monitoring by increasing UDTs, documentation, and pill counts [164].

The DEA is also tasked with the oversight and control of ingredients allocated to drug manufacturers for drug production that are deemed an abuse liability. This task is performed annually and is based on manufacturer projection of legitimate patient needs. Manufacturers of drug products with abuse liability complain of DEA failure to authorize sufficient materials for adequate customer supply, which the DEA defends as resulting from poor business decisions by the manufacturers. This has contributed to patient inability to access needed prescribed opioids [164].

INCREASE IN HEROIN USE

Of great concern is the likelihood that persons addicted to prescription opioids will switch to heroin if their preferred opioid becomes difficult to obtain or extract from ADF opioid preparations. Some experts predicted a resurgence of heroin abuse and fatal overdose, largely driven by opioid analgesic prescribing restrictions and by replacement of some opioid preparations by ADFs [165; 166; 167].

Statistics seem to bear this out. In 2014, the percentage of prescription opioid abuse was lower than the percentages in most years from 2002 to 2012 (although similar to the percentage in 2013) [167]. At the same time, heroin use increased. In 2014, the estimates of both current and past heroin use were higher than the estimates for most years between 2002 and 2013 [168]. In addition, first-time past-year use nearly doubled between 2006 and 2012 [169]. Heroin use continued to increase in 2021 [170]. Past-year heroin initiation rose sharply in all regions in the United States, except the South. Unfortunately, the data do not provide estimates of patients with chronic pain resorting to heroin use when their opioid analgesic prescriptions are decreased or discontinued.

One study examined the impact of ADF OxyContin introduction on the abuse of OxyContin and other opioids. Researchers analyzed the results of surveys given to 2,566 patients entering treatment for opioid addiction between July 2009 and March 2012, before and after the 2010 introduction of ADF OxyContin [171]. During the 21-month post-ADF period, endorsement of hydrocodone or oxycodone agents other than OxyContin as the preferred opioid changed little from before ADF introduction, but endorsement of high-potency fentanyl or hydromorphone as the preferred opioid rose from 20.1% to 32.3%. Of opioids used in the past 30 days to get high, OxyContin fell from 47.4% to 30%, while heroin nearly doubled. More detailed questioning of 103 abusing patients found unanimous preference for the old OxyContin formulation, and 66% of those preferring pre-ADF OxyContin switched to another opioid, most commonly heroin. This switch appeared to be causally linked. No evidence suggested

that OxyContin abusers quit using opioids as the result of ADF introduction; instead, they shifted their drug of choice to other opioids, primarily heroin. The authors concluded that ADF OxyContin successfully reduced OxyContin abuse, but also led to increased abuse of replacement opioids [171].

Analysis of data from the National Poison Data System, which covers the reporting from all U.S. poison centers, indicated that, in the period after ADF OxyContin introduction, abuse exposures decreased 36% for ADF OxyContin, increased 20% for other single-entity oxycodone, and increased 42% for heroin. Accidental opioid exposures decreased 39% for ADF OxyContin, increased 21% for heroin, and remained unchanged for other single-entity oxycodone products. The authors conclude that opioid analgesic ADFs can reduce abuse of the specific opioid product but may also lead to switching to other accessible non-ADF opioids [172].

Thus, the introduction of ADF opioids has driven a movement away from prescription opioids and to heroin and has increased the illicit price of traditional non-ADF opioids as they are phased out of the supply chain. During this abandonment by abusers and addicts of the precisely measured amount of pure drug in prescription opioids for the illicit street market of drug dealers, needles, and kitchen table chemists, public health officials and law enforcement agencies are noting increases in heroin overdoses, crime, and other public health problems [173]. These unanticipated negative consequences provide a compelling reminder that societal problems of substance abuse and addiction are complex and multifaceted. Simplistic solutions seeking only to restrict drug supply have never succeeded in reducing drug demand.

INCREASINGLY RESTRICTED ACCESS TO THERAPIES FOR OPIOID ADDICTION

Restricted access to opioid analgesics is also negatively impacting patients attempting to access treatment for opioid addiction. The opioid analgesics methadone and buprenorphine comprise the backbone of outpatient multidisciplinary treatment of opioid addiction in the United States. A 2013 press release by the ASAM states that investigation into state Medicaid and private insurance coverage found increasing restrictions due to policy changes over coverage, daily dose, prior authorizations, and the requirement of previous failed treatment approaches. The end result of these imposed barriers to accessing opioid addiction medications is an increase in patient denial of services, which ASAM states is senseless and unethical considering the epidemic-level rates of opioid addiction and overdose deaths [174].

PATIENT TERMINATION

Several clinical practice guidelines for safe opioid prescribing explicitly endorse patient termination in the event of abnormal UDT results, aberrant drug-related behaviors, other violations of the patient-provider contract, or deterioration in the provider-patient relationship [97]. This approach is controversial, and as stated by Ballantyne, "The surest way to hurt patients (and society) is to abandon them when they deviate from the constructive relationship envisaged by the treating practitioner, only to trail from physician to physician to obtain the drug they need, or worse still, seek illicit supplies" [175].

Clinician response to aberrant behaviors should involve an assessment of seriousness, underlying cause, likelihood of recurrence, and clinical context of the aberrant behavior [115]. Occasional episodes of non-serious violations can be managed by patient education and enhanced monitoring [176]. The basis of opioid analgesic termination should be consistent with those for any other medication class, where discontinuation is prompted when opioid therapy benefits are outweighed by harms. Reasons given for termination include [177]:

- Opioids are no longer effective.
- Opioids no longer stabilize the patient or improve function.
- Patient has lost control over his or her use of the opioid.
- Patient is diverting drugs.
- Patient is not able to stop using alcohol, benzodiazepines, or other CNS depressants.
- Adverse effects become unmanageable.

PATIENTS WITH CHRONIC PAIN AND SUBSTANCE USE DISORDER

Alcohol, street drugs, and prescription medications are used by patients with chronic pain for diverse reasons, including the self-medication of pain, insomnia, depression or anxiety, or intrusive trauma memories; as recreation with occasional use; as a compulsive act driven by addiction; and to avoid withdrawal symptoms [178]. Chronic pain and substance use disorder often coexist, and each condition is a risk factor for the other. Whenever possible, active substance abuse disorder in patients with chronic pain should be treated because of safety concerns and because active substance use disorder interferes with the therapeutic progress in the pain condition due to overlapping mechanisms. Active addiction augments pain stimuli processing and perception through alterations in the input, processing, and modulation of nociceptive stimuli, sympathetic activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and opioid tolerance (in active opioid addiction). Persons with addiction have reduced pain tolerance and increased pain perception, the result of baseline perceptual pathway reorganization from the interactive effects of both conditions [20].

Some personality traits common in patients with addiction, such as external locus of control and catastrophization, are predictors of poor outcome in pain therapy. Intoxication and withdrawal activate the sympathetic nervous system to augment pain perception and increase muscle tension, irritability, and anxiety. The depletion of brain dopamine associated with withdrawal exacerbates discomfort in addicted patients.

Many patients with addiction have lost their network of social support, another factor associated with poor pain therapy outcome [20].

In susceptible persons with chronic pain, use of opioid analgesics for pain relief can lead to a cyclical relationship between pain symptoms, opioid use, and drug effect that is driven by positive and negative reinforcement. The positive reinforcement from opioids comes from induction of a pleasurable state such as euphoria or relaxation, with negative reinforcement coming from elimination of an unpleasant state such as pain or distress. In some patients with chronic pain and biopsychosocial risk factors for addiction, the reinforcing effects they experience from opioids are sufficiently powerful to compel compulsive efforts to replicate the drug experience. Chronic pain adds a layer of complexity to the development and management of opioid addiction. The positive and negative effects of opioids become more elusive over time, and tolerance develops to the analgesic effect. Attempts to cut back or quit can induce opioid withdrawal or the unmasking of severe pain. The patient becomes increasingly preoccupied with obtaining and using opioid analgesics to alleviate his or her intense physical and emotional distress. This preoccupation can be severe, to the point of involving the entirety of motivational resources. Although patients with chronic pain and opioid use disorder represent a complex and challenging population, these chronic co-occurring conditions can be effectively managed [177].

Some people have achieved durable recovery from their substance use disorder and also require medical care for long-standing pain or pain that developed and became chronic during their recovery. Although the former drug of choice is the agent most likely to lead to cravings and relapse, those with a history of addiction to any drug (or alcohol) are susceptible to developing an opioid use disorder in the context of pain treatment. It is important to note that among patients in recovery from a substance abuse disorder, risk of developing problematic opioid analgesic use is inversely proportional to their duration of recovery. While many patients with a previously active substance use disorder are forthcoming during the comprehensive assessment, some may not be; others may lack an appreciation of either the gravity of their former substance abuse disorder or the clinical importance in disclosing this history to their healthcare provider. Family members can be a valuable resource in providing this information [177].

It is important for the prescriber to determine the recovery status of the patient in order to appropriately tailor the treatment plan. For patients who have achieved stable remission, corroborate and support them in their recovery. If a patient is receiving buprenorphine or methadone maintenance therapy for an opioid use disorder, verify and continue buprenorphine or methadone. If a patient has an active substance abuse disorder, refer him or her to a substance abuse specialist, if possible, for further evaluation [127; 177].

An important point is that clinicians often find patients with chronic pain to be difficult to treat, due to the pain condition often eluding diagnosis and the effects unrelenting pain can have on patient ability to interact calmly and civilly. A comorbid substance abuse disorder amplifies the likelihood of difficult behavior from the patient. Such patients can provoke strong negative responses from treatment providers, often based on either frustration from attempting to treat difficult or intractable problems or clinicians feeling they are working harder for the well-being of the patient than the patient is. It may be helpful for clinicians to remind themselves that, despite the apparent lack of patient motivation, no one would wish the experience of comorbid pain and addiction on anyone [177].

These patients have complex and intense needs, best served by a treatment team approach involving a team of professionals, including [179]:

- Primary care provider
- Addiction specialist
- Pain specialist
- Nurse
- Pharmacist
- Psychiatrist
- Psychologist
- Other behavioral health specialists, such as social workers or marriage and family therapists
- Physical or occupational therapists

To help build a therapeutic relationship with the patient, the following approach is suggested [177]:

- Listen actively.
- Ask open-ended, nonjudgmental questions.
- Restate patient accounts to make sure they have been understood.
- Use clarifying statements (e.g., "It sounds as if the pain is worse than usual this week").
- Demonstrate empathy. One approach is to acknowledge the effort required to simply get through each day with constant pain.
- Use feeling statements (e.g., "This must be very difficult for you").

Referral to an addiction professional for further substance abuse disorder evaluation and possible treatment does not negate patient need for pain treatment, because addiction treatment programs rarely have the resources or expertise to treat pain. Patients who are seeking treatment for chronic pain with an unacknowledged substance abuse disorder may react negatively when told of their referral to an addiction professional. The clinician-patient relationship is especially critical for patients who have comorbid pain and substance abuse disorders. They may anticipate clinician criticism or judgment of their substance use, dismissal of their pain complaints, or misinterpret concern over a possible substance abuse disorder

as lack of concern for their pain. They may blame themselves for the substance abuse problem and expect their healthcare provider to respond in kind. Clinicians should convey respect and concern and reassure patients they fully understand the pain and the substance abuse disorder are uninvited chronic illnesses requiring concurrent treatment. It is important to clearly explain the purpose of the referral, with the following approach suggested [177]:

- Present the substance abuse disorder referral as you would to any other specialist, using a matter-of-fact and unapologetic tone.
- Emphasize the importance of assessing all factors, including substance abuse disorders, that may be contributing to chronic pain and that ongoing problems with substance abuse can interfere with optimal treatment of chronic pain.
- Avoid focusing on patient explanations of their substance use.
- Reassure patients that further evaluation and possible treatment of their substance abuse problem does not mean abandonment by their healthcare provider or neglect of their chronic pain condition. Emphasize that their care will be coordinated among all involved professionals.
- Reassure the patient that federal regulations hold clinicians to a high standard of confidentiality concerning patient drug and alcohol treatment information.

TREATMENT OF SUBSTANCE USE DISORDER

Not infrequently, primary care providers do not have access to specialized addiction professionals or programs for patient referral. Although coexisting pain and addiction rank among the most challenging conditions to manage in primary care, recovery is possible. Providers should practice patience, flexibility, and consistent motivational support with the patient. When addiction specialists are lacking, clinicians should [178]:

- Identify contributory factors to the chronic pain and use of substances
- Encourage and support the patient in developing a self-care program
- Implement or refer to initiate active treatment of the various underlying factors
- Provide regular patient follow-up to monitor self-care and treatments and to revise the plan, as needed

The goals of treatment include avoiding harmful use of substances and achieving physical, psychological, and spiritual well-being. In patients with chronic pain with substance abuse disorders, there is a degree of overlap when substance abuse disorder treatment involves a biopsychosocial approach, as it ideally does. Effective approaches for substance abuse disorder include a combination of [178]:

- Cognitive-behavioral therapy that addresses addiction recovery and chronic pain
- Deep relaxation/meditation through mindfulness, progressive muscle relaxation, and/or other approaches
- Working with an addiction counselor to explore substance use issues and to support recovery
- 12-step program involvement, through Alcoholics Anonymous (AA), Narcotics Anonymous (NA), or Methadone Anonymous (MA), when appropriate. Every 12-step program has sponsors who are support persons successful in their recovery through their respective 12-step program, with a desire to work with new members to help them achieve recovery success. The patient should be encouraged to find a sponsor.
- Alternatives to 12-step programs for peer support in substance abuse recovery (e.g., Smart Recovery and Rational Recovery)
- Chronic Pain Anonymous, the peer-support program for those with chronic pain

Treatment of Opioid Use Disorder in Patients with Chronic Pain

For patients on chronic opioid therapy who have minor opioid abuse relapses but quickly regain stability, involving substance abuse counseling in the medical setting or through a formal addiction program may suffice. One problem is that many addiction treatment programs will not admit patients who require the ongoing use of opioid analgesics for pain. In patients whose frequent relapses indicate a serious opioid use disorder, the best option may be referral to an opioid treatment program for methadone therapy or initiation of buprenorphine [177]. Methadone and buprenorphine can be used in patients with opioid use disorder during detoxification. With this approach, the patient is slowly transitioned from the dose of their illicit opioid to an opioid-free state by switching the illicit opioid to the withdrawal medication and slowly decreasing the detoxification medication dose. However, in the context of treating the opioid use disorder, the patient is placed on methadone or buprenorphine for an extended period. Formerly termed "maintenance therapy," this is now called "medication-assisted treatment" [180].

Treatment of opioid addiction with methadone or buprenorphine is intended to stabilize dysregulated brain pathways, thereby reducing craving and relapse risk. Persons with opioid addiction remain at very high risk of opioid relapse after successful detoxification and cessation of acute opioid withdrawal symptoms. Profound changes in brain function that occur with the development and progression of opioid addiction become unmasked with cessation of opioid use. Factors contributing to relapse vulnerability in persons attempting recovery from opioid addiction include craving for opioids, hypersensitivity to emotional stress, an inability to experience pleasure or reward, and a persistent state of distress, anxiety, or malaise [181]. For many patients with opioid addiction, treatment should address these alterations in neurobiology. By targeting the same brain receptors and pathways as the abused opioid, pharmacotherapy with opioid agonists or partial agonists can effectively manage

opioid withdrawal symptoms and play an essential part in the ongoing treatment plan [182]. Methadone and buprenorphine are the two most widely used and effective pharmacotherapies for opioid use disorder, and both have regulatory approval in the United States for this indication [183]. Naltrexone is also approved for treatment of opioid use disorder [99; 182]. In 2018, the FDA approved the first non-opioid for the management of opioid withdrawal symptoms [184]. Lofexidine may be used for up to 14 days to lessen the severity of symptoms of opioid withdrawal as part of a long-term treatment plan [99].

Methadone Therapy

Methadone has been in clinical use since 1965 as a treatment for opioid addiction. Its use is based on the principle that a long-acting mu opioid agonist at a sufficient dose prevents opioid withdrawal, blocks the desired effects if other opioid drugs are abused, and diminishes the craving for opioids [185]. A network of opioid treatment program regulatory and dispensing systems has been implemented to dispense methadone for opioid addiction, where the patient is administered methadone once a day under staff observation. Some stabilized patients are allowed up to a 30-day supply of take-home methadone, depending on their length of maintenance and compliance with other opioid treatment program rules. However, for some opioid-dependent persons, this system is not feasible due to lack of proximity to an opioid treatment program, a schedule that conflicts with that of an opioid treatment program, or concerns related to the social stigma associated with methadone [186].

Although the appropriate maintenance dose should be tailored to the individual on the basis of genetics and opioid use history, daily doses of 80–120 mg are common and are more likely to produce the desired opioid-blockade effect. Data indicate a greater reduction in illicit opioid use from a daily dose of 80–100 mg than from a dose of 40–60 mg [183; 186].

A potential issue with methadone relates to its metabolism by the hepatic cytochrome P450 CYP3A4 enzyme and the numerous medications that may adversely interact with its metabolism to result in elevation of plasma methadone level or rapid elimination of the drug. This can lead to dangerous toxicity or lack of effectiveness, respectively [99; 183].

Buprenorphine Therapy

What is an advantage of buprenorphine over methadone treatment of opioid use disorder in patients with chronic pain?

Buprenorphine was the first drug approved for treatment of opioid addiction that can be prescribed in an office-based setting [187]. For use in opioid addiction therapy, buprenorphine is formulated into a product combined with the opioid antagonist naloxone and administered sublingually. When taken as prescribed, the naloxone component remains inert, but if the formulation is crushed and injected, the naloxone is activated to produce withdrawal symptoms. Buprenorphine occupies 85% to 92% of brain mu opioid receptors at 16 mg/day dosing and 94% to 98% at 32 mg/day. Daily doses of 4–16 mg are typically effective for most patients, with 16–24 mg the upper limit of recommended dosing [99; 188; 189]. Prior to January 2023, clinicians had to apply for a federally required Drug Addiction Treatment Act (DATA) Waiver (X-Waiver) in order to prescribe medications, like buprenorphine, for the treatment of opioid use disorder. Section 1262 of the Consolidated Appropriations Act of 2023 (also known as Omnibus bill) removed this requirement and allowed clinicians with schedule III authority on their DEA registration to prescribe buprenorphine if permitted by applicable state law [99; 190].

Several pharmacologic aspects of buprenorphine contribute to its safety and effectiveness as therapy for opioid addiction and make it highly suitable for use in primary care [191]. As a partial mu agonist, a ceiling effect exists for its maximal activity—beyond a certain dose, no additional benefit is experienced. In contrast to increases in the dose of pure opioid agonists such as methadone, a greater margin of safety exists from death by respiratory depression. Buprenorphine possesses a short plasma half-life (about four to six hours) and a long duration of action resulting from its high affinity for and slow dissociation from the mu opioid receptor [187]. This slow dissociation likely contributes to a reduction in the severity of withdrawal symptoms during detoxification, and the longer duration of action allows for the potential of alternate-day dosing [192].

Methadone and Buprenorphine Efficacy

The efficacy literature indicates that higher-dose methadone (>50 mg daily, and 60–100 mg per day in particular) is more effective than lower doses in reducing illicit opioid and possibly cocaine use [193]. Higher-dose methadone is comparable to higher-dose buprenorphine (≥8 mg daily) on measures of treatment retention and reduction of illicit opioid use [193]. Although 30–60 mg per day of methadone may be effective in resolving opioid withdrawal symptoms, some patients require a maintenance dose ≥120 mg per day to eliminate illicit opioid use [193]. Patients requiring high-dose methadone for more severe opioid addiction are unlikely to achieve the same benefit from higher-dose buprenorphine [119]. Methadone has been reported to have higher retention rates, whereas buprenorphine has a lower risk of overdose fatality. These risks should be appropriately weighed by the treating or referring physician [191].

Sustained stabilization on methadone or buprenorphine can greatly enhance the capacity for normal functioning, including holding a job, avoiding crime, and reducing exposure to infectious disease from injection drug use or risky sexual behavior. Stabilized patients are much more likely to benefit from counseling and group therapy, essential components of recovery [185]. Although patients may experience sedation during the induction phase, tolerance to this effect develops over several weeks, after which the ability to work safely or operate a car or machinery is no longer impaired. Cognitive research has found that, during stabilization, the methadone-maintained patient is just as capable as a healthy, non-addicted person in job performance, assuming education and skill is

comparable and abstinence from opioids and other drugs of abuse is ongoing [194]. Unfortunately, serious stigma surrounds methadone treatment, experienced most acutely by patients but also by professionals, which may pose a barrier to treatment support [195].

While methadone and buprenorphine can effectively treat pathologic opioid use, they do not appear to significantly reduce non-opioid substance abuse. Both medications are approved for use as part of a broader, comprehensive, recovery-oriented medical and social support plan. Importantly, these medications are compatible with a recovery-oriented treatment approach, which research suggests can be an essential—but not sufficient—element of recovery from opioid addiction [196]. While methadone and buprenorphine can provide the patient with stabilization by suppressing withdrawal symptoms, craving, and dysphoria, many patients also experience mental health problems, deterioration in personal and social relationships, and greatly impaired occupational functioning. The addition of counseling, social services, monitoring, and peer supports can offer much of what pharmacotherapy cannot provide [186].

The effectiveness of methadone and buprenorphine has only been shown in their use as long-term maintenance, and there is little evidence to support their use as a short-term therapy course. This has been a source of patient and provider frustration. In clinicians, this probably reflects the antiquated perception that withdrawal and craving are the cardinal manifestations of addiction that, if properly treated for a brief period, should lead to full remission. It is now known that no short-term treatment can reverse the typically decades-long opioid-induced genetic expression, neurobiologically based cue-induced craving and withdrawal, or alteration in brain reward, motivation, and memory circuits characterizing long-term opioid addiction. There is increasingly widespread awareness that addiction should be viewed as a chronic disease, with great similarity to other chronic disease, such as diabetes and hypertension, whereby remission is dependent on medical management, lifestyle changes, and significant social supports [186].

Considerations in Addressing Chronic Pain

Although methadone and buprenorphine are highly effective in the treatment of some chronic pain conditions, the protocol by which they are administered to treat opioid use disorder is unlikely to provide sufficient analgesia for patients with chronic pain. With methadone, the 4- to 8-hour duration of analgesic action is significantly shorter than the 24- to 48-hour duration it suppresses opioid withdrawal and craving. The typical once-daily dosing results in a narrow window of analgesia, and contrary to popular belief, it is usually not adequate for analgesia in patients with chronic pain. Additional therapies are required. With patients often describing a six- to eight-hour window of analgesia from their usual morning dose, a single long-acting opioid dose in the afternoon or early evening may be sufficient for pain control for the remainder of the day [197].

With buprenorphine therapy, concurrent opioid analgesic use is complicated by buprenorphine pharmacodynamics. With high mu opioid receptor affinity, buprenorphine displaces or competes with full opioid agonists given concurrently. This can result in several types of adverse outcomes [15]:

- Inadequate analgesia from blocking the effect of concurrent opioids
- Opioid overdose when buprenorphine plasma level declines in the presence of high-dose concurrent opioids
- Acute opioid withdrawal syndrome as the buprenorphine plasma level declines in the presence of inadequate additional opioids
- Acute opioid withdrawal syndrome when buprenorphine is administered to patients receiving long-term opioid analgesic therapy

Buprenorphine has an analgesic duration of 4 to 8 hours and a 24- to 48-hour suppression of opioid withdrawal and craving. As a partial agonist, the analgesic effect has a ceiling after which dose escalation does not lead to improved pain control. Thus, patients receiving buprenorphine for opioid use disorder must discontinue this medication if they require full-agonist opioid analgesics for chronic pain control. Before taking this step, the clinician and patient should weigh the risks and benefits, including the risks of prescription opioid abuse and potential relapse to drug use without buprenorphine, and the potential improvements in pain and function that may come with full-agonist opioid analgesic therapy [20].

Patients in recovery from opioid or other substance use disorders may have specific preferences for types of analgesic medications and may have greater awareness of their risk of relapse if given opioids for their chronic pain. Studies of patients with pain in recovery from substance use disorders have found that while some do relapse when receiving long-term opioid analgesic therapy, untreated pain can itself be a trigger for relapse. A prescription opioid agreement may help provide a sense of control that recovering addicts often fear losing when taking opioid analgesics [20].

CASE STUDY

An unemployed man, 64 years of age, is brought to an emergency department by ambulance, after his wife returned from work to find him lying on the couch, difficult to arouse and incoherent. He has a past history of hypertension, diabetes (non-insulin dependent), mild chronic obstructive pulmonary disease, and chronic back and shoulder pain, for which he has been prescribed hydrocodone/acetaminophen for many years. His wife reports that while he seemed his usual self when she left for work that morning, he had, in recent weeks, been more withdrawn socially, less active, and complained of greater discomfort from the back and shoulder pain. She knows little about his actual medication usage and expresses concern that

he may have been taking more than the prescribed amount of "pain medicine."

On evaluation, the patient is somnolent and arouses to stimulation but is non-communicative and unable to follow commands. His blood pressure is normal, he is afebrile, and there are no focal neurologic deficits. Oxygen saturation, serum glucose, and routine laboratory studies (blood counts and metabolic profile) are normal except for mild elevation in blood urea nitrogen (BUN) and creatinine; the urine drug screen is negative except for opioids. Additional history from the family indicates that the patient has been admitted to other hospitals twice in the past three years with a similar presentation and recovered rapidly each time "without anything being found."

Following admission, the patient remains stable-to-improved over the next 12 to 18 hours. By the following day, he is awake and conversant and looks comfortable. On direct questioning, he reports recent symptoms of depression but no suicidal ideation. The patient describes an increased preoccupation with his pain syndrome, difficulty sleeping at night, and little physical activity during the day, in part because of physical discomfort. He is vague about his medication regimen and admits to taking "occasional" extra doses of hydrocodone for pain relief.

The family is instructed to bring in all his pill bottles from home, which they do. In addition to the hydrocodone prescribed by his primary care physician, there is a recent refill of a prescription for the medication given to the patient at the time of his last hospital discharge six months earlier.

ASSESSMENT

A full evaluation, including radiographic studies and consultation with psychiatry and physical therapy, is completed. The working diagnosis for the patient's acute illness is toxic encephalopathy caused by the sedative side effects of opioid medication on the CNS. It is explained that the combination of his advancing age and diabetes likely reduced the efficiency of his kidneys in clearing the medication and its metabolites, making him more susceptible to CNS sedation. It is noted that the patient and his wife have little understanding of the rationale, proper use and safeguards, potential side effects, and limited effectiveness of opioid use for chronic pain.

In addition, the patient is diagnosed with poorly controlled chronic pain syndrome secondary to osteoarthritis and degenerative disc disease; exacerbating factors include deconditioning and reactive depression. The use of an opioid analgesic, at least for the near term, is considered appropriate, if dosed properly, monitored closely, and integrated into a comprehensive, multidisciplinary plan that includes treatment of depression and the use of adjunctive, nonpharmacologic modalities of care. In the setting of possible early diabetic nephropathy, the option of utilizing an NSAID, except for very brief periods of breakthrough pain, is not considered to be a safe option.

At discharge, and in consultation with his primary care physician, a written treatment and management plan addressing all aspects of the patient's care is presented to the patient and his wife for discussion and consent. Among the key issues addressed are:

- Goals: Improvement in subjective pain experience; improved function of daily living manifested by regular walking exercise and improved social interaction with family and friends; relief of depression; and in the long-term, anticipated withdrawal of opioid medication and resumption of part-time work and/or volunteer community activity
- Outpatient physical therapy and back exercise program to increase core muscular strength, improve flexibility, reduce pain, and increase exercise tolerance
- Patient and family counseling regarding the safe use, dosage regulation, side effects, and proper disposal of opioid medication
- Joint patient-physician responsibilities as regards to regular follow-up, monitoring of goals and treatment effectiveness, avoidance of "doctor-shopping," and assent to a single provider for prescription medication

FOLLOW-UP

On follow-up six weeks after discharge, the patient is noticeably improved. He reports that he feels stronger and is sleeping better. His affect is brighter, and he is getting out more. He has maintained his physical therapy and exercise routine and is compliant with his medication. Though he still has pain, it is noticeably less and he is coping better. He and his wife are encouraged by his progress, particularly in regard to his improved functional status.

CONCLUSION

Opioid analgesic medications can bring substantial relief to patients suffering from pain. However, the inappropriate use, abuse, and diversion of prescription drugs in America, particularly prescription opioids, has increased dramatically and has been identified as a national public health epidemic. A set of clinical tools, guidelines, and recommendations are now available for prescribers who treat patients with opioids. By implementing these tools, the clinician can effectively address issues related to the clinical management of opioid prescribing, opioid risk management, regulations surrounding the prescribing of opioids, and problematic opioid use by patients. In doing so, healthcare professionals are more likely to achieve a balance between the benefits and risks of opioid prescribing, optimize patient attainment of therapeutic goals, and avoid the risk to patient outcome, public health, and viability of their own practice imposed by deficits in knowledge.

APPENDIX: BIAS AND VALIDITY IN PAIN RESEARCH

In addition to training, experience, and clinical judgment, safe and effective treatment of pain is guided by developments in the area of pain medicine research. Clinician awareness of refinements, advances, and breakthroughs in the diagnosis and treatment of pain is most directly acquired from reading the published research. Conducting well-designed clinical research is challenging and complex. Obtaining accurate and relevant information to apply to patient care is often made more difficult by inadvertent bias and lack of reliable validity in the reporting of research findings. Outright data fraud is rare, but false claims and biased interpretation of results (often unintentional) are commonplace in publications of medical research in general and pain research specifically. In the area of pain treatment with opioid analgesics, major stakeholder influence over the reporting of dangers, risks, benefits, and effectiveness is pervasive [2; 97; 198; 199; 200].

Clinicians trying to make the most of their limited time by reading study abstracts may also be misinformed. A random selection of studies with abstracts from six widely read and influential medical journals (*JAMA*, *BMJ*, *Lancet*, *NEJM*, *Annals of Internal Medicine*, and the *Canadian Medical Association Journal*) found that 18% to 68% of abstracts reported information that was inconsistent with or absent from the body of the paper [201].

PUBLICATION BIAS

Publication bias occurs when trials showing statistically significant and positive results are disproportionately published, relative to trials with negative or inconclusive findings. This type of bias is common in published pharmacological research. Pharmaceutical industry research sponsorship is associated with significantly higher rates of pro-industry conclusions, publication constraints, and propensity to ignore the publication of negative findings [202; 203; 204; 205; 206; 207].

REPORTING BIAS

Reporting bias includes a diverse range of bias, misrepresentation, distortion, omission, exaggeration, or dismissal of data reported by the authors of a study or of data from other publications [208]. The effect, if not the intent, of reporting bias is to influence reader perception through a persuasive argument that favors the agenda, paradigm, or interest of the author, agency, or institution, or to diminish or discount a competing or opposing perspective. Reporting bias is just as widespread in pain research as it is in other areas of medicine, often appearing as concluding statements of safety or efficacy that are not supported by the actual evidence.

A medical issue or problem is considered "hot" when it becomes the focal point of publicity and intense investigation. Reports of research findings are less likely to be true in hotter areas of research. Prejudice can dominate a hot medical field to further undermine the validity of research findings. Highly prejudiced stakeholders can also create obstacles and obstruct efforts to publish information with opposing results [209].

Pressures of vested interests can lead to disappointing research outcomes being "spun" to present the findings in a more favorable light by creative use of data, statistics, and linguistics. Examples of linguistic spin include [210]:

- "Treatment X is expected to be a very important approach in the management of Disorder Y"
- "Treatment X effect size approached conventional statistical significance."

The use of "spin"—claiming treatment benefit without any supporting evidence from the data—is common, and safety claims with spin without supporting data also occur [211; 212; 213].

BIAS IN CLINICAL PRACTICE GUIDELINES

Concerns have sometimes been raised regarding bias in the development of clinical practice guidelines, involving the reviewed research, misrepresentation of the data, or failure to assess the quality of the evidence supporting the recommendations. Inadequate or weak evidence may lead to conclusions based on value judgments, organizational preferences, or opinion. Guidance is frequently misinterpreted as mandate, when individualized treatment is the best practice [214]. Clinical practice guideline authority and influence usually comes from the sponsoring organization and status of the publishing journal. Once issued, the organization may become the promoter and defender of the guidelines, and panel members the stakeholders in the acceptance of their recommendations [115; 215].

Bias can also negatively affect the validity of systematic reviews and meta-analyses that can form the basis of clinical practice guidelines. For example, several practice guidelines on long-term opioid therapy for chronic pain were published between 2008 and 2011. Although each guideline was based on analysis of essentially the same body of published research, the guideline conclusions differed markedly. The educated reader may look deeper for possible explanations for these discrepancies, including bias. Areas to explore would include the source of funding or sponsorship for development and financial and other material ties of the authors to industry, organization, or agency (e.g., slanted reporting of findings, conclusions consistent with industry of agency interests or agenda); the quality of evidence used to support a recommendation (by either endorsing or discouraging use of a drug, dose level, or therapy duration) and, in particular, weak evidence used inappropriately as definitive proof; whether the authors solely used published studies; and whether the studies used were industry funded [216].

ARGUMENTS USED TO SUPPORT ERRONEOUS CONCLUSIONS IN BIASED RESEARCH REPORTING		
Form of Argument	**Definition**	**Explanation or Example**
False conclusions of causation based on correlation		
Non causa pro causa (no cause for cause)	One or more events suggested as causing another event	Even when data show a statistically significant correlation, assumption of cause and effect is erroneous.
Cum hoc, ergo propter hoc (with this, therefore because of this)	Causation based on an association between two or more event trends or outcomes that occur together in time	1) The correlation may be significant, but correlation is not causation, and more research is needed to rule out other explanations for the association. 2) The direction of causation may be the reverse of the false conclusion.
Post hoc, ergo propter hoc (after this, therefore because of this)	Conclusion of causality based solely on the sequence of events	This is common in observational and open-label studies, because factors that actually influence outcome are not controlled for.
Regression fallacy	Pain severity declines over time to a lower average level during the natural course.	This "regression to the mean" can falsely be attributed to treatment effect.
Texas sharpshooter fallacy	Certain variables showing a close association are selected from a vast array of data, and a cause-effect relationship is concluded.	Common in data-mining studies and erroneous due to: 1) The data cluster may be the result of chance. 2) Even if not random, the cause may differ from what is stated by the researchers.
False arguments used in support of a conclusion		
Argumentum ad ignoratum (appeal to ignorance)	Missing evidence is itself evidence for lack of an effect.	Often seen in pain medicine, as when the lack of long-term controlled studies on opioid safety and efficacy in chronic pain is stated as evidence against long-term opioid use in chronic pain
Argumentum ad verecundiam (appeal to authority)	The high-status source of a publication is used to affirm the results.	In an argument with weak factual support, this is used to mislead the reader into not questioning the accuracy, reliability, or validity of the data the argument is based on.
Argumentum ad populum (appeal to the people or popularity)	The widespread use and acceptance of a practice prove its validity.	Argues that a popular treatment (e.g., homeopathic pain remedies) would not be so widely used if it did not work. Avoids the need to show credible evidence.
Illusory correlation	An expected relationship between data, observations, or events is found when a true causal relationship is absent.	This fallacy has been used when infrequent patient outcomes stand out and are generalized to represent all patient outcomes.
Reductionism	A large, complex phenomenon is oversimplified by reducing it to a smaller, simpler component.	Can occur when data from a small, highly select group of patients with pain, or even data of individual patients by anecdote, is used to characterize an entire population of patients.
The "no true Scotsman" fallacy	Used as an *ad hoc* rescue of a reductionist argument that comes under criticism	Reflected by statements such as "no true patient in pain would abuse their medication"
False dichotomy	Forces simple answers to complex questions with an argument in which only two choices are offered	Epidemiologic studies may record the rate of opioid abuse by the number persons who either did or did not ingest a non-prescribed opioid analgesic in the past year. This neglects any detailed analysis, such as motivation by untreated pain, inadequately treated pain, or desire to get high.
Myths of beneficence	Programs or policies are argued as beneficial to patients or the public and thus should be accepted.	This appeal to altruism and the presumption of good intentions may be used to deter examination of possibly deficient or biased reasoning or harmful unintended consequences.

Source: [217; 218] *Table 12*

FALLACIES OF ARGUMENT

Fallacies of evidence or argument are used in pain medicine research to support or defend a false conclusion (***Table 12***). Many are intended to convince the reader of a cause-effect relationship when the actual evidence is weak or absent. Considerable evidence is required to establish a true cause-effect relationship, and the evidence purported to show causation may actually reflect association instead. It is important to maintain a degree of critical thinking to avoid being persuaded into accepting a falsehood or rejecting a truth.

Cum Hoc, Ergo Propter Hoc Fallacy

A prototypical example of this type of fallacy comes from the 2011 CDC reporting of the same data in three publications related to a stated epidemic in opioid analgesic deaths and addiction and their direct relation to increasing opioid prescribing as reflected by sales data. Evidence to support this argument came from simultaneously increased trends in opioid analgesic sales, opioid analgesic overdose deaths, and addiction treatment admissions for opioid analgesics [212; 213; 219]. Many professionals found this persuasive evidence of a cause-effect relationship, and this conclusion was also reported by the news media and widely referenced in academic papers.

With causation inferred from correlational data, the fallacy in this reporting was that few alternate explanations for the correlations were presented. One credible explanation would have been exaggeration in the true rates of unintended overdose fatalities directly caused by opioid analgesics, a fact conceded by the CDC. Omitted entirely was discussion of the escalating population of patients with chronic pain. Sicker patients may also have been increasingly prescribed multiple medications with overdose potential for their disorders, including opioids.

Another reason that causal inference from correlational data is erroneous is that when causation is based on simultaneously occurring events, it is not possible to determine which event came first. The true direction of causation may actually be the reverse of that reported by researchers. For instance, studies finding a significant correlation between fibromyalgia and obesity in women concluded these female patients developed fibromyalgia because they were overweight. The order of events, such as whether obesity or fibromyalgia came first, was never examined, and it is just as likely the pain and disability associated with fibromyalgia promoted activity avoidance and weight gain or that medications used to treat fibromyalgia promoted weight gain or that medications used to treat fibromyalgia promoted weight gain.

False conclusions of a cause-effect relationship may also occur when data used in support of a conclusion come from small but statistically significant outcomes in a measure of effect, when broader examination of the data suggests otherwise. One example is the conclusion of a cause-effect relationship between higher methadone dose and frequency of the serious adverse cardiac event of QTc interval prolongation. The basis of this conclusion of causality was the finding of a modest yet statistically significant correlation between higher dose and adverse event [220; 221]. However, the conclusion is false because correlation does not equate with causality, and a closer look at the actual data revealed that increased QT interval occurred only in the subgroup who were abusing cocaine, a drug with well-known cardiotoxic effects.

Post Hoc Fallacy

An example of *post hoc* fallacy in reasoning comes from a prospective, observational, open-label study in which single-dose intrathecal midazolam was used in patients with failed back surgery syndrome. The patients showed significant pain reduction and few side effects, and the researchers concluded that single-dose intrathecal midazolam was an effective supplement to standard analgesic therapy [222].

This study was criticized for using a *post hoc*, *ergo propter hoc* argument as the basis for causation in a commentary published in the same journal issue [223]. The commentary noted that just because patients improved after midazolam treatment did not mean they improved because of midazolam treatment. From an evidence-based perspective, the study evidence would also be regarded as low quality because it lacked a control group and the open-label design did not control for placebo response.

Differences in Definitions

Differences in definitions also represent a serious confounding factor. Opioid "misuse" may describe overuse or underuse for medical purposes, nonmedical use, or diversion, and may be a one-time occurrence or more frequent. There is little clarity or consistency across studies in how this variable is defined and measured. Consequently, the prevalence rate of opioid misuse can be expressed as a large or small probability depending on the study biases. This same phenomenon occurs with many other variables studied in pain management and can be very misleading to consumers of research.

Customer Information and Evaluation are located on pages 103–104.

Course Availability List

These courses may be ordered by mail on the Customer Information form located on page 103.
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MODERATE SEDATION/ANALGESIA

#30464 • 15 ANCC / 15 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses with the knowledge required for safe drug delivery based on standardized operational guidelines. Preprocedural, intraprocedural, and postprocedural patient care are presented, as well as a thorough review of the drugs used, their advantages and disadvantages, and the safe administration of these agents.
Audience: This course is designed for all nurses, especially those in procedural and diagnostic areas, such as radiology, endoscopy, cardiac cath, outpatient surgery, intensive care, and emergency departments.
Additional Approvals: AACN Synergy CERP Category A, CCMC

POSTOPERATIVE COMPLICATIONS

UPDATE

#30764 • 15 ANCC / 2 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.
Audience: This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.
Additional Approvals: AACN Synergy CERP Category A, CCMC

PITUITARY AND ADRENAL DISORDERS

UPDATE

#30831 • 15 ANCC / 5 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing struggle with their pituitary or adrenal illness.
Audience: This course is designed for nurses in all practice settings.
Additional Approvals: AACN Synergy CERP Category A, CCMC

NEWBORN ASSESSMENT

#32264 • 10 ANCC Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide an overview of a newborn assessment for all nurses, especially those who either presently care for newborns or those who come in contact with them occasionally.
Audience: This course is designed for all medical-surgical nurses and ancillary nursing personnel involved in the assessment of newborns.
Additional Approvals: AACN Synergy CERP Category A

ACUTE CORONARY SYNDROME

#40944 • 15 ANCC Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to reduce the widening gap between care according to guidelines and actual care delivered by providing healthcare professionals with knowledge necessary to implement the most appropriate approach to diagnosis and treatment.
Audience: This course is designed for physicians, physician assistants, and nurse practitioners to enhance their knowledge of the diagnosis, assessment, management, and secondary prevention of acute coronary syndrome.

PRESSURE INJURIES: PREVENTION AND MANAGEMENT

#48854 • 10 ANCC Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, physician assistants, and nurse practitioners a current review of the pathogenesis, diagnosis, and treatment of pressure injuries, with an emphasis on clinical recognition and staging, risk factor assessment and prevention, and management strategies for collaborative care to improve patient outcomes.
Audience: This course is designed for physicians, primary care providers, and physician assistants involved in the care of patients at risk for pressure ulcer development.

PROMOTING THE HEALTH OF GENDER AND SEXUAL MINORITIES

#91794 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: 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.
Audience: This course is designed for all members of the interdisciplinary team, including physicians and nurses, working in all practice settings.
Additional Approvals: AACN Synergy CERP Category B, CCMC

CHILDHOOD LEUKEMIAS AND LYMPHOMAS

UPDATE

#92344 • 15 ANCC / 5 Advanced Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to enhance healthcare professionals' understanding of treatment options for childhood leukemias and lymphomas, the effects of treatment on normal growth and development, and the psychosocial effect of cancer on a child and his or her family.
Audience: This course is designed primarily for pediatricians, family medicine physicians, nurses, and other healthcare practitioners in the pediatric or family medicine setting.
Additional Approvals: AACN Synergy CERP Category A, CCMC

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

Course Availability List *(Cont'd)*

VAGINAL AND UTERINE BLEEDING

#93604 • 5 ANCC / 1 Advanced Pharm Hour

Book By Mail – $38 • ONLINE – $30

UPDATE

Purpose: The purpose of this course is to outline the many different causes of vaginal and uterine bleeding, describe the FIGO classification system, and discuss diagnostic techniques and treatment options for various causes of bleeding, allowing for improvements in the care of women who present with abnormal vaginal or uterine bleeding.

Audience: This course is designed for gynecologists, primary care physicians, surgical professionals, and other primary care health providers, including physician assistants and nurses, involved in the care of women.

Additional Approvals: AACN Synergy CERP Category A

PHARMACOLOGIC AND MEDICAL ADVANCES IN OBESITY MANAGEMENT

#94280 • 15 ANCC / 12 Advanced Pharm Hours

Book By Mail – $98 • ONLINE – $90

NEW!

Purpose: The purpose of this course is to ensure that providers have current and accurate knowledge regarding the available pharmacologic and surgical options to improve outcomes among their patients, with the ultimate goal of improving patient care and outcomes.

Audience: This course is designed for all physicians, nurses, and allied professionals involved in the care of patients who are overweight or obese.

Additional Approvals: AACN Synergy CERP Category A

DIAGNOSIS AND MANAGEMENT OF SEPSIS

#94344 • 4 ANCC / 3 Advanced Pharm Hours

Book By Mail – $32 • ONLINE – $24

UPDATE

Purpose: The purpose of this course is to provide healthcare professionals with a current review and updated, evidence-based guidance for the diagnosis and management of sepsis and septic shock. The objective is to address knowledge gaps, enhance clinical skill, and enable effective strategies of collaborative care to improve patient outcomes.

Audience: This course is designed for all healthcare professionals who work with patients who present with sepsis, including nurses and physicians.

Additional Approvals: AACN Synergy CERP Category A, CCMC

CHRONIC COUGH IN ADULTS

#94820 • 10 ANCC / 5 Advanced Pharm Hours

Book By Mail – $68 • ONLINE – $60

NEW!

Purpose: Chronic cough is difficult to effectively assess and treat, leading to extended periods before diagnosis and significant negative impact on patients' quality of life. The purpose of this course is to provide clinicians with the knowledge and skills necessary to identify and treat patients with chronic cough, regardless of underlying etiology, in accordance with clinical guidelines.

Audience: This course is designed for physicians, physician assistants/associates, and nurses involved in the care of patients with chronic cough.

Additional Approvals: AACN Synergy CERP Category A

ANTIBIOTICS REVIEW

#95074 • 5 ANCC / 5 Advanced Pharm Hours

Book By Mail – $38 • ONLINE – $30

UPDATE

Purpose: The purpose of this course is to provide a review of the major classes of antibiotics and their characteristics as well as an overview of selected individual agents within each class that are most useful for today's clinical practitioner.

Audience: This course is designed for healthcare providers who prescribe and administer antibiotics to patients, including physicians, physician assistants, pharmacists, pharmacy technicians, nurses, nurse practitioners, and surgical technologists and assistants.

Additional Approvals: AACN Synergy CERP Category A

PSYCHOPHARMACOLOGY

#95231 • 10 ANCC / 10 Advanced Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriate prescribe, administer, and dispense psychopharmacotherapy, with the ultimate goal of improving patient care and public health.

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

Additional Approvals: AACN Synergy CERP Category A, CCMC

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

#95300 • 8 ANCC / 8 Advanced Pharm Hours

Book By Mail – $83 • ONLINE – $75

DEA Mandate

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.

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 Approvals: AACN Synergy CERP Category A, CCMC

Special Approval: This course meets the Federal MATE Act requirement for 8 hours of training for APRNs with a new or renewing DEA license. This course meets the requirements for opioid/controlled substance, pain management, and addiction education.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

#96214 • 5 ANCC / 2 Advanced Pharm Hours

Book By Mail – $38 • ONLINE – $30

UPDATE

Purpose: Attention deficit hyperactivity disorder (ADHD) has a significant effect on day-to-day functioning and quality of life; however, it often goes unrecognized. The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ADHD.

Audience: This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients with attention deficit hyperactivity disorder.

Additional Approvals: AACN Synergy CERP Category A, CCMC

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

Course Availability List *(Cont'd)*

ANXIETY DISORDERS
#96183 • 15 ANCC / 10 Advanced Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.

Audience: This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

Additional Approvals: AACN Synergy CERP Category A, CCMC

OBSESSIVE-COMPULSIVE DISORDER
#96474 • 4 ANCC / 2 Advanced Pharm Hours

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.

Audience: This course is designed for healthcare professionals working with adults or adolescent patients who exhibit symptoms of obsessive-compulsive disorder.

Additional Approvals: AACN Synergy CERP Category A

CHILD ABUSE IDENTIFICATION AND REPORTING: AN UPDATE FOR NEW YORK
#97534 • 2 ANCC Hours

NY Mandate

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to enable healthcare professionals in all practice settings to define child abuse and identify the children who are affected by violence. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of New York for child abuse victims.

Audience: This course is designed for all New York physicians, physician assistants, nurses, and other professionals required to complete child abuse education.

Additional Approvals: AACN Synergy CERP Category B

Special Approvals: This course is approved by the New York State Education Department to fulfill the requirement for 2 hours of training in the Identification and Reporting of Child Abuse and Maltreatment. Provider #80673.

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY
#96791 • 10 ANCC / 8 Advanced Pharm Hours

UPDATE

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide medical and mental health professionals with the knowledge and skills necessary to effectively treat mental disorders using emerging psychedelic and interventional techniques.

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

Additional Approvals: AACN Synergy CERP Category A, CCMC

CANNABINOID OVERVIEW
#98010 • 3 ANCC / 3 Advanced Pharm 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 various cannabinoids.

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

Additional Approvals: AACN Synergy CERP Category A

MEDICINAL MUSHROOM SUPPLEMENTS
#98210 • 3 ANCC / 1 Advanced Pharm Hour

NEW!

Book By Mail – $26 • ONLINE – $18

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

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

Additional Approvals: AACN Synergy CERP Category A

INFECTION CONTROL: THE NEW YORK REQUIREMENT
#98644 • 5 ANCC / 1 Pharm Hour

NY Mandate

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide a review of current infection control practices and accepted standards, with an emphasis on the application of infection control standards and practices in outpatient and ambulatory settings.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals in New York required to complete education to enhance their knowledge of infection control.

Additional Approvals: AACN Synergy CERP Category A

Special Approval: This course is approved by the New York State Department of Health to fulfill the requirement for 4 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #OT10781.

GERIATRIC POLYPHARMACY
#99023 • 5 ANCC / 5 Advanced Pharm Hours

UPDATE

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide clinicians with the knowledge necessary to ensure that geriatric patients are effectively treated while reducing unnecessary polypharmacy.

Audience: This course is designed for advanced practice nurses, nurses, pharmacists, pharmacy technicians, and allied healthcare professionals who work with the geriatric population.

Additional Approvals: AACN Synergy CERP Category A, CCMC

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

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6. Was the course content free of bias?
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8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#98160
Alternative Therapies for Depression and Anxiety
5 Contact Hours

1. ☐ New ☐ Review
2. ____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☒ N/A
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#90824
Clinical Management of Atrial Fibrillation
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. ☒ N/A
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#91413
Prescription Opioids: Risk Mgmt and Strategies for Safe Use
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. ☒ N/A
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#98160 Alternative Therapies for Depression and Anxiety — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____
_____

#90824 Clinical Management of Atrial Fibrillation — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____
_____

#91413 Prescription Opioids: Risk Management and Strategies for Safe Use — 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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