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CONNECTICUT PHYSICIANS & PHYSICIAN ASSISTANTS

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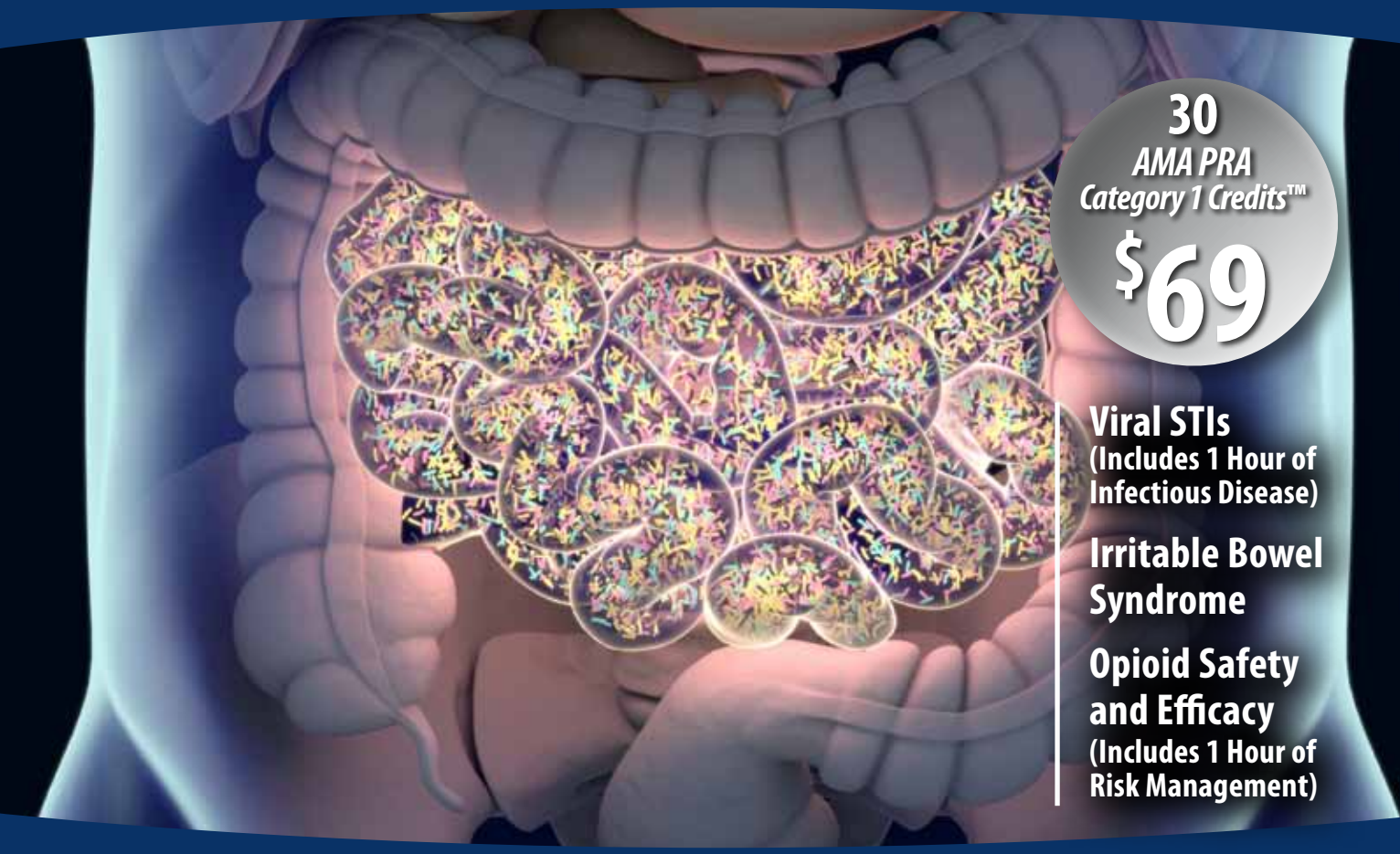

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Viral Sexually Transmitted Infections

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Special Approvals

Connecticut MDs and DOs: This course meets the Connecticut requirement for 1 hour of infectious disease education.

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In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 5 ABIM MOC Points, 5 ABP MOC Points.

Audience

This course is designed for physicians, physician assistants, nurses, and allied health professionals involved in the care of patients at risk for or with viral sexually transmitted infections.

Course Objective

The purpose of this course is to enhance clinician knowledge regarding the most common viral sexually transmitted infections in order to ensure that diagnosis and treatment is initiated early, when transmission risk can be minimized.

Learning Objectives

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

1. Incorporate key elements of a sexual history, including history of sexually transmitted infections (STIs), into clinical assessments.
2. Identify barrier and nonbarrier approaches to preventing viral STIs.
3. Discuss best practice screening guidelines for viral STIs.
4. Describe the approach to diagnosis, prevention, and management of genital herpes infection.
5. Review clinical recommendations for the diagnosis and management of human papillomavirus (HPV) infection.
6. Analyze the appropriate approach to hepatitis A and hepatitis B diagnosis, prevention, and treatment.
7. Discuss clinical issues related to the transmission, detection, and management of HIV infection.
8. Outline issues related to the diagnosis and treatment of STIs in refugees and immigrants.

Faculty

Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden

Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

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

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

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

INTRODUCTION

Sexually transmitted infections, or STIs, are clinical syndromes and infections caused by pathogens acquired and transmitted through sexual activity. All communities in the United States are impacted by STIs, and all individuals directly or indirectly pay for the costs of these diseases. STIs are public health problems that lack easy solutions, because they are rooted in human behavior and fundamental societal problems. However, clinicians can provide sexual health information, assess patient risks, discuss testing, and provide post-test counseling and medical care. This can empower patients to make health-promoting choices and receive treatment that protects their health and prevents transmission of untreated STIs [1; 2].

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This course will address the prominent viral STIs in the United States—referred to as the four Hs: herpes, human papillomavirus (HPV), hepatitis, and human immunodeficiency virus (HIV). The purpose of this course is to enhance clinician knowledge regarding these infections in order to detect and initiate treatment early, when transmission risk can be minimized.

GENERAL STI ASSESSMENT AND PREVENTION COUNSELING

SEXUAL HISTORY TAKING IN PATIENT INTERVIEWS

The "Five Ps" approach elicits sexual history information related to five key areas of interest: partners, practices, prevention of pregnancy, protection against STIs, and past history [1].

Partners

- "Do you have sex with men, women, or both?"
- "In the past two months, how many partners have you had sex with?"
- "In the past 12 months, how many partners have you had sex with?"
- "Is it possible that any of your sex partners in the past 12 months had sex with someone else while they were still in a sexual relationship with you?"

Practices

- "To understand your risks for STIs, I need to understand the kind of sex you have had recently."
- "Have you had oral sex, meaning 'mouth on penis/vagina' sex?"
- "Have you had vaginal sex, meaning 'penis in vagina' sex?"
- "Have you had anal sex, meaning 'penis in rectum/anus' sex?"
- If yes to any of the questions above, "Do you use condoms: never, sometimes, or always?"
  - If "never": "Why don't you use condoms?"
  - If "sometimes": "In what situations (or with whom) do you use condoms?"

Prevention of Pregnancy

- "What are you doing to prevent pregnancy?"

Protection against STIs

- "What do you do to protect yourself from STIs and HIV?"

Past History of STIs

- "Have you ever had an STI?"
- "Have any of your partners had an STI?"
- Additional questions to identify HIV and viral hepatitis risk include:
  - "Have you or any of your partners ever injected drugs?"
  - "Have you or any of your partners exchanged money or drugs for sex?"
  - "Is there anything else about your sexual practices that I need to know about?"

STI BEHAVIORAL COUNSELING

Intensive behavioral counseling interventions to prevent STIs are recommended for all sexually active adolescents and adults at increased risk for STIs.

Risk Assessment

All sexually active adolescents are considered at increased risk for STIs and should be counseled. Other at-risk groups include adults with current or past-year STIs, with multiple sex partners, or who use condoms inconsistently. African Americans have the highest STI prevalence of any racial/ethnic group, and STI prevalence is higher in American Indians, Alaska Natives, and Latino/as than in white populations. Increased STI prevalence rates are also found in men who have sex with men (MSM), persons with low incomes living in urban settings, current or former inmates, military recruits, persons who exchange sex for money or drugs, persons with mental illness or a disability, current or former injecting drug users (IDUs), persons with sexual abuse history, and patients of public STI clinics [3].

Behavioral Counseling Interventions

Behavioral counseling interventions can reduce the risk of acquiring an STI. Interventions ranging in intensity from 30 minutes to more than 2 hours of contact time are beneficial; evidence of benefit increases with intervention intensity [3]. Interventions can be delivered by primary care clinicians or through referral to trained behavioral counselors. Successful interventions provide basic information on STIs and STI transmission; assess patient risk for transmission; and provide pertinent skills training, such as condom use, communication about safe sex, problem solving, and goal setting. Many successful interventions aim to increase motivation or commitment to safe sex practices [3]. Specific counseling messages for patients diagnosed with genital herpes, HPV, or hepatitis are described in later sections of this course.

BARRIER AND NONBARRIER APPROACHES TO PREVENT OR REDUCE VIRAL STI TRANSMISSION AND INFECTION

VACCINATION

Pre-exposure vaccination is one of the most effective methods for preventing transmission of hepatitis A virus (HAV), hepatitis B virus (HBV), and HPV. These are the only STIs for which vaccination is available for prevention. The specific recommendations for vaccination will be discussed later in this course.

EXTERNAL CONDOMS

When used consistently and correctly, external latex condoms (also referred to as male latex condoms) are highly effective in preventing the sexual transmission of HIV infection and reducing risks for HPV infection and HPV-associated diseases, genital herpes, and hepatitis B when the infected area or site of potential exposure is covered [4; 5; 6].

As U.S. Food and Drug Administration (FDA)-regulated medical devices, condoms are subject to quality-control testing. Each latex condom manufactured in the United States is tested electronically for holes before packaging. The rate of condom breakage during sexual intercourse and withdrawal is approximately 2 per 100 condoms used, with slightly higher rates during anal intercourse [7; 8]. Condom failure to protect against STI or unintended pregnancy is usually caused by inconsistent or incorrect use, instead of condom breakage [9]. Latex condoms should not be used beyond their expiration date or more than five years after the manufacturing date, and users should check the expiration or manufacture date on the packaging before use [1].

External condoms made of materials other than latex fall in two general categories: synthetic and natural membrane condoms. Polyurethane and other synthetic condoms provide protection against STIs/HIV and pregnancy comparable to latex condoms and are used mainly as latex condom substitutes by persons with latex allergy. These condoms are more resistant to deterioration and are compatible with oil-based or water-based lubricants. The preventive efficacy of other synthetic external condoms is not well studied, and the FDA restricts their use to persons with latex sensitivity or allergy [6; 10].

Natural membrane condoms (termed "natural skin" or "lambskin") are made from lamb cecum. The pores, no greater than 1,500 nm in diameter, block passage of sperm but are more than 10 times the diameter of HIV and more than 25 times that of HBV. Therefore, sexual transmission of hepatitis B, herpes simplex, and HIV organisms can occur with natural membrane condoms. These condoms are recommended for preventing pregnancy but not STIs/HIV [10; 11; 12].

Providers should communicate guidance to patients to ensure correct external condom use [1]. Consistent, correct use is essential to prevent STIs/HIV infection, and a new condom should be used with each oral, vaginal, and anal sex act. It is important to carefully handle condoms to avoid damage from fingernails, teeth, or other sharp objects. Condoms should be put on after the penis is erect and before genital, oral, or anal contact. To prevent the condom from slipping off, the condom should be held firmly against the base of the penis during withdrawal, which should occur while the penis is still erect.

Adequate lubrication during vaginal and anal sex will help prevent condom breakage. With latex condoms, patients should be advised to use only water-based lubricants such as K-Y Jelly, Astroglide, Aqua Lube, or glycerin. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, cooking oil) weaken latex and should not be used, but are compatible with synthetic condoms.

INTERNAL CONDOMS

Several condoms are available for internal use (also referred to as female condoms), including the FC2 Female Condom, Reddy condom, Cupid female condom, and Woman's condom. Internal condoms can protect from acquisition and transmission of STIs, but data are limited compared with external condoms. Internal condoms are more expensive but offer the advantage of being a female-controlled STI/HIV prevention method, and newer versions may have greater acceptability to both men and women. While internal condoms have been used during receptive anal intercourse, the efficacy is unknown [13; 14].

MALE CIRCUMCISION

Male circumcision has been found to reduce the risk for HIV and some STIs in heterosexual men. By various means, penile foreskin is the primary biologic weak point and conduit for HIV infection during heterosexual intercourse [15]. Several controlled studies of heterosexual HIV transmission in sub-Saharan Africa found circumcision reduced the risk for HIV acquisition in men by 50% to 60% and protected against high-risk genital HPV infection and genital herpes [16; 17; 18]. These benefits of circumcision were sustained over time, and the effects were not solely related to reductions in herpes simplex virus type 2 (HSV-2) infection or genital ulcer disease [19; 20].

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Several organizations now recommend male circumcision to reduce or prevent penile cancers, urinary tract infections, genital ulcer disease, and heterosexually acquired HIV, including the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the American Academy of Pediatrics, the American Urological Association, and the American College of Obstetrics and Gynecology. Much less data are available to confirm male circumcision benefits in MSM [1].

INEFFECTIVE METHODS

Topical Microbicides and Spermicides

Nonspecific topical microbicides are ineffective in preventing HIV, and spermicides containing nonoxynol-9 (N-9) might disrupt genital or rectal epithelium to increase the risk for HIV infection [21; 22]. In one study, condoms plus N-9 were no more effective than condoms alone for the prevention of STIs, and N-9 alone or in addition to a condom is not recommended for STI prevention [23]. N-9 use may also increase the risk for bacterial urinary tract infection in women [24]. As of 2017, no topical antiretroviral agent has been proven effective in preventing HIV, but vaginal and rectal microbicides using tenofovir and other antiretroviral drugs are under investigation [1].

Cervical Diaphragms

Uncontrolled studies found that diaphragms protected against cervical gonorrhea, chlamydia, and trichomoniasis, but controlled studies found that compared with external condoms, diaphragms plus lubricant did not improve protection against HIV or herpes acquisition [25]. Diaphragms should not be solely relied on for protection against HIV/STIs [26; 27].

Non-Barrier Contraception

Contraceptive methods that are not mechanical barriers provide no protection against HIV or other STIs. Sexually active women who use hormonal contraception, nonhormonal intrauterine devices, or have been surgically sterilized or undergone a hysterectomy should be advised to use condoms to reduce risks for STIs [10].

Genital Hygiene

Vaginal washing and douching after sexual exposure are ineffective in protecting against HIV and STIs. These practices may increase the risk for bacterial vaginosis, some STIs, and HIV infection [1; 28].

SCREENING RECOMMENDATIONS

GENERAL SCREENING RECOMMENDATIONS

STI screening is an essential component of overall efforts to reduce STI acquisition and transmission and of individual risk assessment, but it is underutilized. STIs themselves are biologic markers of risk for additional STIs, particularly for HIV in some patients [29]. As such, all persons seeking evaluation or treatment for a suspected STI should be screened for HIV and other STIs. The Centers for Disease Control and Prevention (CDC) has established guidelines for screening for viral STIs in specific populations (***Table 1***). The decision to recommend specific STI screening is determined by community prevalence and by individual demographics and STI risk factors. Clinicians should provide patients with information regarding all STIs for which they are being tested and of tests available for common STIs (such as genital herpes and HPV) that are not being provided [29].

Risk factors also determine STI screening frequency. STI risk factors that help determine screening frequency for any given person include [1]:

- Presentation in high-risk settings: Adolescent or STI clinics, correctional facilities
- At-risk women: A new sex partner, more than one sex partner, a sex partner with concurrent partners or an STI
- High-risk women: Multiple sex partners, exchanges sex for money or drugs, illicit drug use, history of STI
- Pregnant women at high risk for HIV: Illicit drug use, STIs during pregnancy, multiple sex partners during pregnancy, residence in areas with high HIV prevalence, partner with HIV infection
- Men: Multiple sex partners
- High-risk MSM: HIV infection and persistent risk behaviors, sexual partner has multiple partners
- Persons with HIV: Multiple sex partners
- Hepatitis B: Those born in high prevalence (≥2%) regions, past or current IDU, MSM, immunosuppressive therapy, hemodialysis, HIV-positive status
- Hepatitis B, pregnant women: Same as for nonpregnant women, plus more than one sex partner in past six months, evaluated or treated for an STI, hepatitis B surface antigen (HBsAg)-positive sex partner

VIRAL STI SCREENING RECOMMENDATIONS					
Infection	**Population Screened**				
	Women	**Pregnant Women**	**Men**	**MSM**	**Persons with HIV**
Genital herpes	Test during STI evaluation	Not supported without symptoms	Test during STI evaluation	Test if status unknown or if previous undiagnosed genital tract infection	Test during STI evaluation, especially if high risk
HPV	Age 21 to 29 years: Every three years with cytology Age 30 to 65 years: Every three years with cytology or every five years with cytology plus HPV testing	Same as nonpregnant women	Not recommended	Not recommended	Within one year of sexual activity or first HIV diagnosis, using standard or liquid-based cytology. Repeat testing in six months.
Hepatitis B	With increased risk	At first prenatal visit for each pregnancy[a] Retest at delivery if high risk	With increased risk	Test all MSM	Test for HBsAg, anti-HBc, and anti-HBs
HIV	All aged 13 to 64 years (opt-out) and all seeking STI testing and treatment	All during first prenatal visit (opt-out) Retest in third trimester if high risk	All aged 13 to 64 years (opt-out) and all seeking STI testing and treatment	At least yearly if: sexually active, HIV status negative or unknown, patient or sex partner(s) had more than one partner since last HIV test	—

[a]Regardless of whether prior testing was performed.
Anti-HBc = antibodies to hepatitis B core antigen, anti-HBs = antibodies to hepatitis B surface antigen, HBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, HPV = human papillomavirus, MSM = men who have sex with men.

Source: [30] *Table 1*

HIV SCREENING

Many STIs are screened because they are often asymptomatic during initial infection and likely to be unknowingly transmitted; as such, their detection is essential to avoid serious complications from untreated infection. This is certainly true of HIV infection. All persons seeking STI evaluation or treatment should be screened for HIV infection, regardless of whether or not the patient reports behavioral risk factors. Persons with early syphilis, gonorrhea, or chlamydia are at high risk for HIV infection, and rectal gonorrhea and syphilis are risk markers for HIV [31; 32]. These patients should be screened even with a recently performed HIV test. In all healthcare settings, the CDC recommends HIV screening for patients 13 to 64 years of age; they should be notified that testing will be performed and retain the option to decline or defer testing (opt-out) [33; 34].

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HERPES SIMPLEX VIRUS

Genital herpes is the most common ulcerative STI. It is a chronic, lifelong viral infection caused by two strains or types: HSV-1 and HSV-2. Symptomatic HSV-1 usually appears as fever blisters or cold sores on the lips, but it can also infect the genital region through oral-genital or genital-genital contact. Symptomatic HSV-2 typically causes painful, watery skin blisters on or around the genitals or anus [35]. Most cases of recurrent genital herpes are caused by HSV-2, but because the prevalence of oral HSV-1 infection has declined in recent decades, people may have become more susceptible to contracting a genital herpes infection from HSV-1 [3]. It is important for patients to understand that oral herpes lesions can transmit herpes virus to a partner's genitals during oral sex.

In the United States, one in six persons 14 to 49 years of age is infected with HSV-2. The virus remains for life once infection has occurred, and prevalence rates generally increase with age due to cumulative sexual exposure [36]. Most people infected with genital herpes have not been diagnosed, and many with undiagnosed HSV-2 have minimal or no signs and symptoms, but shed virus intermittently in the anogenital area [37]. As a result, most genital herpes infections are transmitted by people who are unaware they are infected or are asymptomatic when transmitting. The risk of transmission is highest when outbreaks develop with new blisters in the anogenital area [3; 35].

HSV-1 and HSV-2 cannot be cured, and even when infection is dormant, the virus remains sequestered in peripheral nerve ganglia from which it can periodically emerge. Management of genital herpes should address the chronic nature of the disease instead of strictly focusing on treating the genital lesions during acute episodes. Pregnant women, especially those with new-onset genital herpes during pregnancy, may pass the infection to their newborns, causing life-threatening neonatal HSV, an infection that affects the infant's skin, brain, and other organs [3; 35].

Several of the recommended steps in the process of diagnosing and treating patients with STIs are common to all or multiple STIs. All patients should be given detailed information on the natural history, transmission, treatment, and complications relevant to genital herpes (and any other diagnosed STI). Patients should also be provided with clear, accurate written information and directed to appropriate web-based patient information.

SYMPTOMS AND SIGNS

As noted, many cases of primary genital herpes do not cause noticeable symptoms, and many people infected with HSV-2 are unaware they have genital herpes. Primary genital lesions develop four to seven days after contact. The vesicles usually erode to form ulcers that may coalesce. Lesions may occur in the following locations [3; 38; 39]:

- Men: The prepuce, glans penis, and penile shaft
- Women: The labia, clitoris, perineum, vagina, and cervix
- Men or women who engage in receptive rectal intercourse: Around the anus and in the rectum

Those symptomatic during primary (initial) HSV infection may experience painful, prolonged, and bilateral anogenital lesions, regional adenopathy, systemic (flu-like) signs and symptoms, and possibly urinary hesitancy, dysuria, urinary retention, constipation, or severe sacral neuralgia. Scarring may follow healing. The lesions recur in 80% of patients with HSV-2 and in 50% of those with HSV-1. Recurrent lesions are usually much less severe, but some will have severe prodromal symptoms that may involve the buttock, groin, or thigh [38; 39; 40].

DIAGNOSTIC CONSIDERATIONS

HSV testing is performed to diagnose active herpes infection in patients with genital sores or encephalitis, in individuals with suspected previous HSV infection, and in newborns suspected of having neonatal herpes. In symptomatic patients, testing can distinguish primary, active infection from a recurrent infection. Diagnosing genital herpes involves type-specific testing (HSV-1 versus HSV-2) and type-common testing (to identify specific immune protein response to herpes infection). Laboratory testing offsets the difficulties with clinical diagnosis that arise because many infected patients lack the characteristic lesions associated with HSV [41].

Direct Detection of the Virus

In patients seeking medical care for genital ulcers or other mucocutaneous lesions, cell culture and polymerase chain reaction (PCR) testing can detect herpes from a vesicle scraping [41]. Cell culture can distinguish HSV-1 from HSV-2, but it takes at least two days to complete. In addition, false negatives can occur with low viral load in the sample, and sensitivity is low, especially with recurrent or partially healed lesions [41]. PCR has sufficient sensitivity to detect HSV in low virus concentrations, and it is preferred for diagnosing systemic HSV infections, meningitis, central nervous system (CNS) involvement (encephalitis), and neonatal herpes [41; 42; 43].

Serologic Tests

HSV serologic testing is used for persons presenting for general STI evaluation (especially with multiple sex partners), those with HIV infection, and MSM at increased risk for HIV. Serologic HSV antibody testing detects the specific immune protein response to herpes infection. Several days after the primary (initial) HSV infection, immunoglobulin M (IgM) antibody is produced, remaining detectable in serum for several weeks. After HSV IgM, the body begins producing HSV IgG antibody. IgG serum levels rise for several weeks, then slowly decline, stabilize, and remain detectable forever in those with HSV exposure [41; 44]. With type-common antibody testing, positive HSV IgM antibody indicates active or recent infection, while positive HSV IgG antibody indicates previous infection. A significant recent increase in HSV IgG antibodies is a sign of active or recent infection. Negative HSV antibody testing implies HSV exposure is unlikely or the body has had insufficient time to produce HSV antibodies [41; 44].

The U.S. Preventive Services Task Force recommends against routine serologic screening for genital herpes simplex virus infection in asymptomatic adolescents and adults, including those who are pregnant.

(https://www.guideline.gov/summaries/summary/50595. Last accessed June 16, 2017.)

Strength of Recommendation/Level of Evidence: D (There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.)

HSV antibody tests can also diagnose herpes by detecting HSV-1 or HSV-2 (type-specific) viral type. The most accurate type-specific HSV serologic assays are glycoprotein G (gG)-based [41; 45; 46].

The presence of HSV-1 antibody alone is more difficult to interpret; many with HSV-1 acquired oral HSV infection during childhood, which might be asymptomatic. However, genital HSV-1 is increasing and can be asymptomatic, so typing alone is not a predictor of the likely infection site [37; 47]. General population screening for HSV-1/2 is not indicated, but all patients with HSV-2 should be tested for HIV infection [3].

MANAGEMENT OF GENITAL HERPES

All patients with suspected first-episode genital herpes should be treated presumptively, because treatment success depends on prompt initiation. The choice of presumptive treatment is based on clinical presentation, epidemiologic factors (e.g., population, community incidence), and travel history. Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management (***Table 2***) [1].

Systemic antiviral drugs can reduce symptoms of new onset and recurrent genital herpes episodes and may be used daily as suppressive therapy. However, it is important for patients to understand that antiviral drugs cannot eradicate latent virus or modify the risk, frequency, or severity of recurrences following discontinuation. The three antiviral medications in use for genital herpes are acyclovir, valacyclovir, and famciclovir. Valacyclovir is the valine ester of acyclovir and has enhanced oral absorption. Famciclovir also has high oral bioavailability. Topical antiviral drugs have minimal benefit and are discouraged [49; 50].

First Clinical Episode

Newly acquired genital herpes can cause prolonged clinical illness, with severe genital ulcerations and neurologic involvement. Even patients with mild first-episode herpes symptoms can develop severe or prolonged symptoms, and all patients with an episode of genital herpes should receive antiviral therapy [50; 51].

Established HSV-2 Infection

Almost all patients with symptomatic first-episode genital HSV-2 will subsequently experience recurrent episodes of genital lesions, and intermittent asymptomatic shedding occurs in genital HSV-2 patients, even with dormant infection [52]. Antiviral therapy for recurrent genital herpes can be administered continuously (daily) to suppress recurrence frequency or episodically to ameliorate or shorten active lesion duration [53]. Many patients prefer suppressive therapy, which also decreases the risk of genital HSV-2 transmission to susceptible partners [54].

Suppressive Therapy

In patients with frequent recurrence, suppressive therapy reduces recurrences by 70% to 80%, and many patients report an absence of symptomatic breakouts [49; 51]. Continuous treatment also benefits patients with less frequent recurrences. Safety and efficacy are documented with daily acyclovir therapy taken as long as six years, and valacyclovir or famciclovir for one year [55; 56]. Suppressive therapy also leads to greater improvements in quality of life than episodic treatment [57].

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TREATMENT OF GENITAL HERPES INFECTIONS	
Infection Stage or Patient Group	**Recommended Treatment Regimen**
First clinical episode	Any of the following[a]: Acyclovir 400 mg oral three times per day for 7 to 10 days Acyclovir 200 mg oral five times per day for 7 to 10 days Valacyclovir 1 g oral twice per day for 7 to 10 days Famciclovir 250 mg oral three times per day for 7 to 10 days
Recurrent: suppressive therapy	Any of the following: Acyclovir 400 mg oral twice per day Valacyclovir 500 mg oral once per day[b] Valacyclovir 1 g oral once per day Famciclovir 250 mg oral twice per day
Recurrent: episodic therapy	Any of the following: Acyclovir 400 mg oral three times per day for 5 days Acyclovir 800 mg oral twice per day for 5 days Acyclovir 800 mg oral three times per day for 2 days Valacyclovir 500 mg oral twice per day for 3 days Valacyclovir 1 g oral once per day for 5 days Famciclovir 125 mg oral twice per day for 5 days Famciclovir 1 g oral twice per day for 1 day
Severe disease[c]	Acyclovir 5–10 mg/kg IV every 8 hours for 2 to 7 days or until clinical improvement, followed by oral antiviral therapy to complete ≥10 days total therapy
During pregnancy[d]	Either of the following: Acyclovir 400 mg oral three times per day Valacyclovir 500 mg oral twice per day For severe disease: Acyclovir IV
Comorbid HIV Infection	
Daily suppressive therapy	Any of the following: Acyclovir 400–800 mg oral twice to three times per day Valacyclovir 500 mg oral twice per day Famciclovir 500 mg oral twice per day
Episodic infection	Any of the following: Acyclovir 400 mg oral three times per day for 5 to 10 days Valacyclovir 1 g oral twice per day for 5 to 10 days Famciclovir 500 mg oral twice per day for 5 to 10 days
Severe HSV disease	Initiate with acyclovir 5–10 mg/kg IV every 8 hours

[a] Treatment can be extended if healing is incomplete after 10 days of therapy.
[b] Valacyclovir 500 mg once per day might be less effective than other valacyclovir or acyclovir dosing regimens in persons who have very frequent recurrences (i.e., ≥10 episodes per year).
[c] HSV encephalitis requires 21 days of intravenous therapy. Impaired renal function warrants an adjustment in acyclovir dosage.
[d] Treatment recommended starting at 36 weeks' gestation.

Source: [1; 48] *Table 2*

Even in the absence of treatment, the frequency of genital herpes recurrences diminishes over time in many patients and may result in psychologic adjustment to the disease. During suppressive treatment, providers should discuss the need to continue therapy, but treatment discontinuation or laboratory monitoring in healthy patients is unnecessary [1].

Daily treatment with antiviral therapy can decrease HSV-2 transmission rates in infection-discordant heterosexual couples. Such couples should be encouraged to consider suppressive antiviral therapy to prevent transmission, to consistently use condoms, and to avoid sexual activity during recurrences. Suppressive antiviral therapy is also likely to reduce transmission by patients with multiple partners (including MSM) and in HSV-2 seropositive patients without a history of genital herpes [49; 51; 52].

Acyclovir, famciclovir, and valacyclovir have comparable efficacy as episodic genital herpes treatment, while famciclovir appears somewhat less effective in suppressing viral shedding [53; 58]. Important considerations with prolonged treatment include costs and the ease of administration. Allergic and adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. However, desensitization to acyclovir has been described [59].

Episodic Therapy

Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodromal period before an outbreak. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin [1].

Severe Disease

Intravenous (IV) acyclovir therapy should be provided for patients with severe HSV disease or complications that require hospitalization, including disseminated infection, pneumonitis, hepatitis, or CNS complications (meningoencephalitis) [1].

Management of Sex Partners

Sex partners of patients with genital herpes can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients with HSV-2. Asymptomatic sex partners should be assessed for a history of genital lesions and offered type-specific serologic HSV testing [1].

Comorbid HIV Infection

Anogenital or oral herpes episodes can be prolonged or severe in immunocompromised patients. HSV lesions are common in patients with HIV infection and may be severe, painful, and atypical. While antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes outbreaks, frequent subclinical viral shedding still occurs. Clinical manifestations of genital herpes may worsen during immune reconstitution following initiation of antiretroviral therapy [60; 61].

Suppressive or episodic oral antiviral therapy decreases the clinical manifestations of HSV in patients with HIV infection [62]. HSV type-specific serologic testing may be offered to persons with HIV infection during their initial evaluation if infection status is unknown, and suppressive antiviral therapy may be considered in those who have HSV-2 infection. Suppressive anti-HSV therapy does not decrease the risk of HIV or HSV-2 transmission by patients with HIV to susceptible sex partners [63; 64].

Management of Genital Herpes in Pregnancy

Pregnant women with genital herpes can transmit HSV-2 to the fetus or neonate during delivery via contact with lesions and/or vaginal secretions containing HSV. The virus is rarely transmitted transplacentally. Mothers of neonates with HSV infection tend to have newly acquired genital infection, often without symptoms at the time of delivery. Managing women with genital HSV acquired during late pregnancy requires specialist consultation [65].

During the third trimester, pregnant women without known genital or orolabial herpes should be advised to abstain from vaginal intercourse or receptive oral sex with partners with suspected genital or orolabial herpes, respectively. The efficacy of antiviral treatment to decrease or prevent HSV transmission to pregnant women by infected partners has not been studied. All pregnant women should be questioned about genital herpes history before and at the onset of labor. Patients with a known history of genital herpes should be assessed for prodromal symptoms and examined carefully for herpetic lesions during labor. Women without genital lesions or prodromal symptoms or signs can deliver vaginally. Cesarean delivery reduces but does not eliminate risk of HSV transmission to the neonate and may be considered for women with active outbreaks [1].

No adverse effects from oral or IV acyclovir to the fetus or newborn have been reported, and acyclovir is safe during breastfeeding and all pregnancy stages [66; 67]. Safety data for prenatal exposure to valacyclovir and famciclovir are limited, but these agents probably pose a low risk. Third trimester antiviral prophylaxis significantly reduces the recurrence of genital herpes at delivery, the need for cesarean delivery due to genital herpes, and detection of HSV-2 at delivery, but it may not prevent transmission to neonates in all cases [68; 69].

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PATIENT COUNSELING

Patient and sex partner counseling on the natural history and transmission of genital herpes, methods to prevent sexual and perinatal transmission, and coping strategies for patients with infection are the foundation of clinical management. When the acute illness subsides, many patients benefit from learning about the chronic aspects of the disease. Websites, printed materials, and several other resources are available to assist patients, their partners, and clinicians involved in counseling [70; 71].

Asymptomatic and symptomatic patients should receive the same education and counseling messages, including [1]:

- The natural history of the disease, with an emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and associated risks of sexual transmission
- The effectiveness of suppressive therapy during and after first-episode genital herpes in preventing symptomatic recurrent episodes and future transmission to partners
- Use of episodic therapy to shorten the duration of recurrent episodes
- Importance of informing current and future sex partners about genital herpes
- Sexual transmission of HSV during asymptomatic periods (most frequently in the first 12 months of infection)
- The need to abstain from sexual activity with uninfected partners when lesions or prodromal symptoms are present
- Ineffectiveness of episodic or suppressive therapy to reduce the risk of transmission to partners at risk for HSV-2
- Use of external latex condoms consistently and correctly to reduce, but not eliminate, the risk for genital herpes transmission
- The possibility for HSV infection in the absence of symptoms, including recommendation of type-specific serologic testing of asymptomatic partners to determine whether they are infected or at risk for acquiring HSV
- Risk for neonatal HSV infection
- Increased risk for HIV infection in HSV-2 seropositive persons exposed to HIV

The psychologic impact of HSV-2 diagnosis in patients with asymptomatic or unrecognized genital herpes is usually minimal [72; 73]. However, for some, the emotional effect can be substantial, and some infected patients develop anxiety disproportionate to actual clinical severity. Common concerns include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children. These patients may benefit from referral to a mental health professional. Clinicians should also dispel the misconception that HSV-1 and HSV-2 cause cancer.

HUMAN PAPILLOMAVIRUS

HPV is the most common STI in the United States. During 2013–2014, the prevalence of genital HPV in adults 18 to 59 years of age was 45.2% in men and 39.9% in women [74]. Around 100 HPV types have been identified, and at least 40 can infect the anogenital area in men and women. HPV types vary by propensity to cause genital warts and recurrent respiratory papillomatosis (HPV types 6 and 11), or cervical, penile, vulvar, vaginal, anal, and oropharyngeal cancers and precancers (HPV types 16 and 18) [35]. Most HPV infections are self-limited, asymptomatic, or unrecognized, and many sexually active persons will be infected with HPV at least once in their lifetime [75].

Persistent oncogenic HPV infection is the greatest risk factor for developing HPV-associated precancers and cancers. In the United States, HPV imposes a high public health burden of cancers and anogenital warts. In 2009, there were an estimated 34,788 cases of newly diagnosed HPV-associated cancers and 355,000 cases of anogenital warts associated with HPV infection [76; 77].

HPV testing is primarily used to screen for cervical cancer and/or identify women who may be at increased risk of cervical cancer. The test determines whether a woman's cervical cells are infected with high-risk oncogenic types of HPV. If long-lasting, the infection can cause changes in cervical cells that could lead to cervical cancer. With high-risk HPV infection now recognized as the cause of almost all cases of cervical cancer, HPV testing has become an essential part of women's health screening [78; 79].

Tests that detect oncogenic high-risk HPV infection are used in cervical cancer screening, management, or follow-up of abnormal cervical cytology or histology. These tests should not be used to diagnose genital warts, as a general STI test in male partners of women with HPV, or in women younger than 25 years of age [1; 78]. Subclinical genital HPV infection typically clears spontaneously [1].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology recommend that women 30 to 65 years of age should be screened with cytology and HPV testing ("cotesting") every five years (preferred) or cytology alone every three years (acceptable).

(https://www.guideline.gov/summaries/summary/36834. Last accessed June 16, 2017.)

Level of Evidence: Expert Opinion/Consensus Statement

Part of a standard gynecologic exam is the Papanicolaou (Pap) test, whereby samples of cells from the cervix are examined under a microscope for signs of cervical pre-cancer or cancer [35]. HPV-related precancer is managed based on existing guidance.

PREVENTION

Prevention of high-risk HPV is most effectively achieved through vaccination. The FDA has approved three vaccines that protect against HPV and the diseases and cancers caused by HPV. A bivalent vaccine (Cervarix) was previously available, but it is no longer used in the United States. The currently recommended vaccines are [80]:

- Quadrivalent Gardasil: Protects against HPV types 6, 11, 16, and 18
- Nine-valent Gardasil 9: Protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

HPV types 16 and 18 cause most cervical cancers, and types 6 and 11 cause most genital warts. As such, Gardasil protects against 66% of cervical cancers. Gardasil 9 protects against five additional HPV types that account for 15% of cervical cancers [80].

All boys and girls 11 to 12 years of age are now recommended to receive HPV vaccines, as they are most effective when given at younger ages, before the onset of sexual activity and initial exposure to the virus. The earliest approved age is 9 years. Both vaccines in clinical use are recommended for girls/women and boys/men. Young sexually active people should still receive the vaccination, because those already infected with one type of HPV may benefit from the protection against other types included in the vaccine. In those who have not received any or all vaccine doses, vaccination is recommended through 26 years of age for all girls/women and for boys/men with increased risk (e.g., HIV infection, MSM) or a desire for vaccination. The vaccine is recommended through 21 years of age for all other boys/men [81].

HPV vaccines are available for eligible children and adolescents younger than 19 years of age through the Vaccines for Children program, and patient-assistance programs are available from the vaccine manufacturers for uninsured persons 19 to 26 years of age. HPV vaccines are not recommended for use in pregnant women and are not licensed or recommended for use in anyone older than 26 years of age [80; 82].

HPV vaccines are given as two or three injections over six months, and the same vaccine product should be used for the entire series. HPV vaccines can be administered regardless of history of anogenital warts, abnormal Pap/HPV tests, or anogenital precancer. Women 21 years of age or older who have received HPV vaccination should continue routine cervical cancer screening, as vaccines do not protect against all cervical cancers.

Safety evaluations have found the HPV vaccines to be well tolerated. Impact-monitoring studies in the United States have demonstrated reductions of genital warts and HPV types contained in the vaccines [83; 84]. The projected impact of vaccinating girls at 12 years of age is a 20% to 66% reduction in lifetime cervical cancer risk, depending on the effectiveness of the vaccine and the duration of protection. Vaccination could also lead to a 21% reduction in low-grade abnormalities on Pap tests over the life of a cohort of vaccinated females. A comparison of HPV prevalence data from the vaccine era (2009–2012) and the prevaccine era (2003–2006) found that the prevalence of the HPV types included in the quadrivalent vaccine decreased by 64% (from 11.5% to 4.3%) among girls 14 to 19 years of age [85]. Considering the modest uptake of this vaccine, the potential impact is significant. HPV vaccination has not been associated with earlier initiation of sexual activity or sexual risk behaviors [86].

GENITAL WARTS

Etiology

Genital warts (condyloma acuminatum) are benign and mainly caused by HPV types 6 and 11. The types affecting the anogenital region are usually transmitted sexually by penetrative vaginal or anal intercourse, but digital, oral, and nonpenetrative genital contact may be involved. The development of genital warts is more common in patients who are immunocompromised. Growth rates vary, but pregnancy, immunosuppression, or maceration of the skin may accelerate the growth and spread of warts [87].

Clinical Features

Anogenital warts appear following an incubation period of one to six months and usually present as flat, papular, or pedunculated growths (often in clusters) on the genital mucosa. While usually asymptomatic, some patients experience itching, burning, pain, or discomfort [88].

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Anogenital warts commonly occur around the vaginal introitus, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Common sites in the anogenital epithelium or within the anogenital tract include the cervix, vagina, urethra, perineum, perianal skin, anus, and scrotum. Intra-anal warts are mostly observed in MSM and others who practice receptive anal intercourse, but they may occur in men and women without histories of anal sexual contact [88].

Diagnosis

The clinical diagnosis of anogenital warts is made by visual inspection and confirmed with biopsy. Biopsy is indicated to rule out anogenital neoplasia if lesions are atypical (e.g., pigmented, indurated, affixed to underlying tissue, bleeding, ulcerated). Especially for patients with immunocompromise, biopsy is indicated when the diagnosis is uncertain; when lesions do not respond to standard therapy; or if the disease worsens during therapy. HPV testing is not recommended for anogenital wart diagnosis, because test results are not confirmatory and do not guide management [88].

Endocervical and anal warts can only be visualized by colposcopy and anoscopy. Visualization and detection of small warts is enhanced before colposcopy by applying a 3% to 5% acetic acid solution for several minutes, which causes the warts to whiten. This procedure should not be used to detect HPV infection [88].

Treatment of Anogenital Warts

Treatment can alleviate symptoms and emotional distress in some patients, particularly those with cosmetic concerns, and it resolves wart(s) in most patients, although it may take several attempts. If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. In immunocompetent people, genital warts may resolve without treatment within one year. For these patients, an acceptable option is deferred treatment to allow for spontaneous clearance. Available therapies for anogenital warts might reduce, but not eradicate, HPV infectivity. Whether future transmission of HPV is decreased by treatment is unknown [1].

No treatment of genital warts is clearly more efficacious than others. Therapy selection is based on wart size, number, and anatomic site; patient preference; costs; convenience; adverse effects; and provider experience (***Table 3***). Some clinicians combine therapies, such as provider-administered cryotherapy along with patient-applied topical therapy [88].

Treatment involves topical therapy (mostly patient-applied) or provider-administered mechanical removal. Some patients prefer to apply treatment themselves for privacy reasons. To ensure patient-applied treatment is effective, all anogenital warts should be accessible and identified during the clinic visit, and patients should be instructed on proper application technique. Follow-up after several weeks allows providers to answer questions about medication use, address side effects, and assess treatment response [1].

Recommended Regimens for External Anogenital Warts

Recommended topical therapies for external anogenital warts include patient-applied imiquimod, an immune enhancer that stimulates production of interferon and other cytokines; podophyllotoxin, an antimitotic drug that causes wart necrosis; sinecatechins, a green tea extract with catechins the active constituent; and clinician-applied trichloroacetic acid (TCA) or bichloroacetic acid (BCA), caustic agents that destroy warts by chemical coagulation of proteins [88].

Soft, non-keratinized warts respond well to podophyllotoxin and TCA. Keratinized lesions are better suited for physical ablative methods such as cryotherapy, excision or electrocautery, or TCA. Imiquimod is suitable for both keratinized and non-keratinized warts. Patients with a low number of smaller warts can be treated with ablative therapy or topical podophyllotoxin from the outset. With patient-applied therapy, clinicians should provide a demonstration on lesion finding and treatment application. Very large wart lesions generally respond better to surgical treatment [88].

Patient-applied treatments differ in recommended application and possible side effects. Imiquimod is applied three times per week (5% cream) or daily (3.75% cream) at bedtime for up to 16 weeks. Local reactions can include redness, irritation, induration, ulceration/erosions, or vesicles, and imiquimod may worsen psoriasis, vitiligo, and other inflammatory or autoimmune skin diseases [89; 90; 91; 92].

Podophyllotoxin is applied twice daily for three days, followed by four days without therapy; this is repeated for up to four cycles. Mild-to-moderate pain or local irritation may develop [88].

Sinecatechins is applied three times daily for up to 16 weeks [93]. Patients should be advised to avoid sexual contact with treated areas during therapy. Common side effects are erythema, pruritus/burning, pain, ulceration, edema, induration, or vesicular rash. Safety and efficacy is not known in patients with genital herpes or HIV and other immune-impaired conditions [94].

RECOMMENDED TREATMENT OF GENITAL WARTS	
Wart Location	**Recommended Treatment**
External anogenital warts (penis, groin, scrotum, vulva, perineum, external anus, perianus)[a]	Patient-applied therapy: Imiquimod 3.75% or 5% cream[b] Podofilox 0.5% solution or gel Sinecatechins 15% ointment[b]
	Provider-administered therapy: Cryotherapy with liquid nitrogen or CryoProbe Surgical removal by tangential scissor or shave excision curettage, laser, or electrosurgery TCA or BCA 80% to 90% solution
Urethral meatus warts	Cryotherapy with liquid nitrogen Surgical removal
Vaginal warts	Cryotherapy with liquid nitrogen[c] Surgical removal TCA or BCA 80% to 90% solution
Cervical warts[d]	Cryotherapy with liquid nitrogen Surgical removal TCA or BCA 80% to 90% solution
Intra-anal warts[e]	Cryotherapy with liquid nitrogen Surgical removal TCA or BCA 80% to 90% solution

[a] Many patients with external anal warts have intra-anal warts; consider anal canal inspection by digital examination, standard anoscopy, or high-resolution anoscopy.
[b] May weaken condoms and vaginal diaphragms.
[c] Do not use a CryoProbe in the vagina because of risk for vaginal perforation and fistula formation.
[d] Consult with a specialist. In women with exophytic cervical warts, a biopsy should be performed before treatment to exclude high-grade squamous intraepithelial lesion.
[e] Consult with a specialist.
BCA = bichloroacetic acid, TCA = trichloroacetic acid.

Source: [1] *Table 3*

TCA and BCA are widely used but have not been studied extensively. A small amount is applied to the warts and allowed to dry before the patient sits or stands. Treatment can be repeated weekly, if needed [1].

Mechanical removal options include cryotherapy, electrocauterization, and laser or surgical excision. Cryotherapy employs thermal-induced cytolysis for wart destruction and requires proper training to avoid over- or undertreatment and resultant complications or inefficacy. Pain is common following liquid nitrogen treatment from necrosis or blistering, and local anesthesia can help facilitate therapy [1].

Surgical therapy can eliminate most warts in a single visit, but recurrence may occur. After local anesthesia is applied, anogenital warts are physically destroyed by electrocautery, and no additional hemostasis is required. Warts can also be removed by tangential excision with a pair of fine scissors or scalpel, by carbon dioxide (CO_2) laser, or by curettage. Because most warts are exophytic, the wound is not deeper than the upper dermis. Hemostasis can be achieved with an electrocautery unit or, in cases of very minor bleeding, a chemical styptic (e.g., an aluminum chloride solution). Most cases do not need suturing. As noted, with large or extensive warts, surgical therapy, including CO_2 laser, is most beneficial, especially for intraurethral warts and in patients lacking response to other treatments [88].

Alternative Regimens

Alternative approaches for anogenital warts have less supportive data and potentially greater side effects. Options include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Patient-applied podophyllin resin is no longer recommended because of potentially severe systemic toxicity; however, provider-administered podophyllin resin 10% to 25% may be considered with strict adherence to recommended use [1; 95; 96].

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Follow-Up

Switch to a new treatment modality is indicated if the patient fails to show substantial improvement or experiences severe side effects. Complications are rare when treatment is administered properly, but persistent hypo- or hyperpigmentation can occur with cryotherapy, electrocautery, and imiquimod cream. Depressed or hypertrophic scars are uncommon but can occur, especially with insufficient healing time between treatments. Rarely, treatment can result in chronic pain syndromes such as vulvodynia, hyperesthesia of the treatment site, or painful defecation or fistulas (with anal warts) [1].

Treatment During Pregnancy

Podophyllotoxin, podophyllin, and sinecatechins should not be used during pregnancy. Imiquimod appears to pose low risk but should be avoided until more data are available. Anogenital warts can proliferate and become friable during pregnancy, and although removal of warts can be considered, resolution might be incomplete or poor until pregnancy is complete.

Rarely, HPV types 6 and 11 can cause respiratory papillomatosis in infants and children, although the route of transmission is not completely understood. Whether cesarean delivery prevents respiratory papillomatosis in offspring is also unclear, and cesarean delivery should not be performed solely to prevent transmission of HPV. Cesarean delivery is indicated for women with anogenital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding. Pregnant women with anogenital warts should be counseled about the low but present risk for warts on the larynx of their infants or children (recurrent respiratory papillomatosis) [1; 97].

Treatment in the Presence of HIV Co-Infection and Other Causes of Immunosuppression

Patients with HPV who have HIV infection or are immunosuppressed are more likely to develop anogenital warts, to present with larger or more numerous lesions, to lack treatment response, and to have more frequent recurrences after treatment [98; 99]. Despite this, treatment should not be altered for patients with HIV. Squamous cell carcinomas inside of, or resembling, anogenital warts are more frequent in immunosuppressed patients, requiring biopsy for diagnostic confirmation in suspicious cases [100; 101]. Biopsy of an atypical wart might reveal high-grade squamous intraepithelial lesions or cancer of the anogenital tract. In this instance, specialist referral for treatment is recommended [1].

MANAGEMENT OF SEX PARTNERS

Patients should be advised to inform current sex partner(s) about having genital warts, because the HPV types that cause warts can be transmitted sexually. Partners should receive counseling regarding the possibility they may already have HPV despite no visible signs of warts. However, HPV testing of sex partners of persons with genital warts is not recommended. Instead, partner(s) may benefit from a physical examination to detect genital warts and tests for other STIs. The duration of viral persistence after warts have resolved is unknown, and no recommendations can be made for informing future sex partners about a genital warts diagnosis [1].

KEY COUNSELING MESSAGES FOR PATIENTS WITH HPV

All patients with HPV should be educated regarding transmission, treatment, and follow-up [1]. Educational messages may include:

- HPV infection is very common and usually infects the anogenital area, but it may infect the mouth or throat. Most sexually active people acquire HPV at some point, but many are unaware of it.
- Sex partners tend to share HPV, and determining which partner transmitted the original infection is not possible. Diagnosis of HPV does not mean the patient or partner is having sex outside the relationship.
- Most persons who acquire HPV clear the infection without treatment or health problems. HPV infection that does not resolve can lead to genital warts, precancers, and cancers of the cervix, anus, penis, vulva, vagina, head, and neck.
- The HPV types that cause genital warts and cancer often differ.
- Many types of HPV are transmitted through vaginal and anal sex. HPV can also be transmitted by genital-to-genital contact without penetration, oral sex, and, rarely, by pregnant woman to an infant during delivery.
- In women, having HPV does not usually interfere with getting pregnant or carrying a pregnancy to term. However, some HPV-related precancers or cancers, and their treatment, may reduce the ability to get pregnant or have delivery without complications.
- Treatment is available for conditions caused by HPV, but not for the virus itself.
- No HPV test can determine which HPV infections will resolve and which will progress, but in certain circumstances, HPV tests can determine an increased risk for cervical cancer. These tests are not used to detect other HPV-related problems, in women younger than 25 years of age, or in men of any age.

Key counseling messages for patients with anogenital warts include [1]:

- Untreated genital warts may resolve, remain the same, or increase in size or number.
- Women with genital warts do not need Pap tests more often than other women.
- The time of HPV acquisition cannot be determined, and warts can develop months or years after acquiring HPV.
- HPV types that cause genital warts can be transmitted to others, even when visible signs of warts are absent. Sex partners tend to share HPV, even when signs of HPV appear in only one or neither partners.
- Although genital warts are common and benign, receiving this diagnosis can be intensely upsetting to some.
- Genital warts can be treated but not cured. Because the virus persists, genital warts can recur after treatment, especially in the first three months.
- Patients with genital warts benefit from testing for other STIs, because genital warts can be sexually transmitted. Sexual activity with new partners should be avoided until the warts are gone or removed.
- Condoms used consistently and correctly might lower the chances of transmitting genital warts, but HPV can infect areas not covered by a condom.
- Vaccines are available to prevent genital warts and wart-causing types of HPV but will not treat existing HPV or genital warts.

VIRAL HEPATITIS

Hepatitis is an inflammatory state of the liver. Most cases of hepatitis are caused by viral infection; other causes include exposure to chemicals, over-the-counter or prescription drugs, heavy alcohol use, inherited diseases, autoimmune disease, and fatty buildup in the liver [102]. In all patients with symptoms that suggest acute viral hepatitis, clinicians should assess the patient and, if necessary, refer for hospital admission. Tests should be performed to assess hepatitis severity, including liver function tests, coagulation tests, and hepatitis serology (i.e., anti-HAV IgM, HBsAg, hepatitis C virus [HCV] antibodies/RNA, and hepatitis E serology/PCR) [103].

HEPATITIS A VIRUS

Hepatitis A is an RNA virus that is highly common in areas with poor sanitation (typically developing countries), where it mainly affects children; it is less common is the United States and other developed countries [103]. HAV replicates in the liver. Starting two to three weeks after exposure, anti-HAV IgM is detectable, but levels then decline. Anti-HAV IgG levels begin to rise three to four weeks after exposure and remain elevated throughout life [35].

HAV is primarily transmitted through the fecal-oral route, most commonly through contaminated food or water; fecal-oral contact during sexual activity is also a transmission risk. Efforts to promote good personal hygiene have not succeeded in curtailing HAV outbreaks. Bloodborne transmission is uncommon, and transmission by saliva is not documented [104; 105]. In the United States, risk factors were identified in only 7% of cases in 2014; most involved international travel, exposure to food/water outbreaks, MSM, IDU, or household contacts with children attending or adults working in nursery school, daycare, or preschool settings [106]. Signs of HAV infection include jaundice (with pale stools and dark urine) and liver enlargement/tenderness.

Clinical Presentation

More than 70% of adults are symptomatic during acute HAV infection, but most children are asymptomatic or have mild, nonspecific symptoms and little or no jaundice [1]. Most symptomatic patients follow a clinical course of a prodromal phase, icteric illness, and recovery. Rarely, patients may develop fulminant infection during acute HAV infection [103].

Prodromal Illness

After an average 28-day incubation (range: 15 to 45 days), patients can experience nonspecific flu-like symptoms (e.g., malaise, myalgia, fatigue), often with right upper abdominal pain. This phase lasts 3 to 10 days.

Icteric Illness

The icteric phase is characterized by jaundice (mixed hepatic and cholestatic) and is associated with anorexia, nausea, and fatigue that usually lasts one to three weeks. This phase can persist 12 or more weeks in a minority of patients who have cholestatic symptoms (e.g., itching, deep jaundice). Fever is rare. Up to 10% of patients experience symptomatic relapse in the six months following acute illness.

In patients with acute HAV infection, acute liver failure develops in 0.4%, but 15% may require hospital care. The overall mortality is <0.1%, which rises to 40% with acute liver failure; these patients should be considered for liver transplantation [103].

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Diagnostic Considerations

Diagnosis of HAV infection requires serologic testing [1; 103]. Diagnosis is confirmed by positive serum anti-HAV IgM, which usually remains positive for 45 to 60 days. As noted, HAV-IgG does not distinguish current from past infection and remains positive for life.

Treatment

Most patients with symptomatic acute HAV infection can be managed as outpatients, with emphasis on rest and oral hydration. Hospitalization is necessary for patients who become dehydrated from nausea and vomiting or who have signs of hepatic decompensation, including changes in personality or level of consciousness. Medications that may damage, or are metabolized by, the liver should be used with caution in persons with HAV infection [1; 103].

Vaccines

Vaccination is the most effective means of preventing HAV transmission among persons at risk for infection. HAV vaccines are prepared from formalin-inactivated, cell-culture-derived HAV. Two monovalent vaccines (Havrix and VAQTA) are FDA-approved for persons 12 months of age or older [1; 107].

HAV vaccines are given IM in a two-dose series at 0 and 6 to 18 months. Protective antibody levels are induced in 94% to 100% of adults by one month after the first dose, and in 100% after the second dose. Kinetic models of antibody decline indicate that protective antibody levels persist for more than 20 years [107].

HAV vaccine should be offered to the following persons seeking STI services [1]:

- All MSM
- Injection and non-injection illicit drug users
- Those with chronic liver disease, including chronic HBV and HCV infection and evidence of chronic liver disease

A combined HAV/HBV vaccine (Twinrix) is FDA-approved for use as a three-dose series in adults 18 years of age or older at risk for hepatitis A and hepatitis B infections. When administered IM on a 0-, 1-, and 6-month schedule, the vaccine has equivalent immunogenicity to that of the monovalent vaccines [108; 109; 110].

Pre-Vaccination Serologic Testing

Around one-third of the U.S. population has serologic evidence of previous HAV infection, and prevalence increases with age. The potential cost savings of pre-vaccination susceptibility testing should be weighed against the cost and probability that testing will interfere with initiating vaccination. Serologic testing should not be a barrier to vaccination of at-risk populations, and vaccinating a person already immune is not harmful. When a history of at least two-dose HAV vaccination is documented, no further vaccination or serologic testing is needed [111].

Post-Exposure Prophylaxis

When given within two weeks of HAV exposure, intramuscular (IM) immunoglobulin is more than 85% effective in preventing HAV infection [112]. Persons exposed to HAV who have not previously been vaccinated should receive a single dose of monovalent hepatitis A vaccine or immunoglobulin (0.02 mL/kg) as soon as possible; efficacy is not established more than two weeks post-exposure. There is limited information on vaccine versus immunoglobulin post-exposure efficacy, and no data are available on patients older than 40 years of age or with medical comorbidities. The decision to use the vaccine versus immunoglobulin should be informed by patient risk for more severe HAV infection (e.g., older age, chronic liver disease) and HAV transmission risk from the exposure [107].

Immunoglobulin is indicated for use in children younger than 12 months of age, patients with immune compromise or chronic liver disease, and when vaccination is contraindicated. Immunoglobulin is also preferred for persons older than 40 years of age, due in part to the greater severity of hepatitis A in this age group. In these cases, the vaccine can be used if immunoglobulin cannot be obtained. For healthy persons 1 to 40 years of age, the vaccine is preferred to immunoglobulin because of the advantages in long-term protection and ease of use [1]. The combined HAV/HBV vaccine may be considered in eligible persons [1].

Counseling Following Confirmed Acute HAV Infection

It is crucial that all patients with diagnosed HAV infection receive information and counseling [103]. Clinicians should provide detailed explanations, verbally and in writing, of the condition, with emphasis on long-term health implications for the patient and partner(s). Pregnant women should be advised of the increased risk for miscarriage/premature labor and to seek medical advice if symptoms develop. All patients should avoid handling food and unprotected sexual intercourse until they are considered noninfectious. Partner notification is necessary for at-risk sexual contacts (oro-anal, digital/rectal, or penetrative anal sex) within two weeks before and up to one week after the onset of jaundice.

HEPATITIS B VIRUS

Hepatitis B is a DNA virus with eight distinct genotypes (A-H) that vary by geographic distribution, pathogenicity, and treatment susceptibility. Left undetected and untreated, HBV can cause serious liver disease resulting in lifelong infection, permanent liver scarring (cirrhosis), cancer, liver failure, and death [103].

Transmission

After an incubation period of 40 to 160 days, HBV concentrations are highest in the blood and present (but in lower concentrations) in wound exudates, semen, vaginal secretions, and saliva. HBV is efficiently transmitted by percutaneous or mucous membrane exposure to infected blood or body fluids. HBV is more infectious and more stable in the environment than other bloodborne pathogens, including HCV and HIV [1].

Routes of HBV transmission include [35; 103; 113]:

- MSM (unvaccinated/non-immune): Higher risk with multiple partners, sex workers, unprotected anal or oro-anal sex
- Heterosexual contact: Partners of patients with acute HBV, sex workers
- Vertical (infected mother to infant)
- Parenteral: Unscreened blood/blood products, shared drug injection equipment, non-sterile acupuncture and tattoo needles, workplace needlestick injuries
- Sporadic: Adults with Down syndrome and other developmental disabilities placed in institutions (route of transmission poorly understood)
- Premastication (e.g., shared chewing gum)

Clinical Course and Patient Presentation

Signs and symptoms of patients in the prodromal and icteric phases of acute HBV infection are similar to hepatitis A, but can be more severe and prolonged in symptomatic patients. Acute HBV infection is asymptomatic in almost all infants and children and in 10% to 50% of adults [103].

Chronic HBV infection usually occurs without physical signs, but some patients may develop fatigue or loss of appetite. After years of infection, signs of chronic liver disease may develop, including spider nevi, finger clubbing, jaundice, and hepatosplenomegaly. Severe cases can develop thinning skin, bruising, ascites, asterixis ("liver flap"), and encephalopathy [114].

Acute liver failure occurs in less than 1% of symptomatic acute cases; prognosis is worse than in hepatitis A. Pregnant women have increased rates of miscarriage/premature labor and risk of vertical transmission. Mortality is less than 1% in acute infection [114].

Chronic infection (longer than six months) occurs in 5% to 10% of symptomatic patients. Risk is inversely related to age when infected; chronic HBV infection develops in roughly 90% of those infected as infants, 30% infected before the age of 5 years, and 2% to 6% of those infected as adults. Risk of premature death from cirrhosis or hepatocellular carcinoma is 15% to 25% with chronic HBV infection [114; 115].

Diagnosis

Diagnosis of acute or chronic HBV infection requires serologic testing [1]. HBsAg is present in acute and chronic infection; the presence of IgM antibody to hepatitis B core antigen (IgM anti-HBc) is diagnostic of acute or recently acquired HBV infection. Antibody to HBsAg (anti-HBs), produced after an infection resolves, is the only HBV antibody marker present after vaccination. Presence of HBsAg and total anti-HBc, with a negative test for IgM anti-HBc, indicates chronic HBV infection. Presence of anti-HBc alone can reflect acute, resolved, or chronic infection or a false-positive result.

All persons with confirmed HBsAg should be reported to the state or local health department. In addition, patients with HBsAg should be retested to assess chronic HBV infection, confirmed by the absence of IgM anti-HBc or the persistence of HBsAg for six months.

Treatment

In patients with severe acute HBV infection, antiviral agents can prevent acute liver failure and improve morbidity and mortality [103]. Otherwise, treatment is supportive for patients with acute HBV. Patients with chronic HBV should receive specialist management. Drugs FDA approved for treating chronic hepatitis B can achieve durable suppression of HBV replication and remission of liver disease [1; 116].

Prevention

The national strategy for eliminating transmission of HBV infection includes [117; 118]:

- Preventing perinatal infection by routinely screening all pregnant women for HBsAg and infants born to mothers with HBsAg
- Routine infant vaccination
- Vaccinating unvaccinated children and adolescents through 18 years of age
- Vaccinating unvaccinated adults at increased risk for infection

High vaccination rates and subsequent declines in the incidence of acute HBV infection have been achieved in infants and adolescents [118; 119]. In addition, the aging of vaccinated children and adolescents has likely led to improved vaccination coverage and lower acute HBV infection rates in adults younger than 30 years of age [120]. However, coverage of adults 30 years of age and older in high-risk groups (e.g., multiple sex partners, MSM, IDUs) remains low, and these groups account for the highest rates of preventable acute infections [117; 121]. Settings that provide STI services should vaccinate those who are unvaccinated, as adults seeking STI services are considered at increased risk for HBV infection.

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Two product types are approved for HBV prevention: hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) [117; 118]. HBIG protects for three to six months against HBV infection and is used in post-exposure prophylaxis as an adjunct to hepatitis B vaccination (in unvaccinated persons) or in persons without vaccine response.

Hepatitis B vaccine contains HBsAg produced in yeast by recombinant DNA and protects from HBV infection as pre-exposure vaccination and post-exposure prophylaxis. Available monovalent hepatitis B vaccines are:

- Recombivax HB
- Engerix-B

As discussed, Twinrix is a combination HAV/HBV vaccine for patients 18 years of age or older.

Hepatitis B vaccines differ by vaccination schedule; some require three injections over 4 or 6 months, while others require four injections over 12 months. Selection should consider the need to achieve completion of the vaccine series and likelihood of extended follow-up [1].

In adolescents and healthy adults younger than 40 years of age, 30% to 55% achieve a protective antibody response (i.e., anti-HBs ≥10 mIU/mL) after the first vaccine dose, 75% after the second, and more than 90% after the third. Vaccine-induced immune memory is demonstrated to persist for at least 20 years. Periodic testing to determine antibody levels is not necessary, and booster doses of the vaccine are not currently recommended [119; 122; 123].

Hepatitis B vaccination is generally well tolerated by most patients; injection-site pain and low-grade fever are reported in a minority. In children and adolescents, anaphylaxis has been reported in 1 patient for every 1.1 million vaccines, but no deaths have been reported in these patients. Vaccination is contraindicated in patients with previous anaphylactic reaction to hepatitis B vaccination or any vaccine component. No other adverse events with hepatitis B vaccine have been demonstrated [117; 118].

HBV vaccination is recommended for the following unvaccinated persons [118]:

- Children and adolescents
- All adults who are IDUs, MSM, or with multiple sex partners
- All adults wanting protection from HBV

As noted, hepatitis B vaccine should be routinely offered to all unvaccinated persons attending STI clinics and those seeking STI evaluation or treatment in correctional facilities, drug-abuse treatment and prevention programs, federally qualified health centers, and settings that serve MSM.

Pre-Vaccination Serologic Testing

Pre-vaccination serologic testing for susceptibility may reduce the costs of completing the vaccine series in populations with a high prevalence of HBV infection (e.g., older IDUs, MSM). Susceptibility testing is recommended for the unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons. Vaccination of those immune to HBV due to current/past infection or vaccination is not harmful and does not increase the risk for adverse events [121].

Anti-HBc is the test of choice for pre-vaccination testing, and those who test anti-HBc-positive should be tested for HBsAg. If HBsAg negative, no further action is required. Persons who are HBsAg-positive should be referred to a specialist in hepatitis B infection management [1].

Post-Vaccination Serologic Testing for Response

Post-vaccination serologic testing for immunity is not necessary after routine vaccination of most healthy adolescents or adults. Such testing is recommended for persons whose clinical management depends on confirming their immune status, including healthcare and public safety workers at high risk for exposure to blood or body fluids. Post-vaccination testing is also recommended for persons with HIV and other immunocompromising conditions and sex and needle-sharing partners of HBsAg-positive persons. If indicated, anti-HBs testing should be performed one to two months after the last dose of the vaccine series [1].

Post-Exposure Prophylaxis

Passive-active post-exposure prophylaxis (i.e., HBIG plus HBV vaccine at separate IM sites) and active post-exposure prophylaxis (i.e., hepatitis B vaccination alone) are both highly effective in preventing transmission after exposure to HBV. HBIG alone is effective in preventing HBV transmission, but it is typically combined with hepatitis B vaccine.

Unvaccinated persons should receive HBIG plus hepatitis vaccine as soon as possible (within 24 hours) after exposure to blood or body fluids from a person with known HBsAg, and the full HBV vaccine series should be completed. Persons exposed during the vaccine process should receive HBIG and complete the series [124].

Unvaccinated persons exposed to blood or body fluids from a person with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated preferably less than 24 hours after exposure [124].

Key Counseling Messages

Sex partners of patients with HBV infection should be advised to use latex condoms for protection from sexual exposure unless they demonstrate immunity post-vaccination (anti-HBs ≥10 mIU/mL) or from previous infection (anti-HBc positive). To minimize transmission risk to others through infected blood or bodily fluids, patients with HBV should:

- Use condoms until sex partner is vaccinated and immunity documented
- Cover cuts and skin lesions
- Not donate blood, plasma, body organs, tissue, or semen
- Not share toothbrushes, razors, or injection equipment

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the New York State Department of Health, all sexually active HIV/HBV co-infected patients should be encouraged to use effective barrier protection consistently and correctly, including latex or polyurethane condoms and dental dams, to reduce the risk of transmission of HIV and HBV.

(https://www.guideline.gov/summaries/summary/47782. Last accessed June 16, 2017.)

Strength of Recommendation/Level of Evidence: AI (Strong recommendation based on one or more randomized trials with clinical outcomes and/or validated laboratory endpoints)

In addition, to protect the liver from further harm, patients with HBV are advised to:

- Avoid or limit alcohol consumption.
- Do not start new medications, including over-the-counter/herbal medications, without checking with a healthcare provider.
- Obtain hepatitis A vaccination.

When seeking medical or dental care, patients should disclose their HBsAg status so they can be appropriately evaluated and managed.

HBV is not usually spread by hugging, coughing, contaminated food or water, shared eating utensils or drinking glasses, or casual contact. It is important that patients with HBV not be excluded from work, school, play, childcare, or other settings because of their infection. Support group involvement can help patients cope with chronic HBV infection.

Pregnancy

Regardless of previous testing or vaccination, all pregnant women should be tested for HBsAg at the first prenatal visit. Those at high risk should also be tested at delivery and receive hepatitis B vaccination. All pregnant women with HBsAg should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist [1].

HIV Co-Infection

HIV infection and other immune suppressing conditions can impair hepatitis B vaccine response. Persons with HIV infection should be tested for anti-HBs one to two months after the third vaccine dose. Modified dosing regimens, including doubling the standard antigen dose and adding additional doses, might increase the response rate [1].

HEPATITIS C VIRUS

HCV is primarily transmitted parenterally, such as through sharing drug-injection equipment. Aside from patients with genital ulcerative disease, STI-related proctitis, or sex partner(s) with HIV infection, sexual transmission of HCV is very infrequent [1].

HIV/AIDS

As of 2011, an estimated 1.2 million individuals 13 years of age or older were living with HIV or_acquired immune deficiency syndrome (AIDS) in the United States [125]. The CDC estimates that approximately 14% of these individuals are unaware of their infection [125].

SIGNS AND SYMPTOMS

The clinical manifestations of HIV disease are determined by the stage of primary infection and the chronicity and degree of the resultant cellular immunodeficiency state. Acute, primary HIV infection may be asymptomatic, but most often it is manifest by a subacute viral syndrome of malaise and fatigue, fever, sore throat, rash, myalgia, headache, and lymphadenopathy—clinical features similar in many respects to that seen with Epstein-Barr virus mononucleosis, cytomegalovirus (CMV), and certain types of herpes simplex infections [126]. A variety of atypical symptoms and signs may be seen, including aseptic meningitis syndrome, genital ulcers, and ulcerations involving the gingiva, palate, or buccal mucosa. The acute illness usually resolves in less than 14 days but may follow a protracted course over many weeks [126].

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Early in the chronic phase of HIV infection, when the CD4 lymphocyte population is only modestly depressed and declining slowly, patients are often asymptomatic or may exhibit generalized lymphadenopathy and recurrent oropharyngeal candidiasis (thrush). During this stage, a reservoir of HIV is established throughout the lymphoid tissue system, including the spleen. Gradually, wandering (infected) macrophages disseminate the virus to certain internal organs, notably the brain, kidney, and adrenal glands.

Chronic HIV disease follows a variable course but eventually leads to a variety of clinical manifestations, some of which are directly related to the impact of chronic infection on vital organs. Common syndromes include HIV encephalopathy and dementia, peripheral neuropathy, interstitial nephropathy, a variety of skin eruptions, and signs of adrenal insufficiency.

The late clinical manifestations of HIV disease are most frequently the result of AIDS that follows progressive depletion of CD4+ T lymphocytes to levels <200 cells/mcL. AIDS-defining illnesses include secondary, opportunistic infections and certain malignancies usually encountered only in clinical settings of severely impaired cellular immunity.

Opportunistic infections are very common in persons with undiagnosed or poorly treated chronic HIV infection and are of two types. The first type is infection newly acquired by exposure to micro-organisms normally nonpathogenic, or of low pathogenicity, for persons with a healthy immune system. Examples are *Pneumocystis jiroveci*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and atypical mycobacteria, all of which are commonly associated with inhalational exposures and transient colonization of the respiratory tract in healthy individuals. The second type is reactivation of latent infection acquired earlier in life, which typically remains dormant throughout life. Examples of this type are CMV, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and *H. capsulatum*. The advent of an opportunistic infection may serve as the herald sign of unrecognized, undiagnosed chronic HIV infection/AIDS.

Clinically, these infections tend to present in one of several distinct syndromes, with useful differential diagnosis considerations:

- Pneumonia: *Pneumocystis jiroveci* pneumonia (PJP), *Mycobacterium avium* complex (MAC), cryptococcosis, histoplasmosis
- Meningoencephalitis: Toxoplasmosis, cryptococcosis, tuberculosis
- Gastrointestinal disease (diarrhea): Common bacterial dysentery, cryptosporidiosis, fungal and atypical mycobacterial infection
- Fever of unknown origin (often with abdominal complaints, hepatosplenomegaly, and/or lymphadenopathy): CMV, MAC, tuberculosis, histoplasmosis

Late clinical manifestations related to HIV-induced malignancy include Kaposi sarcoma of the skin or respiratory tract and lymphoma presenting as lymphadenopathy, splenomegaly, or focal gastrointestinal disease.

Without satisfactory antiretroviral therapy, the usual patient with HIV/AIDS experiences a slow, inexorable wasting illness punctuated by periods of feverishness and diarrhea, becoming increasingly anorectic, malnourished, and lethargic. Late clinical signs include muscle wasting and weakness, anemia and thrombocytopenia, lymphadenopathy, pulmonary infiltrates, and neurologic abnormalities (such as dementia, peripheral neuropathy, and tremors). The median survival of patients with advanced HIV/AIDS (CD4 count <50 cells/mcL) is approximately 12 to 18 months. Patients succumb to complications of uncontrolled infection, malignancy, or critical organ failure (such as uremia or adrenal insufficiency).

TESTING

The initial testing for HIV generally consists of an FDA-approved, fourth-generation antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to identify both established and acute infections [127]. If this test is reactive, repeat testing is recommended to differentiate HIV-1 antibodies from HIV-2 antibodies. If this second test is non-reactive, testing with an FDA-approved HIV-1 nucleic acid test is indicated [127]. It is important to note that HIV-2 is not reliably identified by usual immunoblot antibody tests. Additional testing specific to HIV-2 should be considered if HIV-1 test results are atypical or inconsistent with clinical findings, especially for persons from (or with recent travel to) West Africa [128].

Other available tests, including enzyme-linked immunosorbent assay, may be used if the preferred combination immunoassay is not available. The HIV-1 Western blot and HIV-1 immunofluorescence assay, previously recommended to make a laboratory diagnosis of HIV-1 infection, are no longer part of the recommended testing algorithm [127].

SEXUAL TRANSMISSION PREVENTION

HIV has been isolated from blood, seminal fluid, spermatozoa, pre-ejaculate, vaginal secretions, urine, cerebrospinal fluid, saliva, tears, and breast milk of infected individuals. No cases of HIV infection have been traced to saliva or tears (though traces of the virus are present in these fluids) [129]. The virus is found in greater concentration in semen than in vaginal fluids, leading to a hypothesis that male-to-female transmission could occur more easily than female-to-male. Sexual behavior that involves exposure to blood is likely to increase transmission risks. Transmission could also occur through contact with infected bowel epithelial cells in anal intercourse, in addition to access to the bloodstream through breaks in the rectal mucosa.

Posing the highest risk of infection is unprotected receptive anal intercourse, followed by unprotected receptive vaginal intercourse and unprotected insertive anal intercourse (particularly for uncircumcised men) [130; 131]. Risk is reduced through the use of latex condoms. For the wearer, latex condoms provide a mechanical barrier limiting penile exposure to infectious cervical, vaginal, vulvar, or rectal secretions or lesions. Likewise, the partner is protected from infectious pre-ejaculate, semen, and penile lesions. As discussed, natural membrane condoms (made from lamb cecum) contain small pores and do not block HIV passage. It is estimated that latex condom use reduces the risk of HIV transmission by approximately 70% to 80% [132; 133; 134]. Although abstinence from sexual contact is the sole way to absolutely prevent sexual transmission, sexual activity in a mutually monogamous relationship in which neither partner is HIV-infected and no other risk factors are present is considered safe [135]. However, men who identify publicly as heterosexual and generally have committed relationships with women, but who also engage in sexual activity with other men, may be a transmission bridge to heterosexual women [136]. To better understand the actual extent of this behavior and its impact on HIV transmission, more research is necessary.

Numerous studies have demonstrated that oral sex can result in the transmission of HIV and other STIs. While the risk of HIV transmission through oral sex is much smaller than the risk from anal or vaginal sex, there are several co-factors that can increase this risk, including oral ulcers, bleeding gums, genital sores, and the presence of other STIs. Prevention includes the use of latex condoms, a natural rubber latex sheet, plastic food wrap, a cut open condom, or a dental dam, all of which serve as a physical barrier to transmission [137].

Pre-Exposure Prophylaxis

In 2012, the FDA approved the first medication for the prevention of sexually transmitted HIV infection, the combination drug Truvada (emtricitabine/tenofovir DF) [138]. In conjunction with safer sex practices, Truvada has been found to be partially effective as pre-exposure prophylaxis in high-risk patients. The Chemoprophylaxis for HIV Prevention in Men study, also known as iPrEx, studied the effect of once daily Truvada in 2,499 HIV-seronegative men or transgender women who have sex with men compared with placebo [139]. Researchers found that persons receiving Truvada experienced a 44% reduction in the incidence of HIV after a median of 1.2 years compared with placebo. Pre-exposure prophylaxis was most effective among participants at particularly high risk for HIV (i.e., self-reports of unprotected receptive anal intercourse).

In 2014, the CDC and the U.S. Department of Health and Human Services released clinical practice guidelines for pre-exposure prophylaxis for the prevention of HIV infection [140]. This guideline outlines indications for prophylaxis as one prevention option for HIV transmission. The most important first step in determining if an individual is a candidate for pre-exposure prophylaxis is a thorough history, including sexual and injection drug activities. All candidates will be adults without an acute or established HIV diagnosis. Pre-exposure prophylaxis is indicated for high-risk MSM, meaning those who have had any male sex partners in the past six months, are not in a monogamous partnership with a recently tested, HIV-negative man, and have one of the following [140]:

- Anal sex without condoms (receptive or insertive) in the past six months
- Any STI diagnosed or reported in the past six months
- An ongoing sexual relationship with an HIV-positive man

Prophylaxis is also recommended for high-risk heterosexual adults who have had sex with an opposite sex partner(s) in the past six months, are not in a monogamous partnership with a recently tested, HIV-negative partner, and one of the following [140]:

- Is a man who has sex with both women and men (behaviorally bisexual)
- Infrequently uses condoms during sex with one or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

IDUs are also considered candidates for pre-exposure prophylaxis if they meet certain criteria. The guideline states that persons who have injected drugs not prescribed by a clinician in the past six months may be candidates for prophylaxis if they also are positive for one of the following factors [140]:

- Any sharing of injection or drug preparation equipment in the past six months
- Been in a methadone, buprenorphine, or buprenorphine/naloxone treatment program in the past six months
- Increased risk of sexual acquisition (based on the previously outlined criteria)

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As of 2017, only fixed-dose combination tenofovir and emtricitabine (Truvada) taken daily is approved for pre-exposure prophylaxis, and it is considered the recommended first-line option [138; 140]. However, because tenofovir alone has been proven effective in trials with IDU and heterosexually active men and women, it is the alternative option for these populations [140]. No other antiretroviral regimens should be used for pre-exposure prophylaxis.

All patients prescribed Truvada for pre-exposure prophylaxis must have a negative HIV test prior to initiating treatment and every three months thereafter. In addition, patients should be advised regarding possible side effects and the continued necessity for safe sex practices. Eligible patients should also be screened for hepatitis B and have a confirmed creatinine clearance of 60 mL per minute or greater [140].

MANAGEMENT

Combination antiretroviral therapy, or cART, combines six major classes of agents: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase strand transfer inhibitors (INSTIs), and chemokine (C-C motif) receptor 5 (CCR5) antagonists. Initiated in 1995 in the United States, antiretroviral therapy regimens have been effective in dramatically decreasing HIV-related morbidity and mortality and should be considered for all HIV-infected persons who qualify for such therapy. In addition to combination therapy, the sequencing of drugs and the preservation of future treatment options are also important. Two types of combination regimens are recommended as initial therapy: INSTI-based regimens or a PI-based regimen. The goal of these regimens is to effectively reduce HIV-associated morbidity, prolong the duration and quality of survival, restore and preserve immunologic function, and prevent HIV transmission while also avoiding drug resistance [141]. A significant proportion of patients starting cART are infected with drug-resistant strains of HIV, which may lead to suboptimal virologic responses. Therefore, pretreatment genotypic resistance testing should be used to guide selection of the most optimal initial regimen [141].

Antiretroviral therapy should be initiated immediately for all patients infected with HIV in order to reduce the risk of disease progression and limit transmission [141]. There is growing evidence that early initiation of cART is effective in preventing clinical events (e.g., non-AIDS malignancies, infection, AIDS-defining illness) regardless of pre-treatment CD4 count [142; 143]. Advances in the development of antiretroviral medications and combination tablets makes adherence to therapy more effective, more convenient, and better tolerated than regimens used in the past. Deferral of therapy may be considered in patients with high CD4 counts (e.g., more than 500 cells/mcL) if adherence will be very difficult or impossible, comorbidities complicate or prohibit antiviral therapy, or a patient is considered a long-term non-progressor [141].

For treatment-naïve patients, initial recommended therapy generally consists of two NRTIs in combination with a third active antiretroviral drug from one of three drug classes: an INSTI, an NNRTI, or a PI with a pharmacokinetic enhancer (cobicistat or ritonavir) [141]. These regimens result in maximum reduction of viral load for the longest period of time. When used as initial therapy, these regimens will achieve the goal of no detectable virus in the majority of patients after four to six months [141].

STIs IN IMMIGRANTS AND REFUGEES

A variety of persons migrate to the United States, including legal immigrants granted the indefinite or time-limited right to live in the United States by immigration authorities; undocumented immigrants who have not been granted such a right; and refugees who are unable or unwilling to return to their country of origin due to fears of persecution based on their race or ethnicity, religion, nationality, political opinion, or gender identity or sexual orientation. For simplicity, all three groups are referred to as immigrants [144].

Recent immigrants underuse health services, especially undocumented immigrants, who typically lack health insurance and may avoid seeking medical attention out of fear of being deported. Compared with the United States, many countries of origin have much higher rates of STIs, including hepatitis A (poor sanitation), hepatitis B (sexual contact), and HIV (sexual contact, maternofetal transmission).

Procedurally, STI risk assessment, screening, diagnostic testing, and treatment of recent immigrants are the same as with native-born persons. The process should be nonjudgmental and culturally sensitive during all contacts [144]. In practice, clinicians should be aware of the stigma, discrimination, and complex, stressful circumstances many immigrants experience. In addition to language barriers that require an interpreter, many experience social isolation from loss of social support and cultural identity. Some may have health belief systems, practices, or taboos that impact clinical care.

Torture and rape are highly prevalent in some immigrant populations and place these persons at high risk for STIs and/or hepatitis. Post-traumatic stress disorder and other mental health conditions may be prevalent and can influence behaviors and interaction with the health system. A history of female genital mutilation can alter the appearance of the genital structure, making specimen collection and visualization of the cervix very difficult. Some immigrants have cultural sensitivities toward opposite-sex healthcare providers or discussion of sex practices or condom use. Patient history of traditional/herbal medicine should be taken to minimize toxicities and drug interactions [144]. By taking these factors into account when assessing and treating patients, clinicians may improve the sexual health of recent immigrants.

CONCLUSION

Described as hidden epidemics of substantial health and economic consequence, many Americans are reluctant to address sexual health concerns that include STIs because of the biologic and social characteristics of these diseases and associated stigma. However, all communities in the United States are impacted by STIs. Clinicians have an opportunity to identify patients at risk for viral STIs and intervene early in order to limit transmission and debilitating effects of the diseases.

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

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COURSE TEST - #94180 VIRAL SEXUALLY TRANSMITTED INFECTIONS

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

This 5 credit activity must be completed by June 30, 2020.

1. Which of the following is NOT one of the Five Ps of sexual history taking?
- A) *Privacy*
- B) *Partners*
- C) *Practices*
- D) *Protection against sexually transmitted infections (STIs)*

2. Increased STI prevalence rates are found in
- A) *women who have sex with women.*
- B) *patients without a history of sexual abuse.*
- C) *current or former injecting drug user (IDUs).*
- D) *persons with high incomes living in suburban settings.*

3. Which of the following statements regarding external condoms is TRUE?
- A) *Polyurethane and other synthetics do not provide protection against STIs/HIV and pregnancy.*
- B) *Each latex condom manufactured in the United States is tested electronically for holes before packaging.*
- C) *Sexual transmission of hepatitis B, herpes simplex, and HIV organisms cannot occur with natural membrane condoms.*
- D) *Condom failure to protect against STI or unintended pregnancy is usually caused by condom breakage rather than inconsistent or incorrect use.*

4. Which of the following methods has shown some efficacy in reducing the risk of STI transmission?
- A) *Genital hygiene*
- B) *Male circumcision*
- C) *Non-barrier contraception*
- D) *Spermicides containing nonoxynol-9*

5. Genital herpes screening should be conducted
- A) *for women and men during STI evaluation.*
- B) *every five years in women.*
- C) *within one year of sexual activity.*
- D) *for all persons aged 13 to 64 years (opt-out).*

6. Most genital herpes infections are transmitted
- A) *during severe outbreaks.*
- B) *after treatment has been initiated.*
- C) *by persons who are aware of their infection.*
- D) *by people who are asymptomatic when transmitting.*

7. What is the preferred herpes simplex virus (HSV) test for persons presenting for general STI evaluation (especially with multiple sex partners)?
- A) *Western blot test*
- B) *HSV serologic testing*
- C) *Polymerase chain reaction testing*
- D) *Cell culture from a vesicle scraping*

8. Which of the following is a recommended treatment regimen for the first clinical episode of genital herpes?
- A) *Valacyclovir 125 mg oral twice per day for 5 days*
- B) *Famciclovir 500 mg oral twice per day for 30 days*
- C) *Acyclovir 5–10 mg/kg IV every 8 hours for 2 to 7 days*
- D) *Acyclovir 400 mg oral three times per day for 7 to 10 days*

9. What is the most common STI in the United States?
- A) *HIV*
- B) *Hepatitis A*
- C) *Hepatitis B*
- D) *Human papillomavirus (HPV)*

10. Prevention of high-risk HPV is most effectively achieved through
- A) *vaccination.*
- B) *good genital hygiene.*
- C) *post-exposure prophylaxis.*
- D) *the effective use of condoms.*

Test questions continue on next page ➔

11. Which of the following statements regarding HPV vaccination is TRUE?
- A) *The earliest approved age is 19 years.*
- B) *HPV vaccines are recommended for use in pregnant women.*
- C) *The vaccines are only approved for use in girls/women (not boys/men).*
- D) *Women 21 years of age or older who have received HPV vaccination should continue routine cervical cancer screening, as vaccines do not protect against all cervical cancers.*

12. Genital warts (condyloma acuminatum) are
- A) *malignant.*
- B) *mainly caused by HPV types 6 and 11.*
- C) *less common in patients who are immunocompromised.*
- D) *not transmitted by digital, oral, and nonpenetrative genital contact.*

13. Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) is recommended for the treatment of genital warts occurring on all of the following locations, EXCEPT:
- A) *The cervix*
- B) *The vagina*
- C) *The urethral meatus*
- D) *External anogenital areas*

14. Most cases of hepatitis are caused by
- A) *viral infection.*
- B) *heavy alcohol use.*
- C) *autoimmune disease.*
- D) *exposure to chemicals.*

15. Which of the following is a common sign of hepatitis A virus (HAV) infection?
- A) *Fever*
- B) *Jaundice*
- C) *Liver atrophy*
- D) *Hyperactivity*

16. After an incubation period of 40 to 160 days, hepatitis B virus (HBV) concentrations are highest in
- A) *blood.*
- B) *semen.*
- C) *wound exudates.*
- D) *vaginal secretions.*

17. HBV vaccination is recommended for the following unvaccinated persons, EXCEPT:
- A) *IDUs*
- B) *Pregnant women*
- C) *Children and adolescents*
- D) *Adults with multiple sex partners*

18. Approximately what percentage of persons living with HIV are unaware of their infection?
- A) *1%*
- B) *14%*
- C) *41%*
- D) *84%*

19. Which of the following types of sexual contact poses the highest risk of HIV infection?
- A) *Oral sex*
- B) *Unprotected vaginal intercourse*
- C) *Protected insertive anal intercourse*
- D) *Unprotected receptive anal intercourse*

20. Which of the following patients would be considered a candidate for pre-exposure prophylaxis for HIV?
- A) *Persons who have injected drugs not prescribed by a clinician in the past six months who have also shared injection or drug preparation equipment in the past six months*
- B) *A heterosexual adult who has had sex with an opposite-sex partner in the past six months and is in an ongoing sexual relationship with an HIV-positive partner*
- C) *An MSM who has had a male sex partner in the past six months, is not in a monogamous partnership with a recently tested, HIV-negative man, and was diagnosed with gonorrhea three months ago*
- D) *All of the above*

Be sure to transfer your answers to the Answer Sheet insert located between pages 96–97.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

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Irritable Bowel Syndrome

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 10 ABIM MOC Points, 10 ABP MOC Points.

Audience
This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with irritable bowel syndrome.

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

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

1. Describe the incidence and prevalence of irritable bowel syndrome (IBS).
2. Identify conditions that are commonly comorbid with IBS.
3. Outline the natural history and disease burden of IBS.
4. Review the pathogenesis and pathophysiology of IBS.
5. Discuss risk factors for the development of IBS and underlying etiology.
6. Describe the assessment of patients with suspected IBS, including presenting signs and symptoms, testing, and clinical diagnostic criteria.
7. Identify conditions that should be included in the differential diagnosis of IBS.
8. Discuss the role of laboratory studies and alarm features in reaching a diagnosis of IBS.
9. Evaluate the role of nonpharmacologic therapies for the treatment of IBS.
10. Compare and contract available pharmacotherapies for the treatment of the various IBS subtypes.

Faculty
Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

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

Division Planner
John M. Leonard, MD

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

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 10 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

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INTRODUCTION

Until recently, irritable bowel syndrome (IBS) was considered a diagnosis of exclusion. The pathophysiology was poorly understood, patient outcomes were usually unsatisfactory, and clinicians considered IBS difficult and frustrating to manage [1]. The conceptual and empirical framework to inform the clinical care of patients with IBS took a large step forward in 2016, when the Rome Foundation published the Rome IV diagnostic criteria for IBS. These criteria incorporate the many scientific and clinical advances made since the release of the previous version (Rome III) in 2006. This was part of a larger project to overhaul and update scientific knowledge advances and clinical guidance to optimize the diagnosis and treatment of functional gastrointestinal (GI) disorders [2]. In addition, 18 review papers that detail the latest understanding of functional GI disorders were published by members of the Rome Foundation in 2016.

IBS is characterized by recurrent abdominal pain associated with disordered bowel habits (constipation, diarrhea, or a mix of constipation and diarrhea); abdominal bloating/distention is typically present. The symptoms must not have an organic, metabolic, or drug-induced basis [3]. IBS and other functional GI disorders are now understood as disorders of the gut-brain axis that arise through complex, bidirectional interactions of biopsychosocial factors.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE

IBS can have an insidious onset and frequently does not lead patients to seek medical care. This creates a discrepancy between the incidence of symptom onset (in the community) and first IBS diagnosis (physician visit) and renders estimates of IBS incidence difficult [4]. However, some prevalence estimates are available.

General Population

The lifetime prevalence of IBS in adult North American and European populations is 10% to 20%, but only 5% to 7% have been diagnosed. IBS shows highest prevalence in South America (21%) and lowest prevalence in Southeast Asia (7%) [5; 6].

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Clinical Populations

IBS is the most frequently diagnosed GI condition, accounting for 41% of patients with functional GI disorders [5; 6; 7]. Among clinical populations, IBS accounts for 12% of all patients seen in primary care and 28% in gastroenterology clinics [7]. In the United States, patients with IBS are evenly distributed among three common presenting clinical patterns: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and mixed IBS (IBS-M); in Europe, most patients reportedly have either IBS-C or IBS-M [5; 6].

Of all persons with IBS symptoms, only a subset seek primary care medical attention, estimated at 10% to 70% in European countries and around 30% in the United States. Patients with IBS-D tend to seek medical attention at higher rates than those with IBS-C or IBS-M. Those seeking medical care report greater levels of pain and anxiety and greater impact on quality of life. In contrast, GI symptom severity does not differ greatly between the two groups [4; 8; 9; 10].

Sex

The global prevalence of IBS is 14% in women and 8.9% in men, meaning the rate is 67% greater in women than men. This difference in reported sex-specific prevalence may be influenced in part by stigma associated with the diagnosis or by differing attitudes and behaviors that influence the decision to seek medical care rather than merely a variation in susceptibility and severity of underlying pathology [4; 11]. Alternatively, female sex hormone physiology may alter regulatory mechanisms of the brain-gut axis more easily and thus promote IBS pathophysiology [12].

In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent in women than men, while the female/male distribution is closer to even in Asia. Abdominal pain and constipation are more common symptom complaints in women, with diarrhea more common in men [5; 11].

Age

A meta-analysis of 81 epidemiologic studies found that IBS prevalence decreases with age. The prevalence rate in patients younger than 40 years of age is 11.0%, with decreased rates in each subsequent decade (9.6% for persons in their 40s, 7.8% for persons in their 50s, and 7.3% for persons in their 60s). Patients 50 years of age and older show the lowest IBS prevalence [13; 14].

Challenges to Obtaining Accurate IBS Epidemiology Data

Prevalence estimates for IBS are impacted by stigma associated with seeking health care for IBS symptoms or receiving a functional GI disorder diagnosis. Lower reported prevalence is likely in areas where greater stigma is perceived or where symptoms are so common as to be viewed as variations of normal. For example, diarrhea (from all causes) is common in Mexico and may not be viewed as an illness that requires healthcare contact [15]. The reported prevalence of IBS is likely to be higher in communities with higher perceived stress, lower perceived quality of life, greater potential gain from receiving a diagnosis, or fewer barriers to health care access [4; 16; 17].

The absence of a criterion-standard case definition or standardized diagnostic criteria over time has created difficulty in defining IBS cases for epidemiologic studies. Widely used ancillary data in other disorders are limited in IBS. Relatively few patients are hospitalized for IBS or diagnosed during admission, and IBS is not a cause of death that would show on death certificates [4]. Prescription data are only recently relevant as more medications have received U.S. Food and Drug Administration (FDA) approval for IBS.

COMMON COMORBID CONDITIONS

IBS is associated with numerous comorbidities. Most cluster into functional somatic syndromes (e.g., fibromyalgia, chronic fatigue syndrome, chronic pelvic pain), other GI disorders (e.g., gastroesophageal reflux disease, dyspepsia), and psychiatric disorders (e.g., major depression, anxiety, somatization). These syndromes overlap on multiple dimensions [5; 18].

Panic disorder is highly comorbid with IBS, and the prevalence of IBS symptom characteristics in patients with panic disorder is 25% to 44% [12]. A strong association is also found between IBS and generalized anxiety disorder, and patients with comorbid IBS and generalized anxiety disorder had greater functional impairment and depressive symptoms. Post-traumatic stress disorder (PTSD) is also prevalent, and as many as 36% of patients with IBS meet the criteria for lifetime diagnosis for PTSD. Major depressive disorder is the most frequent psychiatric comorbidity in IBS. Patients with major depressive disorder showed a 27% to 47% prevalence of IBS, although patients with major depressive disorder in remission did not differ from healthy controls in terms of IBS symptoms [12].

IBS severity and abdominal pain intensity are positively correlated with anxiety and depression [19]. Significantly greater levels of anxiety have been found in patients with IBS-D than in patients with IBS-C or IBS-M; patients with IBS-D also show significantly greater incidence of depression [18].

A higher percentage of patients with IBS and anxiety or depression had extra-intestinal physical symptoms than patients without anxiety (44.8% versus 16.8%, respectively) or depression (57.0% versus 21.5%, respectively) [20; 21].

Patients with IBS are much more likely to have psychiatric conditions than persons without IBS. Many patients with IBS receive anxiolytics and antidepressants, and one study found that 62% of patients received these agents prior to being diagnosed with IBS. A greater percentage of patients with severe IBS have at least one psychiatric disorder compared with patients with mild or moderate IBS (94.4% versus 35.7% and 76.1%, respectively) [21; 22; 23].

IBS, fibromyalgia, chronic fatigue syndrome, temporomandibular joint (TMJ) disorder, and vulvodynia syndrome are characterized by distressing symptoms of pain and fatigue in the absence of clinically obvious pathology. This group of conditions have been termed "central sensitivity syndromes." Neuroimaging studies using evoked sensory paradigms have revealed a common sensory augmentation to both painful and nonpainful stimulation, a transformative observation for these syndromes historically considered entirely hysterical or feigned in origin. Whether amplified pain is causal to these syndromes, a predisposing factor, an endophenotype, or an epiphenomenon cannot be discerned without additional research [24].

Roughly 50% of all patients with IBS also experience fibromyalgia, chronic fatigue syndrome, chronic back pain, chronic pelvic pain, chronic headache, or TMJ dysfunction. Symptoms of these functional somatic syndromes considerably overlap with IBS and with each other, and functional somatic syndromes occur almost twice as often in patients with IBS than in the general population [25; 26]. Fatigue, sleep problems, and back pain have been reported by 69.3%, 47.5%, and 37.3% of patients with IBS, respectively [20; 27]. Low back pain was found more common in patients with IBS-C than IBS-D [21].

Patients who have IBS and somatic comorbidities report more severe symptoms than those with IBS alone. More than 50% of patients with IBS report depression or anxiety and experience more severe somatic symptoms than patients without psychiatric conditions [4; 28; 29]. Many physical symptoms affect the overall well-being of patients with IBS (including psychologic health) and should not be overlooked or marginalized [21].

At the time of IBS diagnosis, the likelihood of an organic lesion being found on colonoscopy in patients lacking alarm symptoms is no higher than in healthy controls, and even most patients with alarm symptoms have no organic pathology [4; 30]. In contrast to endoscopy findings at diagnosis, the subsequent risk of developing inflammatory bowel disease was found to be 9 to 16 times greater in patients diagnosed with IBS than the general population, with an average two- to three-year interval between onset of IBS and inflammatory bowel disease diagnosis. These data implicate some overlap in pathogenesis for IBS and inflammatory bowel disease [31].

Colorectal cancer incidence is around 1% in the first year of IBS diagnosis. While initially higher than the general population incidence, colorectal cancer incidence returns to population levels after one year [4; 32].

NATURAL HISTORY

Symptom Patterns

For most patients, the symptoms of IBS are intermittent and over time show considerable fluctuation in frequency and duration. In the first three months after diagnosis, patients experience an average of four distinct symptom episodes per month, with the longest episode averaging five days, and most patients experience symptoms more than 50% of the days. One year after initial diagnosis, 30% to 45% of patients report they now have prolonged symptom-free periods. In the second year of follow-up, some patients experience symptom resolution, while others develop new symptoms and rate of symptomatic IBS episodes remains stable. After 10 years, 50% to 70% of patients report persistent symptoms [33; 34; 35].

Long-term follow-up data from clinical IBS populations indicate that 2% to 18% of patients worsened, 30% to 50% remained unchanged, and 12% to 38% improved over time. Poor outcomes were associated with previous surgery, longer disease duration, higher somatic scores, and higher baseline levels of anxiety or depression [5; 36].

Up to 67% of patients with IBS experience functional dyspepsia. Among patients who report IBS symptom resolution, 45% subsequently develop other functional GI disorders [25; 37; 38]. Even if all GI symptoms resolve, many patients with IBS develop symptoms of other functional disorders. Patients with lower quality of life and higher levels of anxiety are most susceptible to comorbid functional disorders. Converging evidence suggests IBS is one expression of an underlying predisposition for functional disease [4; 25; 39; 40; 41].

Patients may also experience migration between predominant symptoms and IBS subtypes over time. Most commonly, IBS-C or IBS-D switches to IBS-M; switching between IBS-C and IBS-D is less common. A possible confounding factor in natural history studies of IBS is the effect of treatment, which can result in difficulty discerning symptom variation due to medical intervention versus true natural history [5; 42].

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With the passage of time, overlapping symptoms and adjustments in the prevailing diagnostic subtype within a given patient are very common. In one study of 432 primary care patients with IBS-C or functional constipation followed over 12 months, roughly 33% had a change in dominant diagnosis from functional constipation to IBS-C or from IBS-C to functional constipation [43; 44]. In female patients with IBS initially classified as constipation, diarrhea, or mixed subtypes, roughly 25% had the same subtype at 12-month follow-up, while 75% made at least one transition into another subtype [45].

Evidence of lower IBS prevalence in older age groups suggests symptom resolution over time, which is contradicted by natural history studies showing symptom chronicity. One explanation is that the diagnosis changes, rather than resolves. As discussed, patients with IBS are more likely to experience other functional syndromes. In addition, "symptom shifting" occurs in some patients, characterized by resolution of functional bowel symptoms followed by development of extra-intestinal functional symptoms [4].

Mortality

Although patients with IBS have a significantly reduced quality of life, greater risk of depression and suicidal ideation, and higher frequency of invasive procedures and surgery, community-based studies have not associated IBS with increased mortality risk [4; 46].

DISEASE BURDEN

Like other chronic functional disorders, the overall burden of IBS is high and medical treatments for IBS have been suboptimal. Patients with IBS exhibit high rates of psychopathology, low quality of life, and increased suicidal ideation. These patients also miss more days of work, are less productive at work, and use many healthcare resources [47].

IBS significantly diminishes emotional, physical, and occupational functioning and health-related quality of life. IBS accounts for 3.1 million ambulatory care visits and 5.9 million prescriptions annually in the United States, with total direct and indirect annual expenditures exceeding $20 billion [5; 48].

IBS is usually diagnosed and managed in outpatient settings. In 2010, IBS accounted for 0.03% of U.S. hospital discharges, with a mean inpatient stay of 3.7 days costing a mean $21,153 [49].

The impact of IBS subtypes on quality of life was studied in 542 patients with IBS in the United States using the IBS Quality of Life (IBS-QOL) questionnaire. The overall and subscale scores attained from the IBS-QOL range from 0–100, with higher scores suggesting better quality of life. Overall IBS-QOL scores of patients with IBS-D (61.6) and IBS-M (63.0) were lower than those of patients with IBS-C (74.5). Patients with IBS-D scored lower than those with IBS-C on food avoidance (45.0 vs. 61.1) and interference with activity (59.6 vs. 82.3). Compared with patients with IBS-C, patients with IBS-M had greater interference in activities (61.6 vs. 82.3) and impact on relationships (73.3 vs. 84.7). Patients with IBS-M scored lower than IBS-C on food avoidance (47.2 vs. 61.1) and concern over negative social reaction (66.1 vs. 80.0) [50].

Patients with IBS-D or IBS-M are more likely to avoid culprit foods perceived to be symptom triggers than patients with IBS-C. IBS had a significantly greater negative impact on relationships in patients with IBS-M than in those with IBS-C, and more than 50% reported workplace embarrassment. Interpersonal problems were more pronounced in patients with IBS-D. This study indicates that clinicians should pay special attention to food avoidance and negative effects on relationships, daily activities, and social reaction in patients with IBS-D and IBS-M, as these domains drove down the quality of life [50].

Bloating is perhaps the most bothersome IBS symptom to patients. Bloating often leads to seeking medical care and adversely affects energy level, food intake, and physical functioning [51]. A large population-based study in Japan found abdominal bloating to be the most bothersome symptom in patients with IBS-C. The levels of anxiety and distress in daily life were associated with severity of abdominal pain, discomfort, and bloating, and abdominal bloating was more likely to occur after a meal, at work/school, and during times of stress [52].

A study assessed past-week impairments in work productivity and daily activities in American patients with IBS-C. Among those working, the average rate of past-week absenteeism was 10.6%. In addition, 37.4% reported presenteeism, 39.3% overall work productivity loss, and 45.7% daily activity impairment due to general health problems over the past week. The economic cost from lost productivity due to IBS-C is estimated at about $155 per employed patient/week, suggesting IBS-C-related impairment is a significant burden for patients and employers [53].

Perceived stigma is an important consideration in the patient with IBS. Patients with symptoms of IBS or other functional disorders present for medical care with painful, embarrassing, and life-limiting symptoms that lack objective confirmation on routine diagnostic exam and laboratory workup. Moreover, the common inclusion of IBS and fibromyalgia in psychiatric diagnostic classification systems as somatoform disorders (e.g., psychologic distress manifesting as physical symptoms) adds to the consternation. Lacking a consistent and valid illness concept or suitable term for the disorder, some caregivers may be tempted to label the patient with dismissive terms like "difficult patient," "frequent attender," or "heart-sink patient." This type of labeling may result in patient reluctance to seek medical care [54].

ETIOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

GI syndromes/symptoms may be classified into three general diagnostic categories: organic, motility, or functional disorders [2; 15]. Organic (or structural) disorders are characterized by macro- or micro-level pathology of organs or structures and include esophagitis and inflammatory bowel disease. Motility disorders are characterized by pathology of organ (motility) function. Examples of motility disorders are gastroparesis and intestinal pseudo-obstruction.

Functional GI disorders are idiopathic disorders of gut-brain interaction and, unlike organic and motility disorders, diagnosis involves identification of symptom clusters. These disorders may be further categorized as functional bowel, functional esophageal, IBS, noncardiac chest pain, functional gastroduodenal, and other disorders.

IBS is a functional bowel disorder, as are functional constipation, functional diarrhea, and functional abdominal bloating/distension. More precisely termed "disorders of gut-brain interaction," functional GI disorders develop from complex, bidirectional interactions of biopsychosocial factors. These environmental, psychologic, and biologic factors interact to drive the genesis, clinical expression, and chronicity of functional GI disorders (***Table 1***) [2; 15].

Psychosocial factors such as early life events, trauma, social learning, and/or psychiatric and psychologic disorders influence the brain and gut, which interact bidirectionally via the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis through brain-gut mediation. The integrated effects of altered physiology and psychosocial status shape the illness experience and clinical outcome, which in turn influences the severity of the disorder [55].

IBS pathophysiology is complex and multifactorial. Genetic, environmental, and psychosocial factors increase the risk of developing IBS. Factors that trigger IBS onset or exacerbation include gastroenteritis, food intolerances, chronic stress, and surgery. Pathophysiologic mechanisms vary but commonly include altered colonic motility, visceral hyperalgesia, increased intestinal permeability, immune activation, altered microbiota, and disturbances in central nervous system (CNS) function [3].

FACTORS AFFECTING THE DEVELOPMENT, EXPRESSION, AND CHRONICITY OF FUNCTIONAL GI DISORDERS

Genetic and environmental factors
Genetic polymorphism Early life experiences Parental beliefs and behaviors Social learning, support, stress Trauma Infection
Psychologic factors
Psychopathology (anxiety, depression) Cognitive-affective processes: • Health anxiety and somatization • GI-specific anxiety • Attentional bias/symptom hypervigilance • Catastrophizing
CNS structure and function
Structural brain abnormalities Functional network connectivity Emotional and cognitive modulation of visceral afferent signals Fear conditioning
Gut physiology
Gut permeability Motility Sensation Altered bacterial flora Inflammation and immune dysfunction

Source: [2; 15] *Table 1*

CONTRIBUTING FACTORS

Familial and Environmental Factors

Childhood Social Learning

Childhood functional GI disorders aggregate in families. Research into genetic factors is ongoing, but what children learn from parents is considered a greater contributor to the risk for developing functional GI disorders. One important contributor is the learning principle of positive reinforcement or reward. Children whose mothers reinforce illness behavior experience more severe stomachaches and more school absences than other children. In children with functional abdominal pain, cognitive-behavioral therapy (CBT) that targets coping strategies and parent and child beliefs about, and responses to, children's pain complaints leads to greater decreases in pain and GI symptoms than an educational intervention. This effect is mediated by changes in parents' cognitions about their child's pain [39; 55; 56].

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A strong association is found between parental psychologic status, especially anxiety, depression, and somatization, and children's abdominal symptoms [57]. This association may occur through modeling, whereby children observe and learn to display the behaviors they observe—in this context, heightened attention to or catastrophizing about somatic sensations. This effect of parental traits on children's symptoms can also occur through reinforcement. Parents with certain traits or beliefs (e.g., excessive worry about pain) might pay more attention to and reward somatic complaints. Parental catastrophizing about their own pain reinforces these types of responses to abdominal pain in their children, which encourages illness behavior and predicts child functional disability [55; 58; 59].

Childhood and Adult Stressors

Early life trauma is associated with increased risk for IBS and other functional GI disorders, major psychiatric disorders, ischemic heart disease, diabetes, asthma, and other medical disorders in adulthood [60]. Patients with IBS report a high prevalence of adverse life events in general, and childhood physical punishment, emotional abuse, and sexual abuse in particular. This psychosocial history is related to greater functional GI disorder severity and worse clinical outcomes, such as psychologic distress and impaired daily functioning. These effects increase health care seeking and explain the higher prevalence of abuse histories in patients with IBS seen in specialty clinics than in primary care; those with mild IBS symptoms and psychosocial histories may not seek medical care. High frequencies of childhood abuse (approaching 50%) are also found in patients with chronic functional somatic syndromes such as chronic pelvic pain, headaches, and fibromyalgia [61; 62; 63].

Functional GI disorder onset frequently coincides with experiencing a highly threatening event, such as the breakup of an intimate relationship. Stressful life events are associated with symptom exacerbation and frequent health care-seeking in adults with IBS. Chronic life stress is the greatest predictor of IBS symptom severity one to two years after diagnosis and negatively affects functional GI disorder treatment outcomes. Presence of a single stressor within 6 months of initiating IBS treatment predicts poor outcomes and higher symptom intensity at 16-month follow-up [55; 64].

Social Support

Quality of social support is related to many aspects of IBS. Patients have reported that finding social support helps them overcome IBS. Perceived social support adequacy is linked to IBS symptom severity, possibly through reducing stress levels. Negative social relationships with frequent conflict and adverse interactions show a consistently greater effect on poor IBS outcomes than lack of social support. A supportive patient-practitioner relationship improves symptoms and quality of life in patients with IBS, showing the clinically valuable role of social support [55; 65; 66].

Psychologic Factors and Psychiatric Disorders

Psychologic distress is an important risk factor for developing functional GI disorders. The presence of psychologic comorbidity may perpetuate or exacerbate symptoms and negatively affects the clinician-patient relationship and treatment outcomes. Comorbid anxiety or depression strongly predicts postinfectious IBS and functional dyspepsia and can also result from symptoms and quality of life impairment. The absence of co-occurring psychiatric comorbidity does not exclude contribution to functional GI disorder from dysfunctional cognitive and affective processes.

Mood Disorders

The overlap between major depressive disorder and functional GI disorder is about 30% in primary care and slightly higher in specialist care. Depression can influence the number of functional GI symptoms and diagnoses. Suicidal ideation is present in 15% to 38% of patients with IBS and is linked to hopelessness surrounding symptom severity, interference with life, and inadequate treatment. Comorbid major depressive disorder is linked to poor outcomes, including high health care utilization and cost, functional impairment, poor quality of life, and poor treatment engagement and outcomes [67; 68; 69].

Anxiety Disorders

With a prevalence of 30% to 50%, anxiety disorders are the most common psychiatric comorbidity in patients with functional GI disorders. Anxiety can initiate or perpetuate functional GI disorder symptoms by amplifying autonomic arousal (in response to stress) or interfering with GI sensitivity and motor function. Common pathways might exist between vulnerability to anxiety disorders and functional GI disorders, especially through anxiety sensitivity, bodily vigilance, and discomfort intolerance [67; 70].

Somatization, Somatic Symptom Disorder, and Functional Somatic Syndromes

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), somatic symptom disorder replaced the abandoned term "somatization," which described patients who responded to psychosocial stress by experiencing, communicating, and seeking medical help for physical symptoms unconfirmed by pathologic findings. The number of symptom complaints was emphasized [55; 71].

In the DSM-5, somatic symptoms may or may not be medically unexplained but are distressing, disabling, and associated with excessive and disproportionate thoughts, feelings, or behaviors persisting longer than six months. This approach shifts the experience of medically unexplained symptoms from unconscious manifestations of psychologic distress to the abnormal cognitive-affective processes surrounding the symptoms [55; 72; 73].

Somatization is associated with GI processes such as gastric sensitivity and emptying, symptom severity, and impaired quality of life. It is linked to higher health care use and predicts poor treatment response and discontinuing medication from side effects. Somatization remains extensively used in the medical literature to describe syndromes, often with prominent pain, that lack apparent physiologic cause following standard diagnostic workups. Assessing somatization through severity of the multiple somatic symptoms remains clinically useful [73; 74; 75].

Somatization was considered the basis for frequent extraintestinal symptoms in patients with IBS and the high co-occurrence between functional GI disorder and other functional somatic syndromes. The overlap is extensive; 67% of patients with functional GI disorders also have a positive history for conditions such as interstitial cystitis, chronic pelvic pain, headaches, fibromyalgia, or other functional somatic syndromes, independent of psychiatric comorbidity [55; 76; 77].

Cognitive-Affective Processes

The psychologic constructs of health anxiety, GI symptom-specific anxiety, attentional bias/symptom hypervigilance, and catastrophizing are linked to functional GI disorders independent of psychiatric comorbidity (***Table 2***). These are important treatment targets for CBT [55].

GI symptom-specific anxiety is an important perpetuating factor that describes threatening interpretation and out-of-proportion behavioral response to GI sensations. This anxiety is characterized by worry and hypervigilance around GI sensations from normal bodily functions (e.g., hunger, satiety, gas) to symptoms of an existing GI condition (e.g., abdominal pain, diarrhea, urgency). Worry and hypervigilance generalizes into fear that sensations/symptoms will occur and contexts where this could happen. Avoidance or behaviors disproportional to symptoms follows [55; 78].

As an example, a person has not eaten all day and becomes aware her stomach is rumbling. Interpreted to mean the need to defecate may be imminent, anxiety is triggered. In public with friends, the anxiety increases when no restroom is visible, and the person leaves her friends, feeling they would not understand [55].

Other Factors

Genetic Predisposition

Variations in the gene that encodes serotonin reuptake transport system have been found in patients with IBS. It is believed that polymorphism of the 5-HT2A receptor gene may be associated with the development of IBS [79].

Acute Infectious Gastroenteritis

The prevalence of IBS is increased six- to seven-fold in persons who have experienced a prior infectious gastroenteritis or enterocolitis, and postinfectious IBS accounts for 5% to 25% of all cases of IBS [80]. IBS develops in 3% to 30% of patients following acute gastroenteritis, illustrating an acute pathogen and host interaction that predisposes to development of chronic IBS [5; 81]. Factors with the greatest risk for postinfectious IBS are elongating toxin and longer duration of the initial illness [82; 83]. Other predisposing factors include:

- Female sex
- Younger age
- Toxicity/severity of infecting strain
- Cigarette smoking
- Mucosal inflammation
- Immune function
- Microbiome
- Concurrent depression or anxiety
- GI infection severity
- Antibiotic treatment

Psychopathology increases the risk of developing postinfectious IBS by enhancing susceptibility to infectious gastroenteritis [5; 84]. Mucosal inflammation and abnormal gut-host microbial interactions also promote postinfectious IBS. Mucosal immune activation and immune cell proliferation may amplify peripheral sensory signaling to result in visceral hypersensitivity, a primary IBS pain mechanism [5; 84].

Patients with postinfectious IBS are important to identify because roughly 50% will experience spontaneous remission within six to eight years of the initial infection. This disease course differs from the chronic relapsing nature of typical IBS [5; 85].

Acute gastroenteritis is now known to cause marked disruptions in the gut microbiota by pathogen overgrowth and substantial reduction in the diversity of normal flora. In the past, gut equilibrium was assumed to normalize after the infection cleared. However, research indicates individuals recovering from *Campylobacter jejuni* enteritis (a common cause of food poisoning) are as likely to show continued alteration in microflora (with potential progression to IBS-D) as they are full recovery of gut equilibrium [86; 87].

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COGNITIVE-AFFECTIVE PROCESSES INFLUENCING THE SYMPTOM EXPERIENCE IN FUNCTIONAL GI DISORDERS (FGIDs)

Term	Definition	Association with FGID	Outcomes	Management
Illness anxiety	Global tendency to worry about current and future bodily symptoms, formerly referred to as hypochondriasis	Low insight Extensive research into what is wrong Not easily reassured Lack of acceptance Rick factor for the development of FGID	Chronicity Social dysfunction Occupational difficulties High health costs Negative physician-patient relationship Poor treatment response	Responsive to CBT
Symptom-specific anxiety	Worry/hypervigilance around the likelihood/ presence of specific symptoms and the contexts in which they occur	Belief that normal gut sensations are harmful or will lead to negative consequences Promotes GI symptoms	Drives health care use Negatively impacts treatment response	Aerophagia improved with distraction May be differentially responsive to interoceptive exposure-based therapy
Hypervigilance/ attentional bias	Altered attention toward, and increased engagement with, symptoms and reminder of symptoms	Patients with IBS: Higher recall of pain words and GI words compared with healthy controls Patients with NCCP: Hypervigilance toward cardiopulmonary sensations	Dismiss signs of improvement Ignore information suggesting FGID is not serious	Responsive to CBT
Catastrophizing	Individual magnifies the seriousness of symptoms and consequences while simultaneously viewing him/herself as helpless	Symptom amplification Increased pain Inhibits pain inhibition Negatively affects interpersonal relationships Leads to increased worry, suffering, disability	High symptom reporting Reduced quality of life Can impact patient self-report Burdens provider	Improves with CBT Mediates outcome

CBT = cognitive-behavioral therapy, NCCP = noncardiac chest pain.

Source: Reprinted from Van Oudenhove L, Levy RL, Crowell MD, et al. Biopsychosocial aspects of functional GI disorders: how central and environmental processes contribute to the development and expression of functional GI disorders. Gastroenterology. 2016;150(6):1355-1367, with permission from Elsevier. *Table 2*

Alterations in the Intestinal Microbiome

Gut dysbiosis is defined as an imbalanced or maladapted, but stable, gut ecosystem that has reduced capacity for protection and is associated with disease [88]. Gut dysbiosis has potentially significant consequences in psychiatric disorders, cognitive disorders, and chronic visceral pain (due to brain-gut mediation). The intestinal flora of patients with IBS differs from healthy persons, and intestinal flora profiles also differ among IBS subtypes [89]. Deficiency in *Bifidobacterium* has been associated with greater abdominal pain and bloating in patients with IBS. As such, treatment with probiotics has shown some promise in alleviating symptoms in IBS. In one study, probiotic administration was found to alter central processing of emotional stimuli and resting brain connectivity in sensory and affective brain circuits. The hypothesis of a microbiome gut-brain axis is emerging, and there is a possibility that gut microbiota will represent a therapeutic target in the treatment of IBS [55; 90; 91].

Bile Acids and Bowel Dysfunction

Secretory diarrhea results from colonic perfusion of bile acids due to inadequate ileal reabsorption (less than 95%). Excess bile acids entering the colon increase gut permeability, activate adenylate cyclase, stimulate colonic secretion, and increase stool water and colonic motility. Decreased circulating fibroblast growth factor 19 (FGF19) leads to excessive bile acid production and can be primary or secondary to ileal resection or ileitis. Around 10% of patients with IBS-D have severe bile acids malabsorption—defined as less than 5% retention at seven days. In the United Kingdom, bile acid diarrhea accounts for nearly 25% of patients with IBS referred to specialist care for diarrhea [87; 92].

Bile salt overproduction can be identified by reduced seven-day retention of the synthetic radiolabeled bile acid selenium-75 homocholic acid taurine (SeHCAT), but access to SeHCAT is limited. Another approach measures fasting FGF19 using an enzyme-linked immunosorbent assay (ELISA). FGF19 <145 pg/mL predicts reduced SeHCAT retention [87].

The cause of low FGF19 levels is not fully known, but bile acid malabsorption can begin acutely after an ileitis episode, common with *Salmonella* spp. or *C. jejuni* gastroenteritis. Sudden onset and high-volume nocturnal diarrhea are characteristic features [87].

The prevalence and role of ileal malabsorption of bile acids in diarrhea-like symptoms has historically been underestimated in IBS-D. Identification can lead to specific treatment with bile acid sequestrants [15; 93].

Diet

Many patients identify food as an IBS symptom trigger. The contribution of true food allergies to IBS is small, but food intolerances are common in patients with IBS. Gluten (present in wheat products) is increasingly recognized as an important symptom trigger in patients with IBS and inducer of IBS-like symptoms in persons without IBS diagnosis. Non-celiac gluten sensitivity is an emerging syndrome provoked by gluten ingestion in patients in whom celiac disease and wheat allergy are ruled out. Other triggers of non-celiac gluten sensitivity pathogenesis include wheat proteins (i.e., amylase and trypsin inhibitors) and FODMAPs (fermentable oligo-, di-, monosaccharides, and polyols) [94; 95]. Emerging evidence supports gluten-free and low-FODMAPs diets for patients with IBS. FODMAPs are poorly absorbed carbohydrates that can induce osmotic effects, result in increased fermentation in the small bowel or colon, and trigger symptom exacerbation in patients with IBS with abnormal gut function or sensitivity [5; 94].

Dietary constituents also influence the impact of intraluminal factors on gut function. Among these are microflora alterations in short-chain fatty acids; the effects of enteroendocrine cell products (i.e., granins) on nervous, endocrine, and immune cells; and the ratio of secondary to primary bile acids that impact gut transit rates [15; 96].

A six-week placebo-controlled, double-blinded trial in patients with IBS with gluten sensitivity histories found poorly controlled IBS symptoms in 68% randomized to diets with gluten versus 40% receiving a gluten-free diet. In patients receiving a gluten-free diet, double-blinded gluten re-challenge worsened pain, bloating, stool consistency, and fatigue [97]. A study of patients with IBS-D reported that gluten administration led to altered gut permeability and increased stool frequency and immune activation [98].

While these data suggest that symptom exacerbation after ingesting wheat is primarily caused by gluten, wheat also contains fructans and other proteins that may trigger symptoms in patients with IBS [5]. A clinical trial of 920 patients with IBS found that 33% of subjects experienced worsened symptoms of increased abdominal pain and distension after receiving wheat (not limited to gluten), but not after placebo [99].

BRAIN-GUT AXIS AND PROCESSING

Bidirectional interactions involving multiple components of the (peripheral) GI system (microbiome, altered mucosal inflammation, visceral hypersensitivity) and the CNS (emotional arousal, sensorimotor function, salience and executive function, central autonomic function) contribute to the development of IBS. Neurophysiologic mechanisms in the brain-gut axis link psychologic processes, psychiatric comorbidity, and IBS symptoms [2; 100].

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In the brain-gut axis, homeostatic information about visceral physiologic status is continuously signaled to the brain through afferent neural and humoral "gut-brain" pathways. Most gut-brain signals are not consciously perceived under normal conditions. Visceral pain results from the perception of strong gut-brain signaling, triggered by noxious stimuli to warn of potential threat to homeostasis that requires a response [55; 100].

Visceral afferent signals are relayed to the brain and then processed, modulated, and integrated through the afferent network, emotional arousal, and cortical modulatory neurocircuits [55]. Emotional arousal and cortical modulation circuits project "top-down" to brainstem areas, which send descending projection neurons to dorsal horns of the spinal cord, where pain transmission is modulated. This circuitry is termed the descending pain modulation system (DPMS) [55].

ALTERED PAIN PERCEPTION IN PATIENTS WITH IBS

The hallmark symptom of IBS in the Rome IV criteria is chronic visceral pain and/or discomfort, and patient perception of visceral pain in IBS is disproportionate to the intensity of visceral afferent inputs, which is the result of complex psychobiologic processes [55].

Visceral hypersensitivity (also referred to as sensitization) describes lowered thresholds for visceral pain and occurs in the majority of patients with IBS. In these patients, lower pain thresholds are reflected by an exaggerated pain response to normally modest GI discomfort and/or painful response to stimuli that are not normally pain- or discomfort-inducing (e.g., normal bowel function). Visceral sensitivity is amplified in patients with IBS [15].

Psychologic processes and psychosocial factors substantially influence visceral hypersensitivity. In patients with IBS, hypervigilance (defined as a heightened psychologic tendency to focus on and report pain) is considered a greater contributor to lowered pain thresholds than actual increased neurosensory sensitivity. Anxiety and depression levels are directly related to pain severity in patients with IBS [101; 102; 103; 104].

As discussed, extra-intestinal chronic pain conditions are highly prevalent in IBS, and widespread hypersensitivity and extra-intestinal pain syndromes suggest CNS involvement and central sensitization. Descending neural modulatory circuits from the brain can inhibit or facilitate ascending nociceptive transmission, influenced by cognitive processes and mood. Changes in DPMS function are thought to influence pain perception [105]. Dysregulated cortical modulation of descending pain regulatory pathways can amplify sensitivity to noxious and innocuous stimuli [106].

Neural pathways play a major role in modulating visceral pain experience and other IBS symptoms. Spinothalamic tracts localize and differentiate visceral stimuli, while spinoreticular pathways influence the reflexive, affective, and motivational aspects of sensation and pain [81]. Pain modulatory system dysfunction promotes visceral hypersensitivity, and studies of IBS have shown abnormalities in pain signal processing and modulation that include functional and structural abnormalities in sensory, emotional arousal, and prefrontal cortical modulatory regions [55; 106].

Altered Brain Network Function

Colorectal distension in patients with IBS activates brain stress response areas but deactivates brain areas that modulate stress response [80; 107; 108]. This pattern reflects upregulated connectivity in emotional arousal circuitry; the increased sympathetic arousal, anxiety, and vigilance often observed in patients with IBS; and the association between IBS symptoms and functional alteration in multiple brain networks [55].

When anticipating experimentally induced visceral pain, anticipatory response in the locus coeruleus predicts subjective perception and brain response to the actual painful stimulus. Sensory filtering is degraded by anxiety-related dysfunction of the descending pain modulation system [107; 109].

Altered Brain Structure

Alterations in brain structure have been demonstrated in patients with IBS. The role of structural brain changes in IBS and other functional pain disorders is not clear, because these changes may represent pre-existing vulnerability factors or consequences of long-term exposure to the pain [106].

Female patients with IBS have shown increased cortical thickness in the somatosensory cortex and decreased cortical thickness in pain processing regions, including the insula and anterior cingulate cortex. IBS symptom severity is negatively correlated with cingulate thickness, suggesting a role for loss of neural density in symptom generation [106; 110; 111].

Patients with IBS have also shown decreased gray matter volumes in widespread regions, with early life trauma contributing to these decreases [106]. Decreased gray matter density in prefrontal and posterior parietal cortex areas is consistent with the close relationship between IBS and mood disorders. Pain catastrophizing negatively correlates with the degree of cortical thickness in the prefrontal cortex [112; 113; 114].

Abnormal structure of brain white matter tracts have been found in multiple areas in patients with IBS. These white matter changes are associated with symptom severity, trait anxiety, and catastrophizing [115; 116; 117].

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

CLINICAL PRESENTATION

Altered Bowel Habits

Patients with prominent constipation may describe painful or infrequent defecation, non-response to laxatives, and hard, narrow stools. If present, diarrhea is usually described as small volumes of loose stool preceded by urgency or frequent defecation. Postprandial urgency is common, as is alternation between constipation and diarrhea predominance [118]. Stools may also be white or clear (mucosa).

Abdominal Pain

Descriptions of pain associated with IBS often change, but the pain is typically diffuse without radiation. The most common site of pain is the lower abdomen, specifically the left lower quadrant. Acute episodes of sharp pain are often superimposed on a more constant dull ache. Meals can precipitate pain, and defecation may or may not improve pain. Pain from what feels like gas pockets in the splenic flexure can mimic anterior chest pain or left upper quadrant abdominal pain. Termed splenic flexure syndrome, balloon inflation in the splenic flexure will provoke this pain and should be considered to differentiate from chest or left upper quadrant abdominal pain [118].

Abdominal Distention

Patients with IBS frequently report increased amounts of bloating and intestinal gas, but confirmation by quantitative measurements is elusive. People with IBS can experience expanding, and measurable, abdominal circumference throughout the day. Intolerance of otherwise normal amounts of abdominal distention is common [118].

Other Common Symptoms and Complaints

Dyspepsia, heartburn, nausea, vomiting, sexual dysfunction (including dyspareunia and poor libido), and urinary frequency and urgency frequently occur in patients presenting with IBS complaints. Fibromyalgia commonly co-occurs. Careful questioning can reveal stressor-related symptoms; if disclosed, ask further about avoidance of stressors [118].

Perimenstrual Symptom Exacerbation

Many women of reproductive age experience cyclical changes in GI symptoms (including alteration in bowel habits) during their menstrual cycle. Female patients with IBS often experience worsened GI symptoms of abdominal pain, bloating, or diarrhea during menses, possibly due to elevated prostaglandin levels during menses that enhance perception of viscera-somatic stimuli and increases nausea, abdominal distension, and pain [119].

Fatigue

Despite receiving little attention in the medical literature, fatigue is a frequent symptom in patients with IBS and is associated with poor quality of life. A study of 160 patients with IBS found a multidimensional and negative impact from fatigue on daily life [120]. Fatigue may interfere with patients' ability to perform physical activities, work, domestic work, and interact socially. Poor stamina is the most prominent feature, and strategies to limit the bodily consequences of tiredness are common. Severe fatigue is associated with more severe IBS symptoms, anxiety, and depression. Fatigue is a distressing symptom in a sizeable proportion of patients with IBS and should be assessed and, if confirmed, targeted for intervention [120].

CONCEPTUAL AND DIAGNOSTIC ADVANCES

Over time, the definitions of IBS and functional GI disorders have been shaped by societal perspectives of illness and disease, available scientific evidence, and clinician training and bias. Even today, some consider functional GI disorders to be "less legitimate" than pathologically based disorders, and patients with functional GI disorders may be stigmatized for having functional symptoms. This is a carry-over from the influence of dualistic principles that dichotomized organic disorders from functional disorders, which were often considered psychiatric or undefined. However, the definition has changed from the absence of organic disease, to a stress-related or psychiatric disorder, a motility disorder, a disorder of GI functioning, and finally to a disorder of gut-brain interaction [2].

The Rome Foundation was founded in the 1980s to promote global recognition of functional GI disorders, advance scientific understanding of functional GI disorder pathophysiology, optimize clinical management for patients with functional GI disorders, and develop educational resources to achieve these goals. The Foundation is comprised of scientists and clinicians from around the world with expertise in diverse areas relevant to functional GI disorders [121].

The Rome III criteria incorporated scientific data on IBS diagnosis and treatment. Rome III defined IBS as recurrent abdominal pain or discomfort three or more days per month in the preceding three months, associated with two or more of the following: symptom improvement with defecation, symptom onset coupled with altered stool frequency, or symptom onset coupled with altered stool form [122; 123].

Over the past decade, the need to revise Rome III became increasingly apparent. Knowledge of IBS pathophysiology continued evolving, and many clinicians found Rome III criteria unhelpful and lacking in real-world clinical applicability. For example, Rome III did not recommend basic laboratory testing and ignored the fact that, for many patients, abdominal pain worsened rather than improved with defecation. Some Rome III criteria were seen as vague or incorrect [122].

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In 2016, the Rome IV guidelines were published to address these criticisms and improve guidance to healthcare providers based on latest scientific and clinical evidence. Important changes in Rome IV IBS diagnostic criteria include [2; 3]:

- The term "abdominal discomfort" was removed because it was determined to be imprecise and difficult to translate.
- The required frequency and presence of abdominal pain was increased to reflect research that identified pain as a cardinal symptom of IBS.
- Rome IV recognizes that IBS is often associated with irregular bowel habits of constipation, diarrhea, a mix of both, or their alternation and that common symptoms include bloating and distension.
- As IBS is a chronic condition, Rome IV requires symptom persistence for six or more months for diagnosis.
- Rome IV now acknowledges the role of diagnostic tests to exclude other common conditions with similar symptoms to IBS, such as celiac disease, lactose intolerance, and inflammatory bowel disease.
- Replacing the term "functional" was found impractical due to its pervasive use in healthcare nosology, so this term was limited to the extent possible.

By clarifying language, updating the definition, and including the option of laboratory testing, the new criteria should make IBS easier to diagnose. The emphasis on abdominal pain validates clinician reports of this symptom as the essential element of IBS. Rome IV should also help differentiate IBS from intermittent abdominal spasms or cramps and chronic constipation or diarrhea [3; 122]. The revised Rome IV IBS criteria are part of a larger project by the Rome Foundation to overhaul and update scientific data, educational information, and clinical guidance to optimize the diagnosis and treatment of functional GI disorders.

Functional bowel disorders, a functional GI disorder subgroup, describe a spectrum of chronic GI disorders characterized by predominant signs or symptoms of abdominal pain, bloating, distention, and/or bowel habit abnormalities (i.e., constipation, diarrhea, or mixed constipation and diarrhea) [3]. These disorders are distinguished from other GI disorders based on chronicity (more than six months of symptoms at the time of presentation), current activity (symptoms present within the last three months), frequency (symptoms present, on average, one or more days per week), and absence of obvious anatomic or physiologic abnormalities identified by routine diagnostic workup. Functional bowel disorders include IBS, functional constipation, functional diarrhea, functional abdominal bloating/distention, unspecified functional bowel disorder, and opioid-induced constipation, a new entry that differs from other functional bowel disorders by etiology but resembles functional constipation in clinical presentation [3].

Importantly, these disorders significantly overlap and should be viewed as a continuum instead of discrete diagnostic entities. Given the extent of overlap, differentiation of functional bowel disorders may not always be possible [3].

DIAGNOSTIC CRITERIA AND MEASUREMENT SCALES

As noted, IBS is a functional bowel disorder with recurrent abdominal pain associated with defecation or a change in bowel habits. Disordered bowel habits and symptoms of abdominal bloating/distention are typically present. Symptom onset occurs at least six months before diagnosis, and symptoms should be present during the last three months [3].

The National Collaborating Centre for Nursing and Supportive Care recommends that healthcare professionals should consider assessment for IBS if the person reports having had any of the following symptoms for at least six months: abdominal pain or discomfort, bloating, and/or change in bowel habit.

(https://guideline.gov/summaries/summary/49049. Last accessed November 22, 2016.)

Level of Evidence: Consensus Statement/Expert Opinion

For all IBS subtypes, the key requirement is that symptoms must not have an organic, metabolic, or drug-induced origin. A symptom-focused patient history and careful physical examination are mandatory to rule out intestinal or extra-intestinal diseases, symptom-inducing medications, and alarm symptoms that prompt further diagnostic exploration [44].

The Rome IV IBS diagnostic criteria are [3]:

- Recurrent abdominal pain occurring, on average, one or more days per week
- The abdominal pain is associated with two or more of the following criteria:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in form (appearance) of stool

Diagnosis is made with criteria fulfilled the last three months and symptom duration at least six months.

DIAGNOSTIC CRITERIA FOR IBS SUBTYPES		
Subtype	**BSFS Criteria**	**Alternative**
IBS with predominant constipation (IBS-C)	>25% of bowel movements with BSFS types 1 or 2 AND <25% of bowel movements with BSFS types 6 or 7	Patient reports that abnormal bowel movements are usually constipation (BSFS type 1 or 2).
IBS with predominant diarrhea (IBS-D)	>25% of bowel movements with BSFS types 6 or 7 AND <25% of bowel movements with BSFS types 1 or 2	Patient reports that abnormal bowel movements are usually diarrhea (BSFS type 6 or 7).
Mixed-type IBS (IBS-M), in which constipation and diarrhea alternate	>25% of bowel movements with BSFS types 1 or 2 AND >25% of bowel movements with BSFS types 6 or 7	Patient reports that abnormal bowel movements are usually both constipation and diarrhea.
IBS unclassified (IBS-U)	—	Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into one of the other three groups.
BSFS = Bristol Stool Form Scale.		
Source: [3; 44]		*Table 3*

Bristol Stool Form Scale

The Bristol Stool Form Scale (BSFS) illustrates and describes the appearance of seven different stool types that correspond to intestinal transit time ranging from severe constipation (Types 1 and 2) to diarrhea (Type 7). Patients can use the BSFS to record frequency and subtype of their stools [124]:

- Type 1: Separate hard lumps, like nuts (hard to pass)
- Type 2: Sausage-shaped but lumpy
- Type 3: Like a sausage with cracks in the surface
- Type 4: Like a sausage or snake, smooth and soft
- Type 5: Soft blobs with clear-cut edges
- Type 6: Fluffy pieces with ragged edges, a mushy stool
- Type 7: Entirely liquid, no solid pieces

Diagnostic Criteria for IBS Subtypes

IBS is subtyped by predominant bowel habit change, but only after all medications to treat bowel habit abnormalities are discontinued. The BSFS can be used to categorize IBS into subtypes based on stool characteristics (***Table 3***). Predominant bowel habits are based on stool form on days with at least one abnormal bowel movement [3; 44].

Diagnostic Criteria for Related Functional Bowel Disorders

Functional bowel disorders are diagnosed when criteria are fulfilled for the last three months, with symptom onset more than six months before diagnosis [3].

Functional Constipation

In order for a diagnosis of functional constipation to be made, two or more of the following must be present [3]:

- Straining during >25% of defecations
- Lumpy or hard stools (BSFS 1 or 2) in >25% of defecations
- Sensation of incomplete evacuation in >25% of defecations
- Sensation of anorectal obstruction/blockage in >25% of defecations
- Manual maneuvers to facilitate >25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week

In patients with functional constipation, loose stools are rarely present without laxative use. Although symptoms may be similar, these patients do not meet the full criteria for IBS-C.

Functional Diarrhea

Functional diarrhea is characterized by loose or watery stools (>25% of stools) without predominant abdominal pain or bothersome bloating. These patients do not meet the criteria for IBS-D.

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Functional Abdominal Bloating/Distension

Functional abdominal bloating (FAB) or distention (FAD) represent two different sets of signs and symptoms but are combined by Rome IV into the diagnostic entity of FAB/FAD. In patients with FAB/FAD, mild abdominal pain related to bloating and/or minor bowel movement abnormalities may be present. Symptoms of recurrent abdominal fullness, pressure, a sensation of trapped gas, and/or measurable increase in abdominal girth must be present. Abdominal bloating and/or distention predominates over other symptoms, occurring, on average, at least one day per week. These patients do not meet the diagnostic criteria for IBS, functional constipation, functional diarrhea, or postprandial distress syndrome.

CLINICAL EVALUATION AND DIAGNOSTIC WORKUP

IBS is diagnosed by a thorough patient history, physical examination, and limited laboratory testing. While not necessary for diagnosis, a brief psychosocial assessment should be performed in all patients. In most patients who fulfill Rome IV diagnostic criteria and for whom alarm features are absent, the need for diagnostic testing should be minimal; performing a battery of tests in all patients suspected of IBS is not warranted. However, focused diagnostic testing may be required to differentiate IBS from several conditions with mimicking symptoms when ambiguity is present. IBS mimics include inflammatory bowel disease, celiac disease, lactose and fructose intolerance, and microscopic colitis [3].

Clinical History

Abdominal pain is a hallmark of IBS; the absence of abdominal pain precludes the diagnosis of IBS. Pain can be present anywhere throughout the abdomen, although it is more common in the lower abdomen [3].

A history of disordered bowel habits (i.e., constipation, diarrhea, or both) should be identified, along with their temporal association with episodes of abdominal pain. Unpredictable bowel pattern (i.e., three or more different stool form types/week) reinforces the diagnosis of IBS-D. An increasing number of consecutive days without a bowel movement suggests a diagnosis of IBS-C.

Ask patients for specific information regarding bowel habits and stool characteristics, as this informs subtyping of their IBS. A diagnosis of unclassified IBS (IBS-U) is reserved for patients meeting IBS diagnostic criteria whose bowel habits cannot be accurately grouped into one of the three main subtypes; this group is uncommon. Difficulty in accurate subtyping can result from frequent changes in diet or medications or an inability to stop medications that affect GI transit. Subtyping should be based on the patient's reported predominant bowel habit on days with abnormal bowel movements. As noted, the BSFS should be used to record stool consistency [124].

Diagnosing patients with IBS-D or IBS-C is usually straightforward, but IBS-M can be more complex. A detailed history helps determine whether mixed bowel patterns originate from the underlying disease state or are a consequence of medical intervention. All prescription and over-the-counter medications and supplements with known influence on IBS symptoms should be considered. A stool diary helps identify patterns in the erratic bowel habits of many patients with IBS. Patients with IBS-M often report protracted periods when bowel movement is absent or appears with small, hard stools; this is followed by periods of multiple stools of variable consistency interpreted by patients as diarrhea. In most cases, this reflects IBS-C, and radiographic demonstration of fecal loading helps confirm clinical suspicion [5].

Non-Specific Symptoms

Common non-specific symptoms in IBS include abnormal stool frequency, abnormal stool form (BSFS types 1/2 or 6/7), excessive straining during defecation, urgency to defecate, feelings of incomplete evacuation, and mucus with bowel movements. Abdominal bloating is present in most patients with IBS and abdominal distention may be reported, but neither is required for an IBS diagnosis [3].

Patients with IBS frequently report that symptoms are induced or worsened by meals, although these symptoms are not specific to IBS. Many other functional GI (e.g., dyspepsia) and non-GI (e.g., migraine headaches, fibromyalgia, interstitial cystitis, dyspareunia) disorder symptoms are reported in patients with IBS; their presence supports an IBS diagnosis [3].

Physical Examination

A physical examination should be performed for every patient evaluated for IBS. This reassures the patient and helps exclude organic etiology. Physical examination frequently reveals tenderness in the left lower quadrant over a palpable sigmoid colon. A rectal examination is warranted to rule out rectal disease and abnormal function of the anorectal sphincter (e.g., paradoxical pelvic-floor contraction during a defecation attempt), which may contribute to symptoms of constipation [125]. The presence of ascites, hepatosplenomegaly, or abdominal mass warrants further evaluation. An anorectal examination is mandatory to identify anorectal causes of bleeding, evaluate anorectal tone and squeeze pressure, and identify dyssynergic defecation [3].

Differential Diagnosis

Several diseases should be considered in patients with IBS symptoms, including celiac disease, inflammatory bowel disease, and dyssynergic defecation. When detailed history taking, physical examination, and/or routine laboratory testing results make it crucial to rule out a disease that requires diagnostic tests or functional studies not available in primary care, referral to a specialist is indicated.

Celiac Disease

Patients with IBS symptoms have a fourfold increased risk of biopsy-proven celiac disease [5]. However, the prevalence of celiac disease in patients with IBS symptoms varies by region, with European studies, but not American studies, demonstrating a higher prevalence of the disease. Routine celiac disease screening in patients with IBS becomes cost-effective with prevalence ≥1%. Given the potential long-term consequences of a missed celiac disease diagnosis, clinicians caring for patients with IBS should have a low threshold of suspicion, especially in patients with IBS-D [5; 126].

Serologic tests for celiac disease should be performed in patients with IBS-D or IBS-M who fail empiric therapy. Upper GI endoscopy with duodenal biopsies should be performed if serologic tests for celiac disease are positive or clinical suspicion is high; duodenal biopsies can also identify tropical sprue, another mimic of IBS.

Microscopic Colitis

A small subgroup of patients with suspected IBS-D have microscopic colitis. Risk factors for microscopic colitis include age older than 50 years, nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new medications, and comorbid autoimmune disease. When colonoscopy is performed in patients with suspected IBS-D, random colon biopsies should be obtained to rule out microscopic colitis [5; 126].

Inflammatory Bowel Disease

Chronic inflammatory bowel diseases, like Crohn disease, can mimic IBS symptoms during acute inflammatory flares. Nerve and muscle changes can persist following acute inflammation, even in remission. The underlying mechanisms may include altered gut permeability and persistent low-level immune activation, shown by cecal biopsies from patients with inflammatory bowel disease in apparent remission with ongoing IBS symptoms. Other mechanisms may include persisting alterations in enteric nerves and serotonin signaling. This information can help identify patients with inflammatory bowel disease and persistent IBS symptoms who may respond better to dietary restriction and other IBS treatments than to escalated immunosuppression [87; 127; 128].

Because even low-grade chronic inflammation can alter gut permeability, sensitize visceral afferent neurons, and lead to aberrant motility and visceral sensitization, inflammatory bowel disease should be considered in all patients with IBS symptoms. IBS criteria are met by more than 33% of patients with inflammatory bowel disease, but the proportion of patients with inflammatory bowel disease and overlapping IBS symptoms with alarm features is unclear [5].

The pragmatic question is how often inflammatory bowel disease is ultimately identified in patients with typical IBS symptoms who lack alarm features. A prospective U.S. study of more than 900 non-constipated patients with IBS and healthy controls receiving colonoscopy found inflammatory bowel disease in less than 1% of patients with IBS and none in the controls. This argues against routine colonoscopy in patients with typical IBS symptoms who lack concerning features. Noninvasive biomarkers may be more cost-effective than colonoscopy for inflammatory bowel disease screening [5; 129].

Fecal calprotectin, a biochemical assay for intestinal inflammation, is a cost-effective choice in inflammatory bowel disease screening, although 33% of patients with inflammatory bowel disease and IBS-like symptoms show negative results. C-reactive protein levels of <0.5 mg/dL or fecal calprotectin levels of <40 mcg/g confer a ≥1% risk of inflammatory bowel disease in patients with typical IBS symptoms [5; 130]. However, inflammatory bowel disease was found to develop two to three years after initial IBS diagnosis at rates far exceeding population norms, despite negative colonoscopy findings [31].

If inflammatory markers are mildly elevated but the probability of inflammatory bowel disease is low, testing should be repeated before performing colonoscopy (unless other indications for colonoscopy are present). Inflammatory markers are not useful in patients with constipation-predominant symptoms.

Bile Acids Diarrhea

As noted, perfusion of bile acids into the colon stimulates water and electrolyte secretion and accelerates transit. Evidence of bile acid malabsorption may be present in up to 33% of patients with IBS-D symptoms. Clinicians can empirically assess for bile acid malabsorption by initiating a bile acid sequestrant trial. Several tests can identify such malabsorption but are not widely available in the United States [5; 92].

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Dyssynergic Defecation

Dyssynergic defecation is an under-recognized, constipation-associated condition characterized by an inability to coordinate abdominal wall, anal sphincter, and pelvic floor muscles for normal defecation. Symptoms are non-specific and include abdominal pain, discomfort, and bloating. Intervention with biofeedback can improve bowel and abdominal symptoms. Thus, patients with medically refractory IBS-C symptoms should be referred to a specialist for evaluation of dyssynergia by digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging [131; 132; 133].

Laboratory Studies

A complete blood count is useful to rule out anemia or infection in patients with IBS symptoms. In the absence of alarm symptoms or suspicion of abnormalities that other laboratory testing can confirm, no other testing is needed for diagnosis. However, the presence of alarm criteria requires further testing specific to the index alarm finding—colonoscopy in most cases [3; 44].

Thyroid tests are not routinely indicated in all patients but can be ordered if clinically warranted. Stool analysis (for bacteria, parasites, and ova) may be useful if diarrhea is the main symptom, especially in patients recently living in developing countries where infectious diarrhea is prevalent.

Colonoscopy is indicated in the presence of alarm symptoms, family history of colorectal cancer, or persistent diarrhea that has failed empiric therapy. Biopsies of different segments of the colon may be required in patients with chronic diarrhea to rule out microscopic colitis. Colorectal cancer screening colonoscopy is indicated in patients 50 years of age or older (or 45 years of age or older in African Americans) in the absence of warning signs based on national recommendations.

With failure of empiric therapy, other diagnostic options in limited use include [3]:

- Scintigraphic evaluation (75SeHCAT test)
- Postprandial serum C4 (7a-hydroxy-4-cholesten-3-one)
- FGF19

Breath tests to rule out carbohydrate malabsorption may be useful in some patients with IBS symptoms and persistent diarrhea.

Alarm Features

Concerning features that may suggest organic disease require assessment. Although the presence of these features may identify patients with organic disease, most will have negative evaluation findings, and concerning features are valuable for their negative (not positive) predictive value. IBS can be confidently diagnosed in patients who meet symptom-based criteria and lack concerning features, because extensive diagnostic testing is infrequently positive. However, the perspective of IBS as a diagnosis of exclusion remains widespread, and many healthcare professionals are uncomfortable relying solely on symptom-based criteria for its diagnosis [5; 134].

Alarm criteria requiring further testing to rule out organicity include [3; 44]:

- Personal or family history of colorectal cancer, intestinal polyposis, inflammatory bowel disease, or celiac disease
- Symptom onset after 50 years of age
- Recent changes in bowel movement habit

Additional signs and symptoms that may suggest organicity are:

- Nocturnal symptoms
- Fever
- Anemia
- Unintended weight loss not explained by other causes
- Fecal blood in the absence of documented bleeding hemorrhoids or anal fissures
- Severe abdominal pain
- Palpable abdominal mass, visceromegalias, or abnormal digital rectal examination on physical exam

Psychosocial Assessment

As discussed, psychosocial factors influence physiologic functioning of the GI tract (including motility, sensitivity, and barrier function), mediate pain experience and symptom behavior of the patient, and impact treatment selection and clinical outcome [15]. This makes psychosocial assessment a vital part of the evaluation of patients with IBS symptoms.

Primary care clinicians and gastroenterologists can use psychosocial screening to identify patients at risk for refractory symptoms, poor treatment response, or low quality of life. When overt psychopathology or moderate-to-severe symptoms are absent, visceral-specific anxiety, catastrophizing, somatization, and quality of life can be assessed to determine if comprehensive evaluation by a health psychologist or psychiatrist is indicated [55].

Clinicians can include a brief psychosocial assessment for each patient with functional GI disorder, with the precondition that a satisfactory patient-clinician relationship is established earlier in the evaluation. A few specific questions on key psychosocial processes can be woven into routine history taking. If a patient asks about the relevance of this inquiry, a truthful response is, "I always ask my patients these questions as part of my initial assessment—it helps me determine the best way to help. The items may or may not apply to you." This psychosocial assessment will only be satisfactory if the patient is able to speak freely, which requires privacy, a lack of judgment or stigma, and sufficient time. Sensitive areas of discussion include abuse history, depressed mood, possible suicidal thoughts, and the nature of intimate relationships. These may require a second appointment for a full assessment.

The clinician should provide feedback about results of the overall evaluation and discuss treatment options, which can include medical and psychosocial approaches [55]. Consider referring patients with severe symptoms, previous treatment failure, poor treatment adherence, or marked disability to a clinician with special training in psychosocial assessment [55].

Changes in Symptom Severity, Frequency, or Treatment Response

When a plausible explanation for a change in symptoms or treatment response in patients with an established IBS diagnosis is lacking, it is important to assess for an underlying causal condition. Following a new physical examination, time since the last diagnostic workup should be considered. Changes in epidemiologic characteristics of the family should be assessed and recorded. IBS can include phases where symptom severity changes, and patients may perceive they have an inadequately explored organic disease. With these considerations, additional diagnostic testing should generally be limited to the presence of alarm symptoms or signs [44].

TREATMENT

Treatment of IBS should be directed at the dominant symptom type and severity [3]. In this section, interventions for all IBS subtypes (e.g., lifestyle, psychologic interventions, dietary, antidepressants) are discussed first, followed by therapeutic options specific to dominant symptom type (i.e., constipation, diarrhea, abdominal pain).

THE THERAPEUTIC RELATIONSHIP AND TREATMENT ADHERENCE

IBS treatment begins by explaining the condition, providing reassurance of the benign natural history, and educating the patient about the benefits and safety of diagnostic tests and treatment options [3]. Clinical experience suggests that providing the patient with a plausible disease model (e.g., "brain-gut disorder") and accepting patient symptoms and distress as real instead of dismissing them as "psychosomatic" helps to establish a positive therapeutic relationship. An approach that acknowledges the disease, educates the patient about the disease, and reassures the patient may improve treatment outcomes [125].

Steps to Enhance the Therapeutic Relationship

Healthcare professionals who repeatedly perform unnecessary diagnostic studies to rule out pathologic disease, dismiss patient concerns, or do not collaborate effectively in patient care can promote a vicious cycle of symptom anxiety and health care seeking [2]. Effective provider-patient relationships can improve patient satisfaction, treatment adherence, symptom reduction, and other health outcomes. General guidelines can help optimize this relationship with patients with IBS [2]. Patient satisfaction is based on a perception of healthcare providers' humaneness, technical competence, interest in psychosocial factors, and provision of relevant health information; over-emphasis on biomedical issues can have a negative effect. In addition to verbal communication, engagement involves nonverbal communication such as good eye contact, affirmative nods, a gentle tone of voice, close interpersonal distance, and creation of a partner-like interaction.

It is important to conduct the patient history using a nondirective, nonjudgmental, patient-centered approach. This involves active listening and asking questions based on the patient's thoughts, feelings, and experiences, instead of a preset agenda of questions. A good first step is to inquire regarding the reason for the appointment. Immediate reasons for a patient's visit may include [135]:

- New or exacerbating factors (e.g., dietary change, concurrent medical disorder, side effects of new medication)
- Personal concern about a serious disease (e.g., recent family death)
- Personal or family stressors (e.g., recent or anniversary of death or other major loss, abuse event, or history)
- Worsening or development of psychiatric comorbidity (e.g., depression, anxiety)
- Impairment in daily function (e.g., recent inability to work or socialize)

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- A hidden agenda (e.g., opioid or laxative abuse, pending litigation, disability claims)

The next step is a careful physical examination and investigation. Although this obviously assists in diagnosis and assessment of new complaints, a well-conducted physical examination itself has therapeutic value [136].

Determine patient concerns and understanding of their illness and provide an explanation of the disorder that takes into consideration patient beliefs. When possible, provide a link between stressors and symptoms consistent with patient beliefs. Many patients are unable or unwilling to associate stressors with illness, but most understand the impact of illness-related stress on their emotional state.

Patients should be given options and be involved in treatment decision-making. When possible, treatment recommendations should be consistent with patient interests. Identifying and responding realistically to the patient's expectations for improvement can strengthen rapport. However, it is also important to set consistent limits, especially as related to pain management and opioid use.

Finally, patients should be reassured that care will continue and that they should expect an ongoing relationship. It can help to let patients know that many treatment options can be explored to help control IBS.

Steps to Enhance Therapy Adherence

Adherence is essential for the effectiveness of prescribed therapy, including dietary measures, lifestyle changes, and pharmacotherapy. A therapy regimen alone is often insufficient unless the patient understands and accepts the approach and agrees to follow it. This highlights the importance of a trust-based therapeutic relationship that promotes cooperation and empowers patient participation in decision-making and responsibility for self-care [44].

In addition to consideration of best-available therapeutic options, the following measures can facilitate patient engagement and adherence [44]:

- Prescribing therapeutic regimens with the least number of effective daily doses
- Providing simple, easy-to-understand written information and reminders
- Providing adherence "diaries" to the patient
- Including information on the pathophysiology of the condition (according to education level) in patient education
- Including family members and caregivers who can positively reinforce patient behavior

The importance of regularity should be stressed for constipation management. Some patients only use medication intermittently for exacerbations, which is less effective. Other patients avoid laxatives altogether due to false beliefs that laxatives induce dependence or may be ultimately dangerous.

LIFESTYLE MODIFICATION

Limited data suggest that IBS symptoms may be improved by lifestyle modifications that include exercise, stress reduction, and good sleep habits [3]. Greater evidence supports dietary interventions.

Increased physical activity in patients with IBS has been found to improve GI symptoms and help protect against symptom deterioration [137]. In one study, exercise for 12 weeks significantly improved symptoms and extra-intestinal manifestations of IBS in 102 patients, while another 12-week exercise trial significantly improved constipation but not other IBS symptoms [137; 138]. In adolescent patients with IBS, one hour of yoga daily for four weeks significantly improved symptoms [139].

Other recommendations that may improve IBS symptoms include [118]:

- Judicious water intake (particularly for patients with IBS-C)
- Caffeine avoidance
- Legume avoidance

The National Collaborating Centre for Nursing and Supportive Care recommends drinking at least eight cups of fluid per day, especially water or other non-caffeinated drinks, for example herbal teas. Tea and coffee should be limited to three cups per day.

(https://guideline.gov/summaries/summary/49049. Last accessed November 22, 2016.)

Level of Evidence: Consensus Statement/Expert Opinion

Poor sleep quality is relatively common in patients with IBS, and studies have shown that sleep difficulties predict next day exacerbations, fatigue, and depressed mood [140]. Researchers have suggested autonomic nervous system dysregulation may be a common factor underlying both IBS symptoms and sleep disturbances. As such, patients should try to get enough sleep (at least seven to eight hours per night) and should keep good sleep hygiene (e.g., avoidance of electronics in the bedroom, going to sleep and rising at the same time every day).

Perceived high stress levels can also increase the risk for IBS exacerbations and increased symptoms [141]. Avoidance of high-stress situations, when possible, is recommended. However, psychologic interventions may also help provide effective stress-coping strategies.

Dietary Interventions

Dietary and Supplemental Fiber

Dietary fiber supplementation has long been the foundation of treatment in all patients with IBS, and IBS guidelines have consistently recommended dietary fiber by increasing fiber-rich foods or adding soluble fiber (usually *Psyllium* seed, but polycarbophil compounds may produce less flatulence) [44; 118].

While evidence indicates soluble fiber has modest benefits in reducing global IBS symptoms in patients with IBS-C with mild constipation, it can worsen abdominal pain and distension and has little benefit in patients with IBS-D. Eating a fiber-rich diet can worsen symptoms of abdominal pain and distension in all patients with IBS; wheat bran, in particular, can exacerbate problems of abdominal distention, abdominal pain, and flatulence and should be avoided [3; 5; 44]. If fiber is indicated, initiate soluble fiber at a very low dose and gradually increase to total daily intake of 20–30 g [5].

Gluten Restriction

Dietary restriction of gluten may improve symptoms in some patients with IBS. Two small prospective studies in patients with IBS, in which celiac disease was carefully excluded, demonstrated global symptom improvement [97; 98].

Dietary FODMAP Restriction

Numerous short-chain carbohydrates, including lactose, fructose, and polyols, can provoke IBS symptoms [84; 143; 144]. These short-chain fermentable carbohydrates are collectively termed FODMAPs, and there is direct evidence (using magnetic resonance imaging) that some FODMAPs may induce IBS symptoms via increased small bowel water content or increased colonic gas production [84; 143; 144].

FODMAPs promote poor absorption in the small bowel and rapid fermentation in the colon. FODMAP is an acronym for [87]:

- **F**ermentable
- **O**ligosaccharides (e.g., fructo-oligosaccharides, galacto-oligosaccharides, fructans, raffinose, inulin)
- **D**isaccharides (e.g., lactose, sucrose)
- **M**onosaccharides (e.g., fructose)
- **A**ND
- **P**olyhydric alcohols (e.g., sorbitol, mannitol, xylitol, maltitol)

The most common sources of FODMAPs in the western diet are wheat, onions, fruit in which fructose exceeds glucose (e.g., apples, pears), and processed food. Dairy products are important in those with lactose malabsorption.

True lactose intolerance may induce IBS-like symptoms, but only with relatively high lactose loads (20 g) that are easily avoidable. Psychologic factors have a major influence on symptomatic responses to lactose intake [145; 146].

Fructose is a monosaccharide abundantly present in many processed foods. The small bowel has a relatively limited absorptive capacity that particularly affects free fructose—the fraction in excess of the glucose that facilitates fructose absorption. High fructose loading can induce symptoms even in healthy individuals.

Polyols such as sorbitol, mannitol, and xylitol are naturally present in many fruits and vegetables and are added as artificial sweeteners to processed food products and pharmaceuticals. Polyols tend to induce bowel discharges from their stimulant effect on intestinal motility.

Dietary FODMAP restriction is associated with reduced fermentation and significant symptom improvement in some patients with IBS. In a randomized, controlled, single-blind cross-over trial, patients with IBS who had not previously tried dietary manipulation reported significant reduction in overall GI symptom scores compared with those on a standard Australian diet [87]. The complexity of the FODMAP diet makes implementation difficult, but this may be overcome by excluding only the major sources of FODMAPs (e.g., wheat, onions, dairy), avoiding processed food, and not focusing on items with small specific contribution [87]. Adding a gluten-free diet to patients with IBS already on a low FODMAP diet does not appear to offer additional benefit [147; 148; 149].

Probiotics

Manipulation of intestinal microbiota has promise as a potential therapy for gut dysbiosis to ameliorate symptoms of IBS and restore health. The concept of probiotics is more than 100 years old, and modern research methods are establishing empiric support for the perceived benefits of probiotic bacteria, which mainly include *Lactobacillus* and *Bifidobacterium* species [150].

Probiotics are live bacteria, selected on the basis of ability to survive in the GI tract, adhere to intestinal epithelium, and modulate intestinal flora. Probiotics promote gut health, prevent infection from intestinal pathogens, and prevent bacterial translocation by inhibiting potentially pathogenic bacteria, modulating or stimulating immune response, promoting immune cell proliferation, enhancing phagocyte activity, and increasing production of immunoglobulin A [44; 151].

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The therapeutic effects for patients with IBS may occur through multiple mechanisms. *Bifidobacterium infantis* 35624 led to significant improvements in abdominal pain/discomfort, bloating/distention, and/or bowel movement difficulty (vs. placebo) in two randomized controlled trials of patients with IBS [152; 153]. A 2016 meta-analysis that included 43 clinical trials using different products found probiotics to offer benefits for global IBS symptoms, pain, bloating, and flatulence. However, the overall usefulness of these findings has been limited by use of different IBS diagnostic criteria and symptom measurement methods in published randomized controlled trials [154].

Prebiotics/Synbiotics

Prebiotics are food products that promote proliferation of bifidobacteria and other species potentially associated with anti-inflammatory effects (e.g., oligofructose, inulin, galactooligosaccharides, lactulose, breast milk oligosaccharides). Prebiotics do not seem particularly effective in IBS, possibly due to fermentation products that may themselves stimulate IBS symptoms. Trials for prebiotics are few in number, and no definite conclusions can be drawn [84].

Synbiotics aim to simultaneously produce synergic pro- and prebiotic effects, but evidence has not substantiated their theoretical benefits in IBS. Further evidence is required to establish the role of prebiotics or synbiotics in IBS [84].

PSYCHOLOGIC INTERVENTIONS

As discussed, psychologic factors can amplify pain perception and experience, and strong empirical evidence confirms that pain experience is powerfully influenced by pain catastrophizing, fear avoidance behavior, self-efficacy, lack of perceived control, and passive pain coping. Other psychosocial research has found that depression and anxiety mediate the effect of pain on impaired function and that trauma history can negatively influence pain experience, pain and stress coping, and the clinician-patient relationship. This all supports the utility of psychologic interventions in IBS management [62; 155; 156].

Psychologic interventions address the cognitive-affective and psychosocial variables that interact with, reinforce, and perpetuate the physiologic factors that are involved in symptom expression, symptom severity, and impact of the disease on other health outcomes (e.g., quality of life, health care use) [55].

Cognitive-Behavioral Therapy

CBT refers to a family of psychologic treatments rather than a specific technique. CBT is derived from behavior theories that focus on learning processes and cognitive theories that emphasize faulty cognitions or thinking processes. These same learning processes are used to help patients gain control and reduce symptoms of IBS. Cognitive theory views external events, cognitions, and behavior as interactive and bidirectional, with primary emphasis on how patients process information about their environment, self, and the future. Cognitive factors, especially the way people interpret or think about stressful events, can intensify the impact of events on patient response. Emotional, physiologic, and behavioral responses to life events will be problematic to the extent that thought processes are faulty. Clinically modifying patient thinking can change behavior and emotional and physical well-being. Cognitive changes can occur by teaching patients to systematically identify cognitive errors generated by automatic thinking, or by providing experiential learning that systematically exposes patients to the situations that cause discomfort [55; 157].

Unlike traditional, insight-oriented "talk therapy," which identifies the root causes of a problem, CBT focuses on teaching people how to control their current problems by identifying the thoughts and behaviors that are maintaining them. CBT requires active patient participation during and between sessions and patient responsibility for learning symptom self-management skills. With IBS, CBT can include a combination of techniques such as self-monitoring, cognitive restructuring, problem solving, exposure, and relaxation methods [55].

Self-Monitoring

Self-monitoring is the ongoing, real-time recording of problem behaviors. In IBS, the focus of self-monitoring is internal and external triggers and the thoughts, somatic sensations, and feelings that usually accompany flare-ups. Self-monitoring provides clinically relevant information with which to structure treatment and serves as a useful therapeutic strategy by increasing patient awareness of triggers and contributing factors [55].

Cognitive Strategies

Cognitive strategies are designed to modify thinking errors that bias information processing (e.g., tendencies to overestimate risk and magnitude of threat or underestimate one's ability to cope with adversity). These self-defeating beliefs are clinically important because they are believed to moderate excessive stress experiences. Negative beliefs are identified, and the patient works with the healthcare provider to challenge and dispute them. This involves examining the accuracy of beliefs in light of available evidence and replacing biased beliefs with more logical and constructive cognitions [55].

Problem Solving

Problem solving refers to an ability to define problems, identify solutions, and verify their effectiveness once implemented. The intervention is rooted in the problem-solving model of stress, which acknowledges that a causal relationship exists between health and stressors. Using this model, the health or mental health professional teaches patients how to effectively apply the steps of problem solving to actively cope with stress [55; 158].

Relaxation Procedures

Various relaxation techniques are effective in managing IBS symptoms, and relaxation procedures have long been a staple of psychologic treatments for functional GI disorders. These techniques, including progressive muscle relaxation, breath work, and meditation, are designed to directly modify autonomic arousal believed to aggravate GI symptoms [159].

Progressive muscle relaxation training involves systematically tensing and relaxing selected muscle groups throughout the body, from forehead to feet. This exercise helps patients dampen physiologic arousal and achieve a sense of mastery of physiologic self-control over previously uncontrollable and unpredictable symptoms [55; 160].

In breathing retraining, the patient is taught to take slow, deep breaths and focus on bodily sensations during exhalation. This technique is based on the idea that patients with stress-related physical ailments develop inefficient respiratory patterns (e.g., shallow chest breathing), which, if chronic, can intensify physiologic arousal and increase somatic complaints [55; 161].

Meditation is a self-directed practice that can emphasize focused breathing and mindfulness. Mindfulness is defined as purposefully paying attention in the moment without judgement. This nonjudgmental acceptance of thought processes allows the practitioner to achieve a state of calmness, physical relaxation, and psychologic balance. In mindfulness meditation for IBS, the patient disengages him/herself from the ruminative thoughts considered core aspects of pain and suffering by developing a nonreactive, objective, present-focused approach to internal experiences and external events as they occur [55; 162]. Small studies have indicated that engagement in a mindfulness-based stress reduction program can ameliorate IBS symptoms, reduce stress, and improve patients' quality of life, with continued improvements evident after six months [163].

Hypnosis

In hypnosis, a therapist typically induces a trance-like state of deep relaxation and/or concentration using strategically worded verbal cues suggestive of changes in sensations, perceptions, thoughts, or behavior. Most hypnotic suggestions are designed to elicit feelings of improved relaxation, calmness, and well-being. Hypnotic suggestions in IBS are "gut directed," meaning suggestions are conveyed that are incompatible with aversive visceral sensation. Hypnosis might include a suggestion to feel a sense of warmth and comfort spreading throughout the abdominal area [55; 164]. Hypnosis has shown some benefit in decreasing IBS symptoms in adults [165].

Exposure Therapy

Exposure therapy is designed to reduce catastrophic beliefs about IBS symptoms, hypervigilance for IBS symptoms, fear of IBS symptoms, and/or excessive avoidance of unpleasant visceral sensations or situations by helping patients confront maladaptive thoughts and beliefs in a systematic manner. Exposure can include interoceptive cue exposure (i.e., the patient repeatedly provokes unpleasant sensations) or situational/in vivo exposure (i.e., feared situations or activities are confronted). Through exposure treatments, patients learn the stimuli that led to fear and avoidance are neither dangerous nor intolerable and that fear will subside without resorting to avoidance, a behavior that reinforces fear and hypervigilance in the long-term [166; 167]. In an experimental study of 13 patients with IBS, 70% improved on measures of GI symptoms, pain catastrophizing, and quality of life following 12 sessions of exposure therapy [168].

Efficacy of Psychologic Treatments

Two meta-analyses have concluded that psychologic therapies, as a class of treatments, are at least moderately effective for relieving symptoms of IBS when compared with a pooled group of control conditions. The Internet has been used as a treatment delivery platform to give a larger proportion of patients with functional GI disorder access to, and engagement in, therapy than would have been feasible through clinic-based treatment [169; 170; 171].

Another meta-analysis investigated the duration of psychologic therapy effects in reducing GI symptoms in patients with IBS. Forty-one trials recording data from 2,290 subjects (1,183 assigned to therapy, 1,107 assigned to a control condition) were analyzed. Compared with a mixed group of control conditions, psychologic therapies had a medium effect size on reducing GI symptom severity immediately after treatment. On average, subjects receiving psychotherapy had greater post-therapy reduction in GI symptoms than individuals assigned to a control condition. After short-term follow-up (1 to 6 months after treatment) and long-term follow-up (6 to 12 months after treatment), this effect remained significant and medium in magnitude [172].

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ANTIDEPRESSANT MEDICATIONS

Although antidepressants are used extensively in the treatment of IBS and other functional GI disorders, the accumulated clinical experience, lack of other effective treatment options, and evidence from other functional somatic syndromes such as fibromyalgia make these agents viable options for treating pain and improving quality of life in patients with IBS. In general, antidepressant medications should be reserved for patients with moderate-to-severe symptoms with significant impairment of quality of life for which other first-line treatments have not been sufficiently effective [173; 174].

Choice of Agent

The choice of antidepressant agent is determined by the patient's predominant symptoms, disease severity, presence of comorbid anxiety or depression, prior experience with medications in the same class, and patient and prescriber preference. The three broad antidepressant classes most often used in IBS are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-noradrenalin reuptake inhibitors (SNRIs) [55].

Tricyclic Antidepressants

TCAs such as amitriptyline, imipramine, desipramine, doxepin, and trimipramine are the most widely used psychotropic agents for treating neuropathic (e.g., postherpetic neuralgia, diabetic neuropathy) and functional (e.g., fibromyalgia) pain syndromes. Their analgesic effect is thought to be independent of antidepressant mechanisms and effects because TCAs can benefit patients with diverse pain syndromes in whom psychopathology is modest or absent and because they are often effective for pain at low (sub-psychiatric) doses [106; 175; 176].

In general, TCAs are the first antidepressant choice for pain in non-constipated patients with IBS due to their dual mechanism of action (serotonin and norepinephrine reuptake inhibition). Nortriptyline or desipramine is better tolerated than amitriptyline or imipramine due to fewer anti-histaminergic and anti-cholinergic effects. The usual starting dose is 25–50 mg at night and can be titrated up as needed up to about 150 mg/day, while carefully monitoring side effects and/or blood levels. Typically, lower doses than the full antidepressant dose are effective for visceral pain if no psychiatric comorbidity is present [55].

In one study, amitriptyline 10 mg/day in patients with IBS-D significantly improved overall IBS symptoms, reduced frequency of loose stool and feelings of incomplete defecation, and led to complete response (remission) in some [165; 177].

SSRIs

SSRIs are less effective for pain and are less commonly prescribed as monotherapy for IBS. Review papers have arrived at different conclusions concerning SSRI utility in IBS treatment, with some authors concluding no convincing evidence has been reported for functional GI disorders and others reporting beneficial effects for overall IBS symptoms [3; 93; 165].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Gastroenterological Association (AGA) suggests against using selective serotonin reuptake inhibitors for patients with IBS.

(https://guideline.gov/summaries/summary/49122. Last accessed November 22, 2016.)

Strength of Recommendation/Level of Evidence: Conditional recommendation/low-quality evidence

However, SSRIs are considered useful in patients with high levels of anxiety that contribute directly to IBS exacerbations and symptom severity. SSRIs and SNRIs have a more narrow therapeutic range, and therefore, the doses used for the treatment of pain are closer to the doses used for mood and anxiety disorders. Starting doses are usually within the lower range of the psychiatric dose (e.g., citalopram 20 mg or duloxetine 30 mg) and titrated up as needed [173; 174; 178].

A systematic review of SSRIs found benefits over placebo for overall IBS symptoms. Several clinical characteristics, including the predominant stool complaint, presence of insomnia, or comorbid anxiety, can influence antidepressant selection for individual patients with IBS [165].

SNRIs and Other Psychotropics

For SNRIs, especially venlafaxine, higher doses (≥225 mg) are usually required to attain effective analgesia because the noradrenergic mechanism of action is only evident at these doses. If nausea and weight loss are concerns, the addition of a low dose (15–30 mg) of mirtazapine can be helpful.

Atypical antipsychotics, such as quetiapine, are only recommended for patients with severe, refractory IBS, especially if severe anxiety and sleep disturbances are also present and the patient has failed to respond to other centrally acting agents. A low starting dose of 25–50 mg is recommended and can be titrated up as required [173; 174].

Augmentation of Therapy

Augmentation, or the use of a combination of drugs from different classes in submaximal doses instead of one drug at a maximal dose, is common in psychiatry and is increasingly used in the treatment of functional GI disorders. Examples of augmentation include adding buspirone to an SSRI, TCA, or SNRI to enhance therapeutic effect, or adding a low-dose antipsychotic (e.g., quetiapine) to a TCA or SNRI to reduce pain and anxiety and improve sleep. If there is a component of abdominal wall pain associated with the GI pain, pregabalin or gabapentin can be added to a TCA or SNRI [173; 174].

Combination Antidepressant and Psychologic Treatment

Combining antidepressants with psychologic therapy can be an effective augmentation strategy. Antidepressants can improve pain and vegetative depression symptoms, and psychologic therapy improves higher cortical functioning, including coping, reappraising maladaptive cognitions, and adapting to previous losses and trauma. Psychotherapy can optimize medication adherence, while antidepressants can sufficiently increase physical and psychic energy to improve the level of engagement in therapy. The difference in effect size with combined treatment can exceed 50% compared to either treatment alone [106; 179; 180; 181].

Although drugs work faster and are readily available, psychologic treatments have several advantages. They are safe and effective, their effects persist beyond the duration of the treatment, and they may be more cost-effective. Potential barriers to the use of psychologic approaches in the treatment of IBS are a longer treatment duration, the need for patient motivation, and limited availability and access to a mental health professionals trained in IBS treatment [55; 182].

Adherence

Careful patient selection, initiation at a low dose with gradual escalation, monitoring for side effects, and a good patient-clinician relationship are important for medication adherence and, by extension, therapeutic response. In particular, eliciting and addressing any potential concerns/barriers to taking psychotropic medications for IBS, discussing potential side effects, setting realistic expectations, and involving the patient in decision making result in improved adherence [55; 174].

DIARRHEA-PREDOMINANT IBS

Chronic diarrhea in IBS is usually associated with a non-infectious cause, and symptomatic drug therapy is indicated when definitive treatment is unavailable. Pharmacologic agents for IBS-D are diverse in mechanism of action, and prescribing these agents requires proper diagnosis and differential diagnosis in order to ensure effectiveness [183].

Mu Opioid Receptor Agonists

Loperamide is a synthetic, peripheral-acting mu opioid receptor agonist with limited ability to penetrate the blood-brain barrier (and therefore limited abuse potential). It decreases peristaltic activity, inhibits secretion, increases water and ion absorption, reduces colonic transit, and increases resting anal sphincter tone. This results in reduced fluid and electrolyte loss and improved stool consistency [93; 183]. Loperamide is available over the counter.

Diphenoxylate is another mu opioid receptor agonist, but unlike loperamide, it can cross the blood-brain barrier and is therefore combined with atropine to reduce abuse potential. Both of these agents are effective in reducing diarrhea in general, but research for the treatment of IBS-D is not well developed [93].

Several small randomized controlled trials of loperamide in IBS-D have shown reduced bowel frequency and improvements in stool consistency, urgency, and subjective overall response. Pain outcomes were mixed, with reduced pain intensity or increased nightly abdominal pain both reported in separate trials [3; 183]. However, loperamide may improve quality of life by allowing the planning of trips and socializing, which anxious patients with IBS-D often avoid for fear of fecal urgency or even incontinence [87].

Adverse effects with loperamide or diphenoxylate are rare, but include bladder dysfunction, glaucoma, and tachycardia. These may be more likely with diphenoxylate due to the atropine constituent [93].

Bile Acid Binders (Sequestrants)

As discussed, the underlying pathophysiology in some patients with IBS-D is bile acid perfusion into the colon, and bile acid sequestrants are used as treatment for these patients. Cholestyramine is the agent generally considered first-line treatment for IBS-D with bile acid diarrhea [3; 183]. Other options include colesevelam and colestipol. Cholestyramine granules are often poorly tolerated due to poor taste and adherence to the teeth [93].

Nonabsorbable Antibiotics

Antibiotics have traditionally been used as adjunctive IBS treatment. However, they are associated with systemic side effects, and there are concerns of promoting antibiotic-resistant microbes [184].

Rifaximin is a synthetic antibiotic derived from rifamycin and has anti-microbial activity against Gram-positive, Gram-negative, aerobic, and anaerobic bacteria. It is not absorbed by the intestinal mucosa, allowing intraluminal activity without systemic circulation and effects [185]. Rifaximin targets the GI tract to reduce gas-producing bacteria and alter the predominant bacterial species; it may also reduce mucosal inflammation and visceral hypersensitivity [93].

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In 2015, rifaximin was approved by the FDA for the treatment of IBS-D in adults [93]. Clinical trials have demonstrated that rifaximin improved IBS-associated symptoms of bloating, flatulence, stool consistency, and abdominal pain. The drug showed a side-effect profile similar to placebo. Some patients experience relief of IBS symptoms after a course of rifaximin, while others require retreatment at the same dosage [184; 186]. Improvement in symptoms relative to placebo showed a gradual reduction over time, but significant improvement persisted for 10 weeks after the treatment course [3]. The usual dosage is 550 mg three times per day for 14 days [93].

The AGA suggests using rifaximin (over no drug treatment) in patients with IBS-D.

(https://guideline.gov/summaries/summary/49122. Last accessed November 22, 2016.)

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

Clinical experience suggests that many rifaximin responders eventually develop recurrent IBS symptoms. Data from re-treatment patients suggest that second and third courses produce efficacy similar to the initial course. The role of other antibiotics in IBS treatment remains unknown, but antimicrobial resistance with repeated courses of systemically absorbed antibiotics is a concern [5]. Overall, rifaximin appears to be safe and beneficial as a management option for IBS-D, although optimal dosing and treatment duration and potential resistance require further study [184; 186].

5-HT3 Receptor Antagonists

Serotonin (5-HT) plays an important physiologic and pathophysiologic role in regulating GI function [187]. As such, 5-HT3 receptor antagonists (5-HT3RAs) can be effective treatment for IBS-D by slowing transit, reducing bowel frequency, normalizing stool consistency, and reducing urgency—a key symptom that impairs quality of life in patients with IBS-D [87].

Randomized controlled trials have found the potent, selective 5-HT3RAs alosetron and cilansetron may be effective in the treatment of IBS-D. However, alosetron was voluntarily withdrawn due to postmarketing reports of ischemic colitis (a potentially serious class-wide adverse event) and complications of constipation, while cilansetron was never marketed [187]. Alosetron was subsequently reintroduced to market and is currently available for women with severe IBS-D refractory to conventional therapy under an FDA Risk Evaluation and Mitigation Strategy program [188]. Alosetron is effective at relieving pain and reducing stool frequency and rectal urgency in women with IBS-D [3].

The 5-HT3RA ramosetron has also been studied as IBS-D therapy but has not received FDA approval. Ramosetron reduces defecation induced by corticotropin-releasing hormone and inhibited colonic nociception in preclinical studies. In randomized controlled trials of patients with IBS-D, ramosetron increased patient rates of global IBS symptom relief. In trials limited to male patients with IBS-D, ramosetron was as effective as mebeverine (an agent approved outside the United States) in improving stool consistency, relieving abdominal pain/discomfort, and improving health-related quality of life. Ramosetron shows a lower incidence of constipation versus other 5-HT3RAs and has not been associated with ischemic colitis [187]. In data stratified by sex, women reported significant relief of IBS symptoms only after two months, while men reported significant relief of IBS symptoms at all time points. Reasons for these differences are unknown [21].

The much less potent 5-HT3RA ondansetron (4 mg/day, range 2–6 mg/day) has also been found highly effective at improving stool consistency, reducing stool frequency, and reducing urgency. In one study, 70% with ondansetron (versus 16% with placebo) reported adequate IBS-D symptom relief. Worth noting is that ondansetron has been used for more than two decades without reports of ischemic colitis and has an excellent safety record; these features are important for IBS therapy selection [87].

Eluxadoline

Eluxadoline was approved in 2015 for IBS-D treatment in adults. This drug has therapeutic activity as a mixed mu-opioid receptor agonist and delta-opioid receptor antagonist, a novel mechanism of action developed to control GI function and decrease GI pain while mitigating the constipating effects of unopposed mu receptor agonist activity [21; 87].

FDA approval of eluxadoline was based on two multi-center, multi-national randomized controlled trials with 2,426 patients with IBS-D receiving twice-daily eluxadoline (75 mg or 100 mg) or placebo for 26 weeks. Therapeutic response was defined as concurrent improvement in diarrhea (using the BSFS) and abdominal pain. In both trials, the proportion of patients with reduced abdominal pain and improved stool consistency was significantly higher with eluxadoline than placebo, at both doses. Eluxadoline reduced IBS-D symptoms in men and women, and efficacy was sustained over six months with the 100-mg, twice daily dose. The most common adverse events were nausea (8%), constipation (8%), and abdominal pain (5.0%) [189; 190].

A small but definite risk (0.3%) of acute pancreatitis resulted from sphincter of Oddi spasm; all patients who developed this adverse effect had a history of cholecystectomy or significant ethanol consumption. Eluxadoline should be used at the lower dose with careful monitoring in these patients, who should also receive education of the risk [3; 87].

Mast Cell Stabilizers

In patients with IBS-D, jejunal mucosal biopsies have shown mast cell activation and hyperplasia, providing the theoretical basis for possible benefits with mast cell stabilizers [191]. Disodium cromoglycate and ketotifen act primarily by stabilizing the plasma membrane of mast cells and have been evaluated in the treatment of IBS-D [93].

In a six-month trial of disodium cromoglycate for IBS-D, jejunal biopsies showed reduced release of tryptase and reduced expression of toll-like receptor 2 and 4, and patients showed clinical improvement of bowel function [192]. In an earlier trial of patients with IBS-D with food intolerance, disodium cromoglycate (250 mg, four times per day) plus exclusion diet was associated with prolonged symptomatic benefit compared with exclusion diet alone [193; 194].

Ketotifen is a mast cell stabilizer with antihistamine properties that showed substantial improvement in patients with IBS despite no effect on mast cell parameters [195]. Further research suggests the effects mediated by histamine-blocking properties, and ketotifen may also be used in the treatment of abdominal pain-predominant IBS.

Muscarinic Type 3 Receptor Antagonists

Muscarinic type 3 (M3) receptor antagonists have beneficial effects in chronic diarrhea that include delayed small bowel and colonic transit, reduced rectal sensitivity, and reduced enterocyte secretion [93]. Preliminary evidence suggests greatest benefit with otilonium in IBS-D, with benefits shown in increased sensory thresholds to colonic volume and pressure, and reduction in abdominal pain [93; 196]. Otilonium is investigational in the United States.

Glutamine

Patients with IBS-D have increased gut permeability, and symptomatic patients with IBS have decreased intestinal glutamine synthetase levels. In a preliminary report of a placebo-controlled trial of 10 g glutamine three times per day in 61 patients, the glutamine arm was associated with improved abdominal pain, bloating, and diarrhea and restored intestinal permeability [93; 197].

Summary

During clinical development, rifaximin and eluxadoline demonstrated significant improvement in IBS-D endpoints versus placebo. In the absence of comparative randomized controlled trials, direct comparisons of alosetron, rifaximin, and eluxadoline efficacy cannot be made, but general efficacy estimates suggest similar and responses using outcome measures of adequate relief and combined improvements in abdominal pain/stool form. Clinical use of these agents is suggested to follow a sequential scheme that considers patient symptoms and severity, prior medical history, mode of action, cost, availability, managed care coverage, and adverse event profiles [198].

CONSTIPATION-PREDOMINANT IBS

Constipation is one of the most common functional bowel disorder symptoms encountered in primary care and specialty practices. IBS-C and other disorders of chronic constipation are associated with significant medical costs and a negative impact on quality of life [199].

Laxatives

Osmotic laxatives contain nonabsorbable ions or molecules that retain water in the bowel lumen. Polyethylene glycol (PEG), lactulose, and magnesium salts are most commonly used. Osmotic laxatives are generally useful to treat constipation but can promote or worsen abdominal pain and distension in IBS and are not recommended [44].

Stimulant laxatives promote water and electrolyte secretion in the colon or induce colonic peristalsis. They include diphenylmethanes (phenolphthalein, bisacodyl, sodium picosulfate) and anthraquinones (*Senna*, bearberry, *Aloe vera*). While useful for constipation, they can worsen abdominal pain and distension in patients with IBS [44]. In patients with IBS-C, a randomized controlled trial of PEG vs. placebo found stool frequency, stool consistency, and straining were improved, but abdominal pain and bloating were unimproved during the four-week study [142].

Secretagogues

Secretagogues act through different pharmacologic mechanisms to stimulate chloride release into the intestinal lumen, which stimulates intestinal fluid secretion to counteract constipation symptoms in IBS-C [200]. The most commonly used agents are lubiprostone and linaclotide.

Lubiprostone

Lubiprostone is a prostaglandin-derived fatty acid that activates intraluminal chloride channels and chloride ion secretion. This leads to a passive influx of water and sodium, which increases intestinal peristalsis and colonic laxation and decreases intestinal stool transit time. Lubiprostone does not affect pain thresholds during rectal distension [5; 87].

In patients with IBS-C, lubiprostone has proven effective in reducing constipation symptoms, but reduction of abdominal pain is much more modest (7% greater than placebo) and generally develops after one month of therapy. Side effects mostly involve mild-to-moderate nausea and diarrhea, and lubiprostone should be taken with food to limit dose-dependent nausea [3; 5].

Lubiprostone is approved for the treatment of chronic constipation and opioid-induced constipation for men and women at 24 mcg twice daily, and for IBS-C in women at 8 mcg twice daily. No dosage adjustment is required in patients with impaired renal function [44]. Additional research may expand its clinical use [87; 199].

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Linaclotide

Linaclotide binds and activates guanylate cyclase C (GC-C) receptors expressed locally on the luminal surface of intestinal epithelium. GC-C receptor activation increases cyclic guanosine monophosphate concentrations, which activates the cystic fibrosis transmembrane conductance regulator to stimulate secretion of chloride and bicarbonate into the intestinal lumen. This leads to increased intestinal fluid and accelerated stool transit [87; 189].

In patients with IBS-C, randomized controlled trials have shown highly similar results across studies. Improvements in constipation, abdominal pain, discomfort or bloating, and stool consistency were 15% to 30% greater compared with placebo. These benefits persisted for 26 weeks. Diarrhea, the most commonly reported adverse event, occurred in 19.7% of participants and led to drug discontinuation in 4.5%. Efficacy and safety were similar in elderly and middle-aged adults [44; 87; 186]. Patients should take linaclotide (290 mcg) 30 to 60 minutes before breakfast to minimize the chance of diarrhea [5].

The AGA recommends using linaclotide (over no drug treatment) in patients with IBS-C.

(https://guideline.gov/summaries/summary/49122. Last accessed November 22, 2016.)

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

While lubiprostone and linaclotide led to improvements in stool frequency, constipation severity, and abdominal pain/discomfort in IBS-C, the relatively low response rates, higher costs, and adverse effects generally limit these agents to second-line therapy in IBS-C [201].

5-HT4 Receptor Agonists

5-HT4 receptors are expressed on enteric neurons and in cardiac tissue. 5-HT4 receptor agonists (5-HT4RAs) facilitate fast excitatory cholinergic synaptic transmission between enteric neurons, which stimulates GI motility and secretion [93]. Prucalopride, mosapride, and three other 5-HT4RAs (velusetrag, naronapride, and YKP10811) are in development for IBS-C treatment. These drugs have greater cardiovascular safety compared with older 5-HT4RAs due to higher specificity at intestinal 5-HT4 receptors and low intrinsic activity in cardiac muscle. These agents are expected to show efficacy in IBS-C, but this awaits confirmation by large randomized controlled trials [93].

ABDOMINAL PAIN-PREDOMINANT IBS

Antispasmodics (Spasmolytics)

Abnormal contraction of smooth muscle within the colon and the GI tract underlies pain and other IBS symptoms in some patients, providing the rationale for using agents that relax smooth muscle [21]. Spasmolytics fall into three groups based on mechanism of action [44; 202]:

- Calcium channel blockers (e.g., alverine, otilonium, pinaverium bromide)
- Direct smooth muscle relaxants (e.g., mebeverine)
- Antimuscarinic/anticholinergic agents (e.g., hyoscine, cimetropium bromide, dicyclomine hydrochloride)

A review of 23 randomized controlled trials using various antispasmodics found that these agents improved IBS symptoms to a greater extent than placebo, but efficacy of individual antispasmodics varied. Only otilonium (investigational), hyoscine bromide, cimetropium bromide, pinaverium bromide, and dicyclomine showed significant improvements beyond placebo [196; 203].

Antispasmodic drugs with anticholinergic or calcium-channel blocking mechanisms are used for relieving diarrheal symptoms, abdominal pain and distension, and spasms in all IBS subtypes. However, anticholinergic agents may be better tolerated in patients with IBS-D [5; 183]. Otilonium and hyoscine have the best evidence of efficacy, and otilonium bromide is the most effective agent in preventing IBS symptom recurrence. Some patients with IBS have an exaggerated gastrocolic reflex that is in part cholinergic-mediated, and spasmolytics may be best suited for postprandial abdominal cramping and loose stools in these patients [5].

The most commonly reported adverse effects associated with spasmolytics include dry mouth, dizziness, and blurred vision; serious adverse events are rare. Spasmolytics with greater anticholinergic activity are more likely to induce blurred vision, urinary retention, constipation, and dry mouth. Anticholinergics should be avoided in the elderly and in patients with a history of acute myocardial infarction or hypertension. Use during pregnancy and breastfeeding is not recommended [5; 44].

Peppermint Oil

Peppermint oil possesses a calcium-channel blocking mechanism and is classified as an antispasmodic [5]. The spasmolytic properties of peppermint oil may modulate pain by attenuating visceral hypersensitivity [44]. Two systematic reviews found peppermint oil superior to placebo in the management of IBS pain [203; 204]. A 2014 review evaluated five trials enrolling a total of 482 patients and showed a statistically significant positive effect of peppermint oil over placebo [203].

Although peppermint oil is typically well tolerated, with no significant side effects reported with standard doses (250–750 mg two to three times/day), some patients may experience reflux symptoms, and allergic reactions, heartburn, and headache have been described [5]. Peppermint oil is available over the counter, and enteric-coated capsules are preferred [44].

Linaclotide

Linaclotide (290 mcg daily) demonstrated improvement in abdominal pain in two large, phase 3 studies in IBS-C, with one trial extending treatment out to 26 weeks [93].

Antidepressants

As discussed, antidepressants are commonly used to treat pain symptoms associated with chronic functional GI disorders, including IBS. In a Cochrane review, the TCAs desipramine (25–100 mg at bedtime) and amitriptyline (10–50 mg at bedtime) demonstrated some global improvements of abdominal pain [93].

Pregabalin

Pregabalin, an a2d ligand that inhibits release of a number of excitatory neurotransmitters, may alleviate visceral pain in patients with IBS [106; 205]. Pregabalin increases distension sensory thresholds to normal levels in patients with IBS with rectal hypersensitivity. Studies are in progress to evaluate efficacy in centrally mediated abdominal pain syndrome (formerly termed functional abdominal pain syndrome) [93].

Histamine H1 Receptor Antagonists

Ketotifen

Ketotifen is a mast cell stabilizer with antihistamine properties. An eight-week randomized controlled trial showed evidence of improved pain, bloating, flatulence, diarrhea, quality of life, sleep, and sexual functioning in patients with IBS-D, despite lack of reduction in mast cell mediators [195]. The underlying mechanism of action was identified as histamine H1 receptor antagonism, which helped prompt further study of H1 receptor antagonists in patients with IBS [206].

Ebastine

Evidence suggests disordered GI motility, psychosocial distress, and visceral hypersensitivity converge on common pathways, including transient receptor potential cation channel subfamily V (TRPV). TRPV expressed on sensory neurons throughout the gut produces pain when activated by inflammatory mediators [207].

Researchers examined colorectal biopsies of patients with IBS and found greater TRPV-4 metabolite levels, which correlated with abdominal pain and bloating severity, and significantly greater nervous tissue and nerve growth mediators [207]. From these discoveries and results of ketotifen in the treatment of IBS, the histamine H1 receptor antagonist ebastine was studied for possible effects on visceral pain and hypersensitivity in 56 patients with IBS, randomized to ebastine (20 mg/day) or placebo. Over 12 weeks, a significant reduction of abdominal pain was found with ebastine compared to placebo and to baseline. Significantly more patients treated with ebastine (vs. placebo) had at least considerable relief of symptoms (46% vs. 12%) and lower mean abdominal pain scores (0–100 scale: ebastine 38, placebo 62). Quality of life was significantly improved on all IBS-QOL subscales in the ebastine group compared with baseline and placebo [206; 207].

Hypersensitive and normosensitive subgroups did not differ in ebastine response. Visceral pain response, as measured by rectal distension, had no association with clinical response, showing barostat findings as an invalid outcome measure. Most importantly, this study suggests H1-receptor blockade may represent an effective treatment for IBS abdominal pain regardless of subtype. This is encouraging given the lack of targeted treatments for visceral hypersensitivity and abdominal pain in IBS [206; 207].

Fecal Microbial Transplantation

Fecal microbiota transplants have been used in the last decade for severe cases of *Clostridium difficile* infection, with success rates greater than 90%. Fecal microbiota transplants may be a therapeutic option for severe refractory IBS or inflammatory bowel disease, but current FDA regulations limit use to the treatment of severe C. *difficile* infection [208].

Concerns over introducing pathologic organisms must be addressed before fecal microbiota transplant is approved in clinical management of inflammatory bowel disease. An example is the case of a female patient with C. *difficile* infection who received fecal microbiota transplant from an obese person and subsequently became obese herself [208].

SPECIALIST REFERRAL

Specialist referral from primary care should be considered for patients with IBS who do not respond or are intolerant to management with dietary and lifestyle changes, common laxatives, spasmolytics, or antidepressants [44]. Referral is also indicated if defecation dysfunction is suspected, there is unexplained worsening in clinical status, or there is an unambiguous need for a second expert opinion.

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CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such an important aspect of the care of patients with IBS, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient or caregiver understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. (In many cases, the terms "interpreting" and "translating" are used interchangeably, but interpreting is specifically associated with oral communication while translating refers to written text.) Frequently, this may be easier said than done, as there may be institutional and/or patient barriers.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as gender, class, religion, educational differences, and power/authority perceptions of the patient. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is the fact that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient in the needed language/dialect. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness. They are also well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital.

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter. If an interpreter is from the same community as the patient, the patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner must acknowledge that an interpreter is more than a body serving as a vehicle to transmit information verbatim from one party to another. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats, and sensitive topics that might arise. It is important for the patient, interpreter, and practitioner to be seated in such a way that the practitioner can see both the interpreter and patient. Some experts recommend that the interpreter sit next to the patient, both parties facing the practitioner.

The practitioner should always address the patient directly. For example, the practitioner should query the patient, "How do you feel?" versus asking the interpreter, "How does she feel?" The practitioner should also always refer to the patient as "Mr./Mrs. D" rather than "he" or "she." This avoids objectifying the patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role. This will prevent the patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention. The practitioner should also be attuned to the age, gender, class, and/or ethnic differences between the patient and the interpreter. For example, if the patient is an older Asian male immigrant and the interpreter is a young Asian woman, the practitioner should be sensitive to whether the patient is uncomfortable given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

IBS is common in the general population and has a significant medical and socioeconomic impact. Standard management of IBS has involved psychologic support, dietary measures, and pharmacotherapy directed at symptoms. IBS has long been considered a notoriously difficult condition to manage, because the pathophysiology has been poorly understood. Advances in the understanding of the disease's etiology and pathophysiology are informing the use of novel treatment approaches. This course has striven to provide clinicians with the information necessary to appropriately diagnose and treat IBS and improve patients' quality of life.

RESOURCES

American College of Gastroenterology
http://gi.org

American Gastroenterological Association
https://www.gastro.org

International Foundation for Functional Gastrointestinal Disorders
http://www.iffgd.org
http://www.aboutibs.org

National Institute of Diabetes and Digestive and Kidney Diseases
https://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/irritable-bowel-syndrome

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
http://www.naspghan.org

The Rome Foundation
http://theromefoundation.org

Society of Gastroenterology Nurses and Associates
http://www.sgna.org

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

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COURSE TEST - #98930 IRRITABLE BOWEL SYNDROME

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

This 10 credit activity must be completed by November 30, 2019.

1. Which of the following statements regarding the epidemiology of irritable bowel syndrome (IBS) is TRUE?
- *A) Most persons with IBS seek primary care medical attention.*
- *B) IBS is the most frequently diagnosed gastrointestinal (GI) condition.*
- *C) The lifetime prevalence of IBS in adult North American populations is 0.5% to 2%.*
- *D) In the United States, patients with IBS are most likely to present with the diarrhea-predominant subtype (IBS-D).*

2. What is the most frequent psychiatric comorbidity in IBS?
- *A) Panic disorder*
- *B) Major depressive disorder*
- *C) Generalized anxiety disorder*
- *D) Post-traumatic stress disorder (PTSD)*

3. In the first three months after diagnosis of IBS, patients typically experience an average of
- *A) one distinct symptom episode per month.*
- *B) four distinct symptom episodes per month.*
- *C) eight distinct symptom episodes per month.*
- *D) 12 distinct symptom episodes per month.*

4. What is perhaps the most bothersome IBS symptom to patients?
- *A) Fatigue*
- *B) Nausea*
- *C) Indigestion*
- *D) Abdominal bloating*

5. Functional GI disorders are
- *A) idiopathic disorders of gut-brain interaction.*
- *B) described as disorders of immune dysregulation.*
- *C) characterized by pathology of organ (motility) function.*
- *D) characterized by macro- and micro-level pathology of organs or structures.*

6. Which of the following is a genetic/environmental factor that affects the development, expression, and chronicity of functional GI disorders?
- *A) Late life experiences*
- *B) Altered bacterial flora*
- *C) Genetic polymorphism*
- *D) Exposure to household toxins*

7. Which of the following statements regarding the impact of childhood and adult stressors on IBS is TRUE?
- *A) Early life trauma is not associated with an increased risk for IBS.*
- *B) Life stressors are not a significant contributor to IBS symptom severity.*
- *C) Functional GI disorder onset rarely coincides with experiencing a highly threatening event.*
- *D) A history of childhood sexual abuse is associated with greater functional GI disorder severity.*

8. Which of the following factors is associated with the greatest risk of developing postinfectious IBS?
- *A) Male sex*
- *B) Older age*
- *C) Longer duration of initial illness*
- *D) Concurrent depression or anxiety*

9. All of the following statements regarding the intestinal microbiome in patients with IBS are true, EXCEPT:
- *A) Intestinal flora profiles differ among IBS subtypes.*
- *B) The intestinal flora of patients with IBS differs from healthy persons.*
- *C) There is a possibility that gut microbiota will represent a therapeutic target in the treatment of IBS.*
- *D) Excessive Bifidobacterium has been associated with greater abdominal pain and bloating in patients with IBS.*

Test questions continue on next page ➔

10. Which of the following statements regarding the role of diet in IBS is TRUE?
- A) *The contribution of true food allergies to IBS is significant.*
- B) *FODMAPs trigger symptom exacerbation in patients with normal gut function.*
- C) *Gluten is increasingly recognized as an important symptom trigger in patients with IBS.*
- D) *Gluten-free and low-FODMAPs diets are generally not recommended for persons with IBS.*

11. Visceral hypersensitivity
- A) *is a rare occurrence in patients with IBS.*
- B) *typically does not extend to the GI system.*
- C) *describes heightened thresholds for visceral pain.*
- D) *results in an exaggerated pain response to normally modest GI discomfort.*

12. Which of the following alterations in brain structure have been demonstrated in patients with IBS?
- A) *Decreased gray matter volumes in widespread regions*
- B) *Decreased cortical thickness in pain processing regions*
- C) *Increased cortical thickness in the somatosensory cortex*
- D) *All of the above*

13. The most common site of pain in patients with IBS is the
- A) *anterior chest.*
- B) *upper esophagus.*
- C) *lower left abdomen.*
- D) *upper right abdomen.*

14. Which of the following was a change in the Rome IV IBS diagnostic criteria?
- A) *Increased emphasis on the term "functional"*
- B) *Removal of the term "abdominal discomfort"*
- C) *Requirement for symptom persistence for three months*
- D) *Acknowledgement that diagnostic tests are not useful in the diagnosis of IBS*

15. What measurement tool is used to describe stool subtypes?
- A) *Manchester Stool Chart*
- B) *Bristol Stool Form Scale*
- C) *Surrey Bowel Questionnaire*
- D) *Edinburgh Stool Assessment Scale*

16. IBS with predominant diarrhea (IBS-D) is diagnosed with
- A) *>75% of bowel movements with BSFS types 6 and 7.*
- B) *>25% of bowel movements with BSFS types 1 and 2 AND <25% of bowel movements with BSFS types 6 and 7.*
- C) *>25% of bowel movements with BSFS types 6 and 7 AND <25% of bowel movements with BSFS types 1 and 2.*
- D) *>25% of bowel movements with BSFS types 1 and 2 AND >25% of bowel movements with BSFS types 6 and 7.*

17. All of the following are necessary for the diagnostic workup of IBS, EXCEPT:
- A) *Physical examination*
- B) *Psychosocial assessment*
- C) *Thorough patient history*
- D) *Limited laboratory testing*

18. Unclassified IBS (IBS-U)
- A) *is the most common IBS subtype.*
- B) *is reserved for patients who do not meet the full criteria for IBS.*
- C) *was replaced with the diagnostic category of mixed IBS (IBS-M) in the Rome IV.*
- D) *describes patients meeting IBS diagnostic criteria whose bowel habits cannot be accurately grouped into one of the main subtypes.*

19. Which of the following is a common non-specific symptom in IBS?
- A) *Urgency to defecate*
- B) *Abnormal stool frequency*
- C) *Mucus with bowel movements*
- D) *All of the above*

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20. Serologic tests for celiac disease should be performed in
- A) *all patients with suspected IBS.*
- B) *patients with IBS-C with perceived food sensitivities.*
- C) *patients with IBS-D or IBS-M who fail empiric therapy.*
- D) *patients with IBS-U in order to better identify the disease subtype.*

21. Which of the following is a risk factor for microscopic colitis?
- A) *Weight gain*
- B) *Nocturnal stools*
- C) *Age younger than 30 years*
- D) *Longer duration of diarrhea*

22. All of the following are indications for colonoscopy in patients with IBS, EXCEPT:
- A) *A diagnosis of IBS-M*
- B) *The presence of alarm symptoms*
- C) *Family history of colorectal cancer*
- D) *Persistent diarrhea that has failed empiric therapy*

23. Which of the following is an alarm feature in patients with IBS requiring further testing to rule out organicity?
- A) *Abdominal pain*
- B) *Symptom onset before 20 years of age*
- C) *Lack of changes in bowel movement habit*
- D) *Personal or family history of colorectal cancer*

24. Patient engagement and adherence can be facilitated by
- A) *providing adherence "diaries" to the patient.*
- B) *providing only verbal information and reminders.*
- C) *excluding family members and caregivers who can reinforce patient behavior.*
- D) *prescribing therapeutic regimens with the greatest number of effective daily doses.*

25. Lifestyle modifications that may improve IBS symptoms include
- A) *caffeine avoidance.*
- B) *limited water intake.*
- C) *increased legume intake.*
- D) *avoidance of physical activity.*

26. Of the following, which is a common source of FODMAP in the western diet?
- A) *Berries*
- B) *Onions*
- C) *Red meat and poultry*
- D) *Leafy green vegetables*

27. In IBS, the psychologic approach of self-monitoring is focused on
- A) *somatic sensations.*
- B) *feelings that usually accompany flare-ups.*
- C) *internal and external triggers and thoughts.*
- D) *All of the above*

28. Which class of antidepressants is the first choice for pain in non-constipated patients with IBS?
- A) *Tricyclic antidepressants (TCAs)*
- B) *Monoamine oxidase inhibitors (MAOIs)*
- C) *Selective serotonin reuptake inhibitors (SSRIs)*
- D) *Serotonin and norepinephrine reuptake inhibitors (SNRIs)*

29. When used for the treatment of IBS-D in adults, the usual dosage of rifaximin is
- A) *25 mg per day for 10 days.*
- B) *150 mg three times per day for 21 days.*
- C) *550 mg three times per day for 14 days.*
- D) *800 mg twice per day for 7 to 10 days.*

30. Which of the following antispasmodics has the best evidence of efficacy in the treatment of abdominal pain-predominant IBS?
- A) *Alverine*
- B) *Otilonium*
- C) *Mebeverine*
- D) *Pinaverium bromide*

Be sure to transfer your answers to the Answer Sheet insert located between pages 96–97.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Optimizing Opioid Safety and Efficacy

Special Approvals

California MDs and DOs: This course fulfills 11 hours of pain management education for California-licensed physicians who must complete 12 hours of pain management and the appropriate care and treatment of the terminally ill.

Connecticut MDs, DOs, and PAs: This course meets the Connecticut requirement for 1 hour of risk management education.

Massachusetts MDs and DOs: This course meets the Massachusetts requirement for 10 hours of risk management education and 3 hours of pain management education.

Michigan MDs and DOs: This course meets the requirement for 3 hours of continuing education credit in pain and pain symptom management.

Nevada MDs and PAs: This course meets the Nevada requirement for 2 hours of ethics education as related to controlled substances.

New Mexico MDs, DOs, and PAs: This course meets the New Mexico requirement for 5 hours of pain management education for MDs, 3 hours of pain management education for PAs, and 5 hours in non-cancer pain management education for DOs.

Ohio PAs: This course meets the Ohio requirement for 12 hours of pharmacology education for PAs who are authorized to prescribe.

Oregon MDs, DOs, and PAs: This course meets 6 of the 7 hours of continuing education in pain management as required by the State of Oregon.

Pennsylvania MDs and DOs: This course meets the Pennsylvania requirement for 12 hours of patient safety/risk management education.

Texas MDs and DOs: This course meets the requirement for 2 hours of continuing education in medical ethics/professional responsibility as required by the Texas Medical Board.

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In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 15 ABIM MOC Points, 15 ABA MOC Points, 15 ABP MOC Points.

Audience

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients who may benefit from the use of opioids to address pain.

Course Objective

The purpose of this course is to provide clinicians with the information necessary to choose the appropriate opioid agents for their patients, with a resultant improvement in patients' quality of life and compliance with prescribed treatments.

Learning Objectives

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

1. Define terms often used in discussion of opioid prescribing.
2. Analyze common myths related to opioid analgesic safety.
3. Recall the epidemiology of pain.
4. Outline the individual and societal impact of undertreated pain.
5. Describe risk factors for and comorbidities of chronic pain.
6. Evaluate barriers to adequate pain care.
7. Describe the endogenous opioid system and effects of opioid analgesia.
8. Discuss the classification and properties of the various mu opioid receptor full agonist agents.
9. Compare and contrast other types of opioid analgesics and antagonists.
10. Identify pharmacokinetic factors in opioid analgesic response.
11. Outline the Centers for Disease Control and Prevention's (CDC's) guidelines for opioid prescribing for chronic pain.

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12. Recall other general recommendations for safe and effective long-term opioid use for chronic pain.
13. Identify patient factors that affect opioid analgesic response.
14. Describe issues that affect choices regarding opioid selection, rotation, and titration.
15. Discuss the identification and appropriate treatment of opioid analgesic side effects.

Faculty

Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

Faculty Disclosure

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

Division Planner

John M. Leonard, MD

Division Planner Disclosure

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

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This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for lifelong learning and self-assessment. This activity contributes to the patient safety CME requirement for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 15 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

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INTRODUCTION

Opioid analgesics are approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate or severe pain. However, individual patients differ greatly in clinical response (e.g., efficacy, side effects, safety) to different opioid analgesics, and patient populations show widely variable response to the same opioid and dose [1]. These response variations make opioid prescribing challenging. Scientific advances have improved the understanding of how opioid response is conditioned by genetic factors, comorbidity, drug interactions, and opioid dynamics and/or kinetics. Informed health professionals are now better able to match patients with a selected treatment option to maximize safety, efficacy, and tolerability when prescribing opioid analgesics.

The important role of opioid analgesics is broadly accepted in acute pain, cancer pain, and palliative and end-of-life care, but it is controversial for the management of chronic noncancer pain [2]. As of 2017, the climate surrounding opioid analgesics is decidedly negative, a response to the excessive prescribing and increases in fatal overdose during the 2000s. This backlash has prompted concerted broadcasting of opioid analgesic public health hazards, culminating in the 2016 Centers for Disease Control and Prevention (CDC) opioid prescribing guidelines that focus on curtailing prescribing and patient access [3; 4]. However, guidance on improving prescription opioid analgesia and tolerability by carefully matching the patient to the selected opioid, unaddressed in the CDC guidelines, is also essential for effective treatment of pain [5; 6].

Prescription opioid analgesic use and overdose both appear to be in multi-year declines from their 2011 peak [7]. This course will provide perspective and address common misperceptions of opioid analgesic safety and potential benefits in order to help establish the basis for a balanced risks/benefits discussion and convey that with appropriate due diligence, opioid analgesics can be prescribed safely to benefit patients in pain who lack response to, or are unlikely to benefit from, other analgesics.

Opioids are not a panacea for pain, nor are they safe and effective for every patient. However, they can be a useful tool, and knowledge of medical advances can give clinicians greater confidence to safely and effectively prescribe these drugs. In this course, chronic pain management is emphasized because the potential patient/opioid interactions are more complex and current guidance can be enhanced. Unless stated otherwise, this course focuses on noncancer pain.

DEFINITIONS

Acute pain: Pain from tissue injury that resolves with tissue healing [16]. Acute pain may be protracted without mechanistic conversion to chronic pain, resolving with treatment [17].

Addictive drug: A disproven concept that some drugs are inherently "addictive." Addiction results from individual susceptibility and not from a substance. Most people do not respond with addictive behavior when prescribed opioids with abuse potential, while predisposed persons may abuse any opioid analgesic [9; 10; 11].

Analgesic tolerance: Diminished or lost analgesia requiring dose titration to regain pain relief. A concerning complication in long-term opioid therapy, long-term trials of transdermal fentanyl or extended-release (ER) oxycodone suggest analgesic tolerance is much less frequent and clinically relevant than previously believed [8].

Centralized pain: Refers to peripheral and central sensitization without detectable peripheral origin and includes fibromyalgia, irritable bowel syndrome, and tension-type headache. Also known as dysfunctional pain.

Central sensitization: The process by which pain initially generated from peripheral injury becomes embedded in the central nervous system (CNS) through pathologic adaptation to become self-perpetuating and amplified, uncoupled from original tissue origin, very difficult to treat, and potentially intractable [19].

Chronic pain: Pain lasting longer than three months or longer than expected healing time. Previously, chronic pain has been conceptualized as merely the continuation of acute pain beyond a chosen temporal cut-off point, a notion now considered overly simplistic. The transition from acute to chronic pain is now understood to involve a shift in pathogenic mechanisms from that associated with early-phase tissue injury and healing to a later period of abnormal, maladaptive sensory processing and neuronal plasticity that develops within peripheral and central pain pathways. Importantly, psychologic status, cultural background/beliefs, and relationships/interactions in the workplace, home, and healthcare environments contribute to development and persistence of chronic pain [18].

Inflammatory pain: Nociceptive pain with a localized immune response that generates pro-inflammatory mediators to facilitate tissue repair.

Neuropathic pain: Originates from injury to specific peripheral nervous system (PNS) or CNS structures or to all peripheral sensory nerves (e.g., with diabetes or postherpetic neuralgia).

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Neuroplasticity: The capacity of nerve cells to adapt and regenerate.

Nociceptive pain: The normal acute response to peripheral tissue injury or damage.

Pain: Physical discomfort. Pain is classified into four types (nociceptive, inflammatory, neuropathic, and centralized); chronic pain usually involves multiple pain mechanisms [13; 14; 15].

Pseudoaddiction: An iatrogenic condition whereby patients display drug-seeking behaviors mimicking opioid use disorder but driven by intense need for pain relief. Resolves with adequate pain control [12].

OPIOID ANALGESIC SAFETY, RISKS, AND BENEFITS: FACTS VERSUS FALLACIES

Safety considerations are the foundation of opioid analgesic prescribing, reflecting the basic principles of good medical practice [20]. As such, any comprehensive review of opioid analgesic therapy should address the assumptions that surround opioid analgesic prescribing for pain.

From the late 1990s through 2011, opioid analgesic prescribing and fatal overdose greatly increased [21]. The CDC identified this pattern, and their prompt attention and broadcasting elevated physician and public awareness and assisted in closing "pill mills" that served as conduits for millions of opioid doses into illicit markets [3]. The reaction to opioid overprescribing and overdose prompted efforts to curtail opioid prescribing, in part, by swaying physician and public opinion against opioids [6; 7; 22; 23; 24; 25]. This section addresses common misperceptions about opioid analgesics.

PRESCRIPTION OPIOID ANALGESIC FATAL OVERDOSE RATES

There is a misperception that overdose deaths from legally obtained prescription opioid analgesics continue rising, perpetuating an opioid epidemic. In fact, prescription opioid analgesic overdose deaths have steadily declined since 2012.

This perception is in part the result of CDC data indicating 18,893 prescription opioid overdose deaths in 2014, up sharply from 16,300 deaths in 2013 [26]. However, the 2014 increase was the result of a change in reporting standards. Starting in early 2014, the CDC began classifying all fentanyl overdoses as prescription opioid analgesic deaths, because laboratory tests were unable to distinguish clandestine from pharmaceutical fentanyl [27]. Also in 2014, there was an influx of fentanyl into the illicit opioid market, largely from Mexico and often sold as heroin or oxycodone. This resulted in a significant increase in fentanyl overdose deaths.

However, the total number of prescribed fentanyl dose units in 2014 (6.7 million) and 2013 (6.8 million) was unchanged [29]. In 2016, the CDC stated that the increase in overdose deaths in 2014 was mainly from adding fentanyl overdoses, almost all from clandestine fentanyl [28]. The CDC also provided an adjusted 2014 estimate (14,000 opioid overdose deaths), which was a continued decrease from the prescription opioid analgesic overdose deaths peak in 2011 (16,917 deaths) [30].

It should also be noted that heroin overdose deaths are often undercounted, and morphine deaths overcounted, because heroin rapidly metabolizes into morphine. Many medical examiners are reluctant to label a death heroin-related without 6-monoaceytlmorphine present. However, this metabolite, unique to heroin, quickly metabolizes into morphine. The actual figures of heroin overdose reported as morphine are unknown, but when heroin overdose deaths increase, morphine overdose deaths also tend to increase [31].

PRESCRIPTION OPIOID ANALGESIC PRESCRIBING RATES

Many healthcare professionals believe that continued increases in opioid analgesic prescribing are fueling the opioid epidemic. In fact, the prescription rates of several opioid products are in multi-year declines. Total dispensed opioid prescriptions decreased 4.5% between 2011 and 2014, despite increases in tramadol (25.5%) and buprenorphine (49.4%) prescribing rates [29].

In late 2010, oxycodone ER was introduced as an abuse-deterrent formulation (ADF) to reduce abuse and overdose. After this product was released, there was a 39% prescribing decrease between 2010 and late 2012 [32]. In addition, oxycodone "doctor shopping" decreased 50% and overdose fatalities reported to the manufacturer decreased 65% [33].

Though it is still early, hydrocodone/acetaminophen combination product prescribing appears to be decreasing after it was rescheduled as a Schedule II controlled substance in 2014. After one year, there were 26.3 million fewer (-22%) prescriptions and 1.1 billion fewer (-16%) dispensed tablets [34]. Decreased hydrocodone/acetaminophen prescribing by primary care physicians during this period is also notable, with a 33% decrease from 2011 (144.5 million) to 2015 (97 million) [29; 35; 36].

While it is true that the United States uses 99% of global hydrocodone, this is partially due to the fact that the few countries with adequate opioid access prefer dihydrocodeine or low-dose morphine for moderate/moderately severe pain [37]. Liberal opioid analgesic prescribing in some European countries has not led to the addiction and overdose rates seen in the United States, which reflects contribution from uniquely American factors beyond opioid analgesic exposure [38; 39; 40].

PRESCRIPTION OPIOID ANALGESICS AND HEROIN

The use of prescription opioid analgesics has long been proposed as a "gateway" to heroin. However, progression from opioid prescription misuse to heroin initiation is infrequent. Among non-medical users of opioid analgesics, 3.6% initiate heroin use within five years of initial abuse of prescription opioids [41]. Although most persons who misuse opioids do not progress to heroin use, it is also true that the majority of current heroin users initially misused prescription opioids.

EVIDENCE OF LONG-TERM OPIOID BENEFIT FOR CHRONIC PAIN

No analgesic used for the treatment of chronic pain (opioid or other class) has evidence of long-term safety and efficacy from randomized controlled trials lasting longer than one year [39]. Although this has been used to support the belief that opioids are unsafe for prolonged treatment of chronic pain, this level of evidence is lacking for any analgesic drug in use for chronic pain [30; 39; 42]. Thus, the absence of evidence is not evidence of absence [43; 44]. Many non-randomized controlled trials of opioid analgesics lasting one year or longer have substantive clinical value.

In general, opioid and other analgesic drug trials are seldom longer than 12 weeks in duration, and many obstacles interfere with the ability to conduct long-term opioid trials [45; 46]. First, ethical standards prohibit randomizing 50% of subjects in substantial pain to placebo. In addition, complexity and expense deter researchers from using active-drug controls in randomized controlled trials; these trials are unattractive to industry funding. There are also very high dropout rates of subjects with chronic pain randomized to placebo.

Several factors make analgesic efficacy of opioid analgesics difficult to demonstrate in tightly controlled randomized trials [8; 44; 45]. Studies report average opioid response of large patient numbers under rigid, predetermined starting dose and titration. However, opioid response in chronic pain is bimodal and not normally distributed; patients primarily show substantial or negligible analgesic response. When individual patient response is pooled and averaged, modest benefit is reported.

The strict, inflexible dosing parameters in randomized controlled trials lead to high dropout rates from analgesic failure or intolerability. This underestimates efficacy and overestimates toxicity. Many such patients would gain analgesia and tolerability using an approach tailored to patient factors that influence opioid response.

PRIMARY CONTRIBUTORS TO OPIOID ANALGESIC-RELATED FATALITIES

Misuse or abuse of prescribed opioid analgesics may account for a smaller proportion of poisoning overdoses than assumed. Data from Florida during 2007–2013 found 12% of 5,254 patients treated for non-fatal prescription opioid overdose in Broward County were diagnosed with opioid use disorder; 88% were legally prescribed users without diagnosable opioid use disorder [55]. These findings suggest prescription opioid abuse may be a less frequent cause of overdose than commonly assumed.

Studies show that the majority of opioid analgesic deaths stem from combining opioids with sedative hypnotics and/or alcohol [6; 47]. The extent to which contributing factors drive overdose rates is a more complex problem.

Methadone

Methadone analgesic prescribing began in the late 1990s [48]. In 1999, 784 overdose deaths were attributed to methadone. By 2011, this number increased to 4,418 (26% of opioid analgesic deaths) [48]. Factors that have contributed to increased methadone deaths include prescriber knowledge deficits of its complex pharmacology and its designation by insurer/third-party payers as the first-line chronic pain drug on the sole basis of cost savings [7; 49; 50].

Benzodiazepines

In 2011, benzodiazepines were associated with 31% of opioid analgesic fatalities, compared with 18.4% in 2004 [51]. However, this 2011 figure may understate the true benzodiazepine contribution. In a study of 607,156 people 15 to 64 years of age, 84.5% of those prescribed opioids for pain who died of opioid analgesic overdose were co-prescribed benzodiazepines [52]. In another study of more than 2 million North Carolina residents receiving one or more opioid analgesics, benzodiazepines were present in 61.4% who fatally overdosed. Benzodiazepines contribute to a significant number of opioid analgesic deaths, particularly with higher-dose opioid prescribing [47].

Alcohol

Alcohol coingestion may also contribute to opioid analgesic-related deaths. In 2010, 20% of opioid overdose deaths involved alcohol [53].

Prescriber Knowledge Deficits

Studies indicate that fatal respiratory depression events often occur in the first five days of initial opioid therapy, with most in the initial 24 hours. This reflects initiation of therapy at too high a starting dose or failure to consider other risk factors, such as co-prescribed CNS sedatives [54].

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EPIDEMIOLOGY OF PAIN

Persistent pain affects one in three adults in the United States and costs more than $600 billion annually [60]. The Institute of Medicine (IOM) estimates that more than 100 million Americans suffer from persistent or chronic pain, with roughly 10% experiencing chronic, disabling pain [2]. Chronic pain is experienced by 20% to 30% of adults in the United States, similar to the rates reported in Canada, Australia, and European countries.

Pain is a leading cause of chronic illness in persons older than 60 years of age, a major cause of disability, and the cardinal feature of arthritis, migraine, cancer, metabolic disorders, and neuropathies. Pain control in these diseases is notoriously difficult and often requires opioids [61; 62]. Neuropathic pain, which includes diabetic neuropathy, complex regional pain syndrome, radiculopathy, phantom limb pain, human immunodeficiency virus (HIV) sensory neuropathy, multiple sclerosis-related pain, and post-stroke pain, affects 5% to 10% of the U.S. population [63].

Chronic pain prevalence varies by subgroup. In general, older adults have a much greater prevalence than younger adults. Higher rates of chronic pain are found in women, those recently hospitalized, obese individuals, and those who never graduated high school. Roughly 50% of adults rating their health as fair or poor suffer from chronic pain [64].

Chronic pain rates are likely to continue increasing as the population ages and more people develop pain-associated conditions such as obesity, diabetes, cardiovascular disorders, arthritis, and cancer. Other contributors to chronic pain include improved trauma care (with more surviving with chronic pain), the increase in surgical procedures, and greater public understanding of chronic pain and access to health insurance [2].

The most common anatomic locations of pain in U.S. adults are the low back (28.1%), knee (19.5%), severe headache or migraine (16.1%), neck (15.1%), shoulder (9.0%), finger (7.6%), and hip (7.1%). The lifetime prevalence of spinal pain ranges from 54% to 80% [2]. In patients with low back pain or neck pain, 25% to 60% report pain lasting longer than one year from onset; high pain and disability levels were found in 23% of patients with low back pain and 15% of patients with neck pain. Low back pain is linked to greatest declines in function and quality of life [65].

As noted, adult women have an overall higher prevalence of chronic pain than men [66]. Some chronic pain syndromes occur only, or predominantly, in women, including chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, vulvodynia, and temporomandibular disorders. Roughly 50 million women have one or more of these conditions, which frequently co-occur [2].

CONSEQUENCES OF UNTREATED OR UNDERTREATED CHRONIC PAIN

Pain is a distressing sensory and emotional experience for the patient, imposing potentially life-altering physiologic, psychosocial, and quality of life alterations [2]. The negative impact of chronic pain on quality of life is more severe than heart failure, renal failure, or major depression and comparable to terminal cancer [67; 68].

Failure to manage pain has serious pathophysiologic consequences, including cardiovascular (hypertension, myocardial ischemia, cardiovascular collapse) and physiologic (appetite loss, failure to thrive, immune dysfunction, endocrine failure) consequences, suppression of physical activity leading to joint and muscle deterioration, chronic sleep disturbance, dementia, and premature death [2; 13; 69]. Among 6,940 primary care patients followed over 10 years, those with poorly controlled moderate-to-severe chronic pain had a 68% greater risk of death than those with cardiovascular disease and 49% greater risk than all other causes combined [70].

Psychosocial consequences of unmanaged pain can be severe, with adverse psychologic (impaired cognitive function, pathologic anxiety/depression, suicidal ideation, despair, hopelessness) and social/interpersonal (relationship disruption, loss of employment, financial difficulties) outcomes [2; 13; 71; 72; 73]. Chronic pain is second only to bipolar disorder as a medical cause of suicide [74; 75; 76].

Chronic undercontrolled pain activates CNS glial cells and leads to neuroinflammation, tissue destruction, loss of CNS tissue mass and receptors, and unresponsiveness to usual-dose opioids and other analgesics. These patients often require higher-dose opioids; the modest analgesic response can reduce suffering and prevent suicide [77].

Negative attitudes by primary care providers and other clinicians toward patients with chronic pain who use/misuse illicit or prescription drugs are widespread, with hedonistic pursuit the assumption. Reality may be more complex, as patients with chronic pain potentially use substances to alleviate poorly controlled pain. This was explored in a study of adult primary care clinic patients who tested positive for illicit drug use or prescription drug misuse. Of the 589 patients [78]:

- 87% reported chronic pain (13% mild, 24% moderate, 50% severe)
- 74% reported impairment from pain (15% mild, 23% moderate, 36% severe)
- 51% of those who used illicit drugs (cannabis, heroin) stated they did so to treat pain
- 81% of those who misused prescription drugs stated they did so to self-medicate pain
- 38% of those who reported past three month heavy drinking stated they did so to treat pain

Chronic pain and impairment from pain were the norm in primary care patients with positive drug screens. Nearly one-third reported both severe pain and disabling impairment. This study suggests that poor pain control is common, apparent substance use disorder may reflect pseudoaddiction, and pain requires attention in patients counseled about their substance use [78].

RISK FACTORS FOR CHRONIC PAIN

PSYCHOSOCIAL RISK FACTORS

Intense persistent pain and persistent emotional distress are both powerful physiologic stressors that activate the hypothalamic-pituitary-adrenal (HPA) axis, the body's primary stress-control mechanism. The HPA axis becomes dysregulated from prolonged activation, causing a cascading effect that activates immune and inflammatory factors and glutamate receptor complex elements [69]. Neuroplasticity, the alteration in activity and function of synapses and neuronal networks, mediates the development, chronicity, and treatment resistance of pain and psychiatric conditions through diminished neurogenesis, synaptic deficits, decreased neurotrophic factors (e.g., brain-derived neurotrophic factor), and dendritic pathology [79]. Neuroplastic changes lead to central sensitization and hyperalgesia in patients with chronic pain and in patients with major depression even when ongoing pain is absent [80].

Abuse and Trauma

Early childhood trauma greatly influences experiences of pain, and childhood physical and sexual abuse negatively and independently influences adult health status, even after controlling for psychiatric disorders [66]. Abuse in childhood strongly predicts depression and pain in adulthood, and childhood sexual abuse highly predicts later chronic pain.

Childhood trauma stimulates the release of inflammatory cytokines and the development of central sensitization, greatly elevating later risks of immune, endocrine, and nervous system dysregulation [81]. Adults with depression and a history of childhood abuse show amplified stress response and altered adrenocorticotropic hormone and cortisol release. Glucocorticoid receptor dysfunction and downregulation is a bidirectional cause/effect of abnormal HPA-axis regulation in patients with depression [82]. Neuroinflammation is the common mediator of comorbid chronic pain and depression [83].

Coping and Social Support

Multiple psychologic mechanisms can alter pain outcomes and facilitate the progression of acute pain to chronic pain. Pain tolerance is adversely affected by mood, and factors such as pain coping skills and social support can affect pain and functionality [84; 85]. Low socioeconomic status, characterized in part by lower education level and inequality in healthcare access, also correlates with chronic pain [66].

The presence of maladaptive coping styles such as catastrophizing, kinesophobia (i.e., fear of movement), and somatization (i.e., emotional distress expressed through physical symptoms) predicts development of chronic pain [65]. Craving is strongly associated with drug misuse in patients prescribed opioids for chronic pain, and pain catastrophizing is associated with craving even after controlling for demographic, psychologic, medical, and medication regimen variables. This underscores the importance of including psychologic interventions in the overall pain care [86].

Passive avoidant behavioral patterns, lack of engagement in self-care, and job dissatisfaction also elevate the risk of chronic pain [87; 88]. Emotions and expectancies are strongly linked; negative emotions are associated with a generalized expectation of negative outcomes. The goal to avoid pain is often pursued with concurrent and often competing goals. Patients with chronic pain frequently weigh the value of pain avoidance against the costs related to loss of desired activities [84].

Neurobiologic mediation of social pain overlaps with physical pain. Social exclusion, bullying, isolation, and lack of support cross-sensitizes and amplifies physical pain. This relationship is bidirectional and highly relevant to patients with chronic pain who commonly encounter a process of rejection and social separation [66]. Passive pain coping and low levels of social support predict functional disability in patients with arthritis-related pain [89].

Addressing coping skills and bolstering social support can improve long-term pain outcomes and mitigate problematic medication use [85]. Patients with chronic pain and a history of prescription opioid use disorder who do not abuse their prescribed opioids are more likely to be active members of 12-step groups and have stable support systems [90].

MEDICAL RISK FACTORS

Obesity

Obesity is a pro-inflammatory state, and adipose tissue releases inflammatory mediators that increase chronic pain risks. Increased body weight and joint load can also promote or exacerbate painful conditions such as osteoarthritis [91].

Past Surgeries

Of patients undergoing surgery, 10% to 50% experience persistent pain and 2% to 10% experience severe pain. Inadequately treated postsurgical acute pain is common and increases the risk for developing chronic pain [2]. Chronic pain develops after thoracic surgery in 25% to 60% of patients and after herniorrhaphy in 14% [85].

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COMMON COMORBID CONDITIONS

Major Depressive Disorder and Anxiety Disorders

Major depressive disorder is the single most important and prevalent chronic pain comorbidity. It is difficult to treat and renders pain control nearly impossible; anhedonia (i.e., inability to feel pleasure) is a frequent symptom [8; 66]. Primary care patients with muscle pain, headache, or stomach pain complaints are 2.5 to 10 times more likely to have diagnosable panic disorder, generalized anxiety disorder, or major depressive disorder than those without pain. Patients whose pain level results in work interference show elevated risk of panic disorder and major depressive disorder. Conversely, major depressive disorder increases the odds of muscle pain complaints, headache, stomach pain, and pain interference with daily functioning. These results reflect the complex interaction between pain and medical/psychiatric comorbidities [92].

Sleep Impairment

Disturbed phase 2/3 and rapid eye movement sleep decreases pain threshold, impairs immune function, decreases insulin sensitivity, and undermines pain treatment response. Roughly 50% to 70% of patients with chronic pain experience sleep disturbance, and pain, sleep, and mood are connected and mutually reinforcing—sleep disturbance exacerbates pain, and pain disrupts sleep. The bidirectional association results from lowered pain threshold, promotion of hyperalgesia, and increased release of inflammatory cytokines [8; 93]. Sleep recovery has an analgesic effect [85].

Medical Comorbidity

The presence of chronic pain is substantially elevated in patients with chronic respiratory disease, cardiovascular disease, or neurologic, metabolic, endocrine, and gastrointestinal (GI) disorders [94]. Among multi-morbid primary care patients older than 65 years of age, chronic low back pain was the most prevalent pain condition, significantly associated with cardiometabolic conditions in both sexes and depression in women [95].

BARRIERS TO ADEQUATE PAIN CARE

Pain arises in the nervous system but represents a complex, evolving interaction of biologic, behavioral, environmental, and societal factors. Biopsychosocial factors greatly influence pain perception, persistence, and treatment outcomes in patients with chronic pain [2]. As such, a coordinated multimodal approach with pharmacotherapy, cognitive-behavioral or other coping skills therapy, and a progressive strengthening or functional restoration modality is recommended [96; 97]. Despite substantially greater efficacy than uncoordinated symptomatic care, few patients with chronic pain receive multidisciplinary pain care [85].

Chronic pain affects all domains of life, and clinicians have few effective tools at their disposal to help these patients [98]. Opioids remain the strongest group of analgesic drugs available [99]. Millions of patients are safely and effectively maintained on relatively high-dose opioids for chronic, severe pain and require these medications to function. Public pressure and the mischaracterization of patients as "drug addicts" has increasingly deterred prescribers from treating patients with chronic pain successfully managed with opioids for years or decades rather than improving safety practices [22; 100]. However, opioids, like many medications, have serious risks and should not be treated like a cure-all [56]. This dichotomy has resulted in many patients for whom opioid analgesics are appropriate increasingly experiencing barriers to pain relief.

The IOM has stated that the uncertain diagnosis in many chronic pain cases, combined with stigma toward patients in pain, interferes with treatment seeking and adherence to follow-up. Negative provider interactions are powerful deterrents to future help-seeking by adults with chronic pain, particularly the elderly. Patient perception of having their pain complaint dismissed or of not being listened to by their initial pain provider can discourage subsequent care seeking or result in changing providers [2].

These observations are echoed by the National Pain Strategy (NPS), adding that in addition to prevalent stigma, increasing reluctance of many clinicians to prescribe opioids jeopardizes adequate pain control for patients with chronic pain. For most pain conditions, medications (including opioids) may be essential for improved quality of life, and rationing, medication shortages, and inadequate reimbursement decreases patients' access to medications, causing considerable hardship in this vulnerable population [101].

At greatest risk of unrelieved pain from stigma and bias are children, the elderly, racial and ethnic minorities, active duty or military veterans, and those with cancer, HIV, or sickle cell disease. Pain undertreatment in black patients is especially widespread, from prevalent misperceptions that this group has higher pain tolerance and is more likely to abuse their opioid prescription [102].

The CDC guideline recommends that pain specialists, not primary care providers, manage patients requiring >90 mg daily morphine equivalent dosage (MED), but this is often unrealistic in practice. The number of pain specialists is inadequate to manage the large number of patients with pain severity and disability that requires >90 mg MED. Patients may feel abandoned or panicked about the potential loss of effective pain control. Adherence to this recommendation can therefore have potentially serious consequences for patients requiring opioids, and the growing problem of opioid medication access is likely to worsen [56].

THE ENDOGENOUS OPIOID SYSTEM AND OPIOID ANALGESIC MECHANISMS

Opioid analgesics produce therapeutic and side effects by mimicking endogenous opioid activity, although some opioids produce analgesia by activity outside the opioid receptor complex. Opioids widely differ in levels of affinity and activation of opioid receptor subtypes. In addition, inter-individual variation in analgesic response and side effects is significant, largely driven by genetic factors [103]. The complex interaction between unique opioid properties and individual patient characteristics dictates that a patient-tailored approach is required for opioid selection, dose initiation, and titration to optimize safety, analgesia, and tolerability.

Naturally occurring opioid compounds are produced in plants (e.g., opium, morphine) and in the body (the endogenous opioids) [104]. Endogenous opioids are peptides that bind opioid receptors, function as neurotransmitters, and help regulate analgesia, hormone secretion, thermoregulation, and cardiovascular function. The three primary endogenous opioid peptide families are the endorphins, enkephalins, and dynorphins, and the three primary opioid receptor types are mu, kappa, and delta [105; 106]. A quick overview of this complex pain modulation system is helpful in understanding how opioid analgesics work.

ENDOGENOUS OPIOID PEPTIDES

Endogenous opioid peptides are neurotransmitter molecules in the opioid receptor complex that produce specific physiologic effects determined by neuronal distributions of the activated opioid receptor type [107]. The endogenous opioid peptides are cleaved from the pro-hormone precursors proenkephalin, pro-opiomelanocortin, and prodynorphin. The endogenous delta opioid receptor peptides are met-enkephalin and leu-enkephalin, cleaved from proenkephalin. Prodynorphin gives rise to kappa opioid receptor agonists dynorphin A and B. Pro-opiomelancortin encodes the peptide beta-endorphin, which has agonist activity at all three classical opioid receptors. Some endogenous opioid ligands lack specificity for opioid receptor subtypes, such as b-endorphin and the enkephalins [108; 109].

Endorphins

Endorphins are synthesized in the hypothalamus and the pituitary gland. Pain, strenuous exercise, excitement, and orgasm stimulate their release, binding, and activation. Endorphins are popularized as the "natural pain killers" from their ability to induce analgesia and a general feeling of well-being. They are thought to largely mediate analgesia from acupuncture, massage, hydrotherapy, and transcutaneous electrical nerve stimulation therapy [110].

Dynorphins

Dynorphin peptides are synthesized from the precursor pro-dynorphin and have primary affinity and binding at the kappa opioid receptor. Dynorphins are distributed throughout the CNS, with highest concentrations in the brain stem, hypothalamus, and spinal cord. Their physiologic actions are diverse, and their primary function is the modulation of pain response, appetite and weight, circadian rhythm, and body temperature. Dynorphins are linked to stress-induced depression and drug-seeking behavior, and drugs that inhibit dynorphin release are under evaluation for possible use in the treatment of depression related to drug addiction [110].

Enkephalins

Enkephalin peptides, derived from pro-enkephalin, are located throughout the brain and spinal cord and are involved in regulating nociception. Enkephalins inhibit neurotransmission in pain perception pathways, reducing the emotional and physical impact of pain. Enkephalins also reside in the GI tract, where they help regulate pancreatic enzyme secretion and carbohydrate metabolism [110].

OPIOID RECEPTORS

Opioid receptors are expressed throughout the CNS and PNS on key nodes within the pain pathway and are highly concentrated in areas involved with integrating pain information [61]. Opioids vary greatly by receptor affinity, binding, and activity and can bind to produce agonist, partial agonist, or antagonist receptor activity [105]. As noted, the analgesic activity and the side effects result from mimicry of endogenous opioids, achieved by the beta-phenylethylamine group moiety shared by endogenous and exogenous opioid receptor ligands that facilitate opioid receptor binding [111].

Mu Opioid Receptors

Mu receptors are the primary mediators of analgesia produced by opioid analgesics in clinical use. Their greatest CNS concentration is in the thalamus, medulla, periaqueductal gray area, neocortex, amygdala, dorsal horn, inferior and superior colliculi, and brain stem [105; 110; 112]. PNS occupancy includes the peripheral sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, oleum, and proximal and distal colon. Mu receptors in non-neural tissue are found in the vascular and cardiac epithelium, keratinocytes, vas deferens, and Sertoli cells [113].

Mu opioid receptors in the amygdala and nucleus accumbens mediate opioid reward response (e.g., euphoria). In this brain region, opioids bind to and activate mu receptors, which inhibit gamma-aminobutyric acid (GABA) to increase dopamine transmission [61]. Mu opioid receptors broadly distributed in the limbic system mediate emotional response to pain and analgesia. In the medial thalamic nuclei, they relay spinothalamic inputs from the spinal cord to the cingulate gyrus and limbic structures [114].

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Kappa Opioid Receptors

Kappa opioid receptors bind dynorphin as the primary endogenous ligand. In the CNS, they are highly concentrated in the caudate-putamen, nucleus accumbens, amygdala, brain stem, neural lobe of the pituitary gland, and hypothalamus. In the PNS, these receptors are found in the sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, oleum, and proximal and distal colon. They are primarily found in the limbic system, brain stem, and spinal cord. Their major effects include spinal analgesia, sedation, dyspnea and respiratory depression, dependence, and dysphoria [113]. The kappa opioid receptor subtype k3 is considered the primary analgesic mediator [49].

Delta Opioid Receptors

Delta receptors are mostly confined to CNS structures of the pontine nuclei, amygdala, olfactory bulbs, and deep cortex, but are also found in the GI tract and the lungs. They mediate spinal and supraspinal analgesia and the psychomimetic and dysphoric effects of opioid analgesics [16; 110].

Other Potential Opioid Receptors

Other opioid-like receptors have been identified in the CNS, including the opioid receptor like-1 (ORL-1). In contrast to the classic opioid receptors, the ORL-1 receptor is insensitive to the opioid antagonist naloxone. Opioids can bind to and activate the toll-like receptor 4 (TLR4), an innate immune pattern-recognition receptor [61].

OPIOID ANALGESIC MECHANISM

Opioid analgesia results from a complex series of neuronal interactions, largely mediated by the high density of opioid receptors in the dorsal horn of the spinal cord and in subcortical regions of the brain [107]. The analgesic effects of opioids result from two general processes: 1) direct inhibition of ascending transmission of pain signaling from the dorsal horn of the spinal cord, and 2) activation of descending pain control circuits from the midbrain to the dorsal horn of the spinal cord [110]. All three opioid receptor types mediate spinal analgesia. Supraspinal analgesia is primarily mediated by mu opioid receptor subtype 1. Opioid receptors are coupled to the superfamily of inhibitory G proteins. Receptor activation inhibits adenylate cyclase, reducing generation of cyclic adenosine 3,5 monophosphate and other second messengers. Potassium conduction is activated, inhibiting calcium influx to hyperpolarized target cells and reducing their response to depolarizing pulses. Neurotransmitter release is inhibited, and generation of postsynaptic impulses is decreased [61; 107].

Although drugs such as morphine are highly selective for mu opioid receptor and bind multiple mu receptor subtypes, mu opioid agonists greatly differ by interaction with different receptor variants and other opioid and non-opioid receptors [106].

Spinal Level

The spinal cord dorsal horn is a primary analgesic site of opioids and is densely populated with mu (70%), delta (20%), and kappa (10%) opioid receptors. Opioid receptors are localized on presynaptic afferent fibers, interneurons, and postsynaptic projection neurons [61]. Opioids bind to and activate mu receptors, which inhibit the release of pain mediators such as substance P, glutamate, and nitric oxide from nociceptive afferent neurons. Spinal level analgesia appears to elevate pain thresholds [107].

Supraspinal Level

At supraspinal levels, opioids produce analgesia by attenuation of the subjective evaluation of pain. After morphine is given for severe pain, patients report pain but without the associated anguish and distress. Conscious awareness and pain response are retained but modified by changes in emotional response to pain, mediated in part through opioid receptors in the limbic system [107].

Opioid receptors are highly concentrated in the medial thalamus, where incoming sensory information associated with intense and deep pain is filtered and then relayed to the cerebral cortex. This opioid effect on medial thalamus pain signal filtering greatly contributes to analgesia [107].

Opioid receptors are highly localized in subcortical brain regions where descending pain-modulating pathways originate. Normally, these pathways are inhibited by GABAergic neurons that project to descending inhibitory neurons of the brain stem. Opioid analgesics bind to and activate mu receptors on GABAergic neurons; this inhibits GABA to activate descending pain-modulating pathways [61; 107]. In addition, opioids activate ascending serotonin/norepinephrine pathways that project to forebrain centers to regulate the emotional response to pain [105].

The greatest factor that contributes to opioid analgesia is concentration of the drug on the mu receptor, which can be altered by pharmacokinetic processes that influence plasma concentration of the opioid by impacting its absorption, distribution, metabolism, or excretion. Intrinsic properties of the opioid, such as lipid solubility, also contribute to opioid receptor concentration [115].

Neuropathic Pain

Opioid analgesics have historically been considered less effective in neuropathic pain, but more recent evidence provides some support for their use. The extent of neuropathic pain reduction correlates with the duration of opioid therapy, possibly accounting for the mixed results in short-term studies [116; 117]. A 2011 study discovered previously unknown mu and kappa receptor expression on numerous peripheral tissues, immune cells, and joint capsules/synovium. The administration of opioids by injection into painful peripheral tissue sites results in pain relief in the absence of CNS activity, which supports the existence of localized peripheral opioid receptors [118].

Opioid effectiveness in neuropathic pain may be influenced by the capacity to inhibit voltage-gated sodium channels and individual channel type. Buprenorphine is more effective in blocking sodium channels than meperidine, lidocaine, and bupivacaine, possibly from greater lipophilicity, as this is a major factor in local anesthetic potency [117]. Sufentanil, fentanyl, and tramadol, but not morphine, are effective in blocking neuronal Nav 1.2 and may have greater clinical effect in some forms of neuropathic pain [119].

Inflammation enhances opioid anti-nociceptive action by peripheral mechanisms that activate during later (but not early-stage) inflammation, suggesting that timing of opioid administration contributes to analgesic efficacy in inflammatory pain [118]. Opioids are also effective in reducing the "air hunger" of dyspnea in patients suffering from cancer or respiratory or cardiovascular insufficiency [105].

OPIOID ANALGESIC PHARMACOLOGY

Opioids have been a mainstay of pain treatment for thousands of years and remain so today. The opium poppy, *Papaver somniferum*, is the oldest and most prevalent source of opium and opioid analgesics. The opium poppy was grown in the Mediterranean region at least as early as 5000 B.C.E. and has since been cultivated in a number of regions throughout the world.

The first historical medical reference to opium dates back to the 3rd century B.C.E. by Arab physicians experienced in its therapeutic uses. In 1806, Friedrich Sertürner reported the isolation of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams [110]. Sertürner also published the first report of morphine toxicity in 1817. In this account, he discussed his experimentation of administering the alkaloid to himself, three young boys, three dogs, and a mouse. One of the dogs died, and the effects of morphine on Sertürner and his three young volunteers were described as "near-fatal." In the 1850s, the first recorded morphine overdose fatality was reported by Alexander Wood when performing one of the first morphine injections on his wife, who subsequently died of respiratory depression [120].

Raw opium contains numerous alkaloids, but only morphine, codeine, thebaine, and papaverine have an identified use in medicine. Because the synthesis of morphine is difficult, the opium poppy plant remains the primary source of morphine [105]. Thebaine is a minor constituent of opium that chemically resembles morphine and codeine but produces a stimulant, rather than calming, effect. Thebaine is not used medicinally but is converted into oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, and buprenorphine [122].

The numerous synthetic derivatives of morphine and thebaine are produced by relatively simple modifications of the parent molecule. For example, morphine is transformed into codeine by methyl substitution on the phenolic hydroxyl group and into diacetylmorphine by acetylation at the 3 and 6 positions (to produce heroin). Structural alteration of opioid molecules has been performed with the goal of producing an opioid molecule with greater opioid receptor affinity, to alter drug activity from agonist to antagonist, to change lipid solubility, and to increase resistance to metabolic breakdown. Although numerous opioid analgesics have been developed with clinical effects similar to morphine, morphine remains the criterion standard by which the analgesic efficacy of new opioids is measured [105].

There are several ways to classify the various opioids (***Table 1***). The traditional approach to opioid classification is grouping by analgesic potency into strong, intermediate, and weak subgroups [16]. Opioids may also be grouped into chemical classes, including phenanthrenes (the prototypical opioids), benzomorphans, phenylpiperidines, diphenylheptanes, and phenylpropyl amines [104]. A more pharmacologically and clinically relevant classification approach is grouping by functional interaction as mu receptor agonists, partial agonists, mixed agonists-antagonists, or antagonists. For the purposes of this course, currently available opioids will be grouped and discussed by functional class.

Each opioid has a unique analgesic and adverse effect profile that reflects differences in opioid receptor selectivity, binding affinity, and activity (***Table 2***) [115]. Understanding the unique receptor activity profile of individual opioids can assist in the selection process. These inter-opioid differences help account for incomplete cross-tolerance, the basis for opioid rotation [173].

MU OPIOID RECEPTOR FULL AGONISTS

Mu opioid receptor agonists include the most powerful analgesics used in medicine and possess the greatest analgesic potency among opioids. Properties of opioids in this group include increasing efficacy with dose escalation, absence of a ceiling effect (defined as further dose increases failing to increase analgesia beyond a certain level), and lack of antagonism of other concurrently administered mu opioid receptor agonists. Despite these shared properties, substantial pharmacologic and clinical differences are found among these agents [16; 123].

Morphine

Morphine (Roxanol, MS Contin, Avinza, Kadian, MorphaBond, Embeda) was first isolated from raw opium in 1803 and introduced as an analgesic in the United States in 1830. Hypodermic syringes were introduced in the mid-19th century, making morphine available for parenteral use with improved analgesic, sedative, and antitussive properties [124; 125]. Morphine is the prototypical opioid and remains one of the most effective drugs for alleviating severe pain, remarkable given its clinical use spanning almost two centuries. The World Health Organization has designated morphine as a drug of choice for moderate-to-severe pain [103].

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OPIOID ANALGESIC CLASSIFICATION SCHEMES		
Category	**Example Drugs**	
Analgesic Potency		
Weak	Codeine	
Intermediate	Buprenorphine Pentazocine Butorphanol Nalbuphine	Hydrocodone Tramadol Tapentadol
Strong	Morphine Oxycodone Hydromorphone Oxymorphone	Levorphanol Fentanyl and analogs Methadone Meperidine
Chemical Class[a]		
Phenanthrenes	Morphine Codeine Hydromorphone Levorphanol Oxycodone	Hydrocodone Oxymorphone Buprenorphine Nalbuphine Butorphanol
Benzomorphans	Pentazocine	
Phenylpiperidines	Meperidine	Fentanyl and analogs
Diphenylheptanes	Methadone	
Phenylpropyl amines	Tramadol	Tapentadol
Functional Activity[b]		
Full agonist	Morphine Codeine Hydromorphone Levorphanol Oxycodone Hydrocodone	Oxymorphone Methadone Fentanyl and analogs Meperidine Tramadol Tapentadol
Partial agonist	Buprenorphine	
Mixed agonist/antagonist	Pentazocine Nalbuphine	Butorphanol
Antagonist	Naloxone Naltrexone	Alvimopan Methylnaltrexone
[a]Under each class, the first listed opioid is the prototypical agent [b]At the mu opioid receptor		
Source: [16; 104]		*Table 1*

Morphine is a strong mu opioid receptor agonist and a weak kappa and delta receptor agonist. It can be administered intramuscularly (IM), intravenously (IV), subcutaneously (SC), rectally, epidurally, intrathecally, or orally. With IM/SC injection, the onset of effect occurs after 15 to 30 minutes, peak effect in 45 to 90 minutes, and duration of effect in roughly 4 hours. Following IV injection, the peak effect occurs in 15 to 30 minutes. When given IV, only a small portion of morphine reaches the CNS due to poor lipid solubility, a high degree of ionization at physiologic pH, protein binding, and rapid metabolism [115]. Morphine produces analgesia, euphoria, and a sensation of warmth. It increases pain threshold and alters the perception of noxious stimuli, even at low doses. Continuous, dull pain and pain originating in visceral organs, skeletal muscles, joints, and bone are most responsive to morphine [110].

RECEPTOR BINDING AFFINITY OF OPIOID ANALGESICS						
Opioid Analgesic	**Opioid Receptor**			**Other Receptors**		
	Mu	**Kappa**	**Delta**	**NE**	**5-HT**	**NMDA**
Agonists						
Codeine	+		+			
Hydrocodone	+	+	+			
Morphine	+++	+	+			
Fentanyl	+++					
Hydromorphone	++		+			
Oxycodone	++	+	+			
Oxymorphone	+++					
Methadone	++		+	+	+	--
Meperidine	+	++	+			
Levorphanol	+++	+	+	+		--
Tapentadol	+			+		
Tramadol	+			+	+	
Partial agonist						
Buprenorphine	+	-				--
Agonist-antagonists						
Pentazocine	-	++				
Nalbuphine	-	+	+			
Butorphanol		+				
Antagonist						
Naltrexone	---	---	-			

+ = Low/moderate agonist
++ = Moderate/high agonist
+++ = High-affinity agonist
- = Low/moderate antagonist
-- = Moderate/high antagonist
--- = High-affinity antagonist
5-HT = serotonin, NE = norepinephrine, NMDA = *N*-methyl-D-aspartate.

Source: [16; 115; 117] *Table 2*

The analgesic and respiratory depressant effects of morphine may not correlate with plasma concentrations, because CNS concentration peaks later and decays more slowly than plasma concentration. When given orally, morphine undergoes extensive first-pass hepatic metabolism, resulting in 40% to 50% of the oral dose reaching the CNS [115]. The elimination half-life of approximately two hours is independent of route of administration or formulation. Morphine administered by sublingual and buccal routes has a delayed onset of action compared with oral morphine (due to smaller peak plasma levels, lower bioavailability, and larger interpatient variability). Compared with the oral form, intrathecal morphine is 100 times more potent and epidural morphine is 10 times more potent (i.e., 0.5 mg intrathecally equals 5 mg epidurally) [103].

Oral morphine preparations are available in short-acting (SA) and ER formulations, including an ER formulation containing naltrexone to discourage tampering and diversion [115].

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Hydromorphone

Hydromorphone (Dilaudid, Exalgo) is a semi-synthetic hydrogenated ketone of morphine with primary activity as a mu receptor agonist. It has roughly five to seven times the potency of morphine, with similar effects but possibly less sedation and greater euphoria [110]. Hydromorphone can be administered by parenteral, IV, rectal, and oral routes and is considered the best opioid for SC administration. Oral hydromorphone has a bioavailability of 50% and plasma elimination half-life of 2.5 hours [103]. Its high water solubility permits very concentrated formulations. A meta-analysis found significantly better analgesia with hydromorphone than morphine for acute pain, without significant differences in adverse effects [126].

Following oral administration of conventional-release hydromorphone, the drug is rapidly absorbed and undergoes hepatic first-pass elimination of approximately 50%. The terminal elimination half-life after IV administration is 2.5 to 3 hours, and the primary mode of elimination is through urinary elimination in the form of hydromorphone-3-glucuronide, the primary metabolite. Some metabolites may have greater analgesic activity than hydromorphone itself but probably do not contribute to its pharmacologic activity. The side effects are similar to morphine [127].

The first ER formulation of hydromorphone (Palladone) was approved for marketing in 2004. However, at the request of the FDA, Palladone was withdrawn from the U.S. market in 2005 by its manufacturer, Purdue Pharma, over the potentially fatal interaction with alcohol [128]. Another ER formulation, Exalgo, has since been introduced without this liability [129].

Codeine

Codeine (Tylenol with Codeine, Capital with Codeine, Vopac) produces analgesia solely through enzymatic conversion into morphine, so it is considered a pro-drug. A pro-drug is a drug ingested in a biologically inactive (or less active) form and biotransformed into an active (or more active) metabolite [130].

The oral bioavailability of codeine is 50%, with roughly 10% metabolized to morphine. However, at least 10% of individuals possess deficient activity of the hepatic enzyme necessary to metabolize codeine to morphine due to genetic variation or polymorphism. In these individuals, codeine has no analgesic effect and should be avoided.

Codeine can be used orally or IM for mild-to-moderate pain but has very limited use in severe pain. Codeine is also used as an antitussive and antidiarrheal. Codeine produces minimal euphoria, has low abuse liability, is less sedating, and is less likely to result in respiratory depression than morphine. Constipation is a common side effect. Because commercially available codeine is combined with acetaminophen or acetylsalicylic acid (ASA), the dosage should be monitored to ensure daily safe limits are not surpassed [104]. Codeine has an analgesic ceiling, with no additional analgesic benefit from doses greater than 60 mg [131].

Oxycodone

Oxycodone (Oxy IR, Percocet, Tylox, OxyContin, Xtampza ER, Targiniq ER) is a semisynthetic opioid analgesic derived from the natural alkaloid thebaine and has been in medical use since 1917. Although oxycodone mu opioid receptor affinity is at least 20 times less than morphine, oxycodone possesses high oral bioavailability and delivers analgesia and other subjective effects comparable to oral morphine [103]. Unlike morphine, oxycodone has moderate affinity and agonist activity at the kappa-2b opioid receptor, which contributes to its efficacy in neuropathic pain [117].

Oxycodone is available in SA and ER oral formulations. Oxycodone SA has a half-life of approximately two to four hours and a bioavailability of 50% to 60%. The overall clinical effects of oxycodone reflect primary mu receptor activity, with analgesia, respiratory depression, euphoria, and abuse liability comparable to other mu agonists. Oxycodone differs from morphine by producing less dysphoria and by more rapid transport through the blood-brain barrier, resulting in greater CNS than plasma concentrations, the reverse of morphine [117].

In addition to its low-dose combination with acetaminophen, oxycodone is formulated as the sole analgesic in 10-, 20-, 40-, and 80-mg controlled-release (CR) tablets and 5-mg SA capsules. Sales of oxycodone CR (OxyContin) 160 mg were discontinued by Purdue Pharma in 2001 over abuse and diversion concerns [132].

Oxymorphone

Oxymorphone (Numorphan, Opana) was first synthesized in Germany in 1914, patented in the United States in 1955, and introduced in 1959 for parenteral injection and in suppository form. It then became available as an oral SA opioid, but this was withdrawn from the U.S. market in the early 1970s. Following reintroduction in 2006 in oral SA and ER formulations, its use in the treatment of noncancer pain has steadily increased [133].

Oxymorphone is a semisynthetic derivative of the parent compound morphine and has a high affinity for the mu opioid receptor and negligible interaction with kappa and delta opioid receptors [134]. The potency is roughly 1.2 times that of morphine, but with less sedative effects [16]. Oxymorphone possesses less protein binding (10% to 12%) than morphine (30% to 35%) and oxycodone (45%), and its highly lipophilic properties provide ease in blood-brain barrier penetration [129]. The oral bioavailability of oxymorphone is approximately 10%, the lowest of the full agonists.

In healthy volunteers, the half-life ranges from 7.2 to 9.4 hours, longer than that of morphine, hydromorphone, and oxycodone. Oxymorphone SA tablets may be given at six-hour intervals, whereas the ER formulation is dosed twice daily. Steady-state conditions are achieved after three to four days. Oxymorphone is subject to hepatic first-pass effects and is excreted by the kidneys. As such, this agent has a prolonged half-life and accumulates in patients with renal failure. In patients with hepatic insufficiency, increasing the dosing interval is recommended [103].

Oxymorphone is an effective opioid analgesic with a safety profile comparable to other mu agonist opioids. It may have a safety advantage in elderly or frail patients for whom adverse drug interactions are concerning [135]. However, in 2017, the FDA requested Opana ER be removed from the market amid abuse concerns [267].

Hydrocodone

Hydrocodone (Zohydro ER, Hysingla ER, Lortab, Vicodin) is a semi-synthetic codeine derivative that more closely resembles morphine in its pharmacologic profile. Hydrocodone was first used medically as a cough suppressant and analgesic in the 1920s [122; 136]. It exhibits a complex pattern of metabolism, including demethylation at the 3-carbon position into hydromorphone, which has stronger mu receptor binding than the parent drug. Thus, similar to codeine, hydrocodone is suggested to be a pro-drug. Its analgesic properties are similar in potency to codeine [16].

Hydrocodone is effective as a cough suppressant and as an analgesic for moderate to moderately severe pain. It is most frequently prescribed in combined formulations with acetaminophen (Vicodin, Lortab), aspirin (Lortab ASA), ibuprofen (Vicoprofen), and antihistamines (Hycomine) and as an antitussive liquid formulation [122]. The hydrocodone/ibuprofen product is intended for short-term (generally less than 10 days) management of acute pain from trauma, musculoskeletal or back pain, postoperative pain, abdominal pain, or dental pain. Two single-entity hydrocodone ER products are now available; in addition to sparing patients with comorbidity or who require long-term use from acetaminophen or nonsteroidal anti-inflammatory drug (NSAID)-related adverse effects, these products are thought to provide more stable analgesic with slow release and less euphoria [137].

Methadone

Methadone (Dolophine, Methadose) was first synthesized as an analgesic in Germany during World War II in response to the difficulty obtaining raw opium to synthesize morphine [138]. Although chemically unlike morphine or heroin, methadone produces many of the same pharmacologic and clinical effects. It was introduced into the United States in 1947 as the analgesic Dolophine.

High-dose methadone can block the effects of heroin and other opioid drugs by diminishing reward and reinforcement effects, and this has been the primary use of methadone in the United States over the last five decades. In the late 1990s, methadone entered clinical use as an analgesic [122].

Methadone is available in racemic form with a 50:50 mixture of two enantiomers: a levo-(R)-enantiomer and a dextro-(S)-enantiomer. The 1(R)-enantiomer produces opioid analgesia as a mu opioid receptor agonist, while the d(S)-enantiomer functions as an *N*-methyl-D-aspartate (NMDA) receptor antagonist and reuptake inhibitor of serotonin and norepinephrine. These pharmacologic properties expand indications for its use beyond those of most other mu receptor agonists [117]. Methadone produces analgesia very similar to other commonly used opioids, but its lack of euphoric effects relative to other agents can make it advantageous in some patient populations. NMDA receptor antagonism can make methadone highly beneficial in managing patients with a history of prolonged opioid use with high opioid tolerance or opioid-induced hyperalgesia [110].

In the inpatient setting, IV methadone can be very effective in managing patients with true morphine allergies. Patients predicted to have long-term opioid requirement can initiate with IV methadone and are easily transitioned to oral methadone [110]. The highly variable elimination half-life is 8 to 60 hours, and single-dose analgesia lasts 4 to 8 hours. This necessitates great caution during initiation and titration, because patients may re-dose when analgesia wears off and pain reappears, leading to accumulation, toxicity, and overdose [110]. Methadone requires a thorough understanding of its pharmacokinetic properties to safely prescribe.

The American Society of Interventional Pain Physicians recommends methadone for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses.

(https://www.guideline.gov/summaries/summary/38257. Last accessed May 26, 2017.)

Level of Evidence: Limited (Evidence is insufficient to assess effects on health outcomes because of limited number of power studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.)

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Levorphanol

Levorphanol is the only commercially available opioid agonist of the morphinan series and the levo-enantiomer of dextrorphan, a potent NMDA receptor antagonist [139]. Levorphanol was first synthesized more than 40 years ago as an alternative to morphine, and it produces effects very similar to morphine, with greater potency. Analgesia is produced by activity as a mu, delta, and kappa opioid receptor agonist, NMDA receptor antagonist, and norepinephrine and serotonin reuptake inhibitor. The NMDA receptor antagonist potency of levorphanol is equivalent to ketamine and superior to methadone [49]. Single-dose analgesic duration is 6 to 8 hours, and the elimination half-life is 11 hours. This increases the potential for drug accumulation, and patients should be observed for toxicity during the initial two to five days. Roughly 50% of oral levorphanol clears first-pass metabolism and is bioavailable [140]. Initiate dosing every four hours, and every six to eight hours when steady state is reached (after one to two weeks) [15; 140].

During the 1980s, levorphanol fell into disuse with the introduction and aggressive marketing of ER forms of morphine, oxycodone, and fentanyl. Renewed interest in this drug was prompted by recognition that many patients with neuropathic pain do not obtain pain control with standard full-agonist opioids. Levorphanol shows promise in treating neuropathic pain, severe pain in hospice patients, and severe pain in patients with chronic noncancer pain uncontrolled by other mu opioid receptor agonists. With empirical confirmation, levorphanol has potential as first-line or second-line therapy for these indications, but little research has been published on this drug [46; 49; 140; 141].

The brand-name drug Levo-Dromoran is discontinued, and no parenteral form is available. The sole available dose and formulation for levorphanol is an oral 2-mg tablet [140]. As a generic drug, levorphanol has not been promoted or marketed [141].

Roxane Pharmaceuticals stopped manufacturing levorphanol in 2015. Shortly thereafter, Sentynl Therapeutics, Inc., released a "new" levorphanol to the market. Unfortunately for pain sufferers who responded well to levorphanol, the average wholesale price of 2-mg tablets increased 2,073%, from $214/100 tablets to $4,650/100 tablets [142].

Fentanyl and Analogs

Fentanyl (Duragesic) is a phenylpiperidine-class opioid and is structurally similar to meperidine. Fentanyl was first synthesized in Belgium in the late 1950s and introduced to the U.S. market in the 1960s as an IV anesthetic. Other fentanyl analogues were subsequently introduced, including alfentanil, an ultra-short acting (5 to 10 minutes) analgesic; sufentanil, an exceptionally potent analgesic (1,000 times more potent than morphine) for use in cardiac surgery; and remifentanil, with similar potency to fentanyl and ultra-short duration of 3 to 10 minutes [105].

Fentanyl has an analgesic potency 80 to 100 times that of morphine. The highly lipophilic nature of the molecule allows rapid blood-brain barrier penetration and quick onset of action (two to three minutes with IV administration). Primary clinical effect comes from mu receptor agonist activity and to a lesser extent from kappa and delta receptor activity [143]. The pharmacologic profiles of fentanyl and its congeners (sufentanil, remifentanil, and alfentanil) are similar to other mu-receptor agonists, although fentanyl produces fewer side effects of sedation, nausea and vomiting, urinary retention, and pruritus than morphine or hydromorphone [110]. The fentanyls are distinguished from other mu opioid receptor agonists by shorter time to peak analgesic effect, rapid termination of effect after small doses, and relative cardiovascular stability, making them very popular for surgical use. The respiratory depression potential is similar to other mu receptor agonists, with a more rapid onset [105]. Fentanyl formulations include several transmucosal and buccal preparations for rapid-onset analgesia in breakthrough pain, and a transdermal preparation for sustained analgesia in chronic pain.

Transmucosal immediate-release fentanyl formulations are approved by the FDA for use in breakthrough pain. Transdermal fentanyl was developed to circumvent unsuitability for oral use and is indicated for continuous sustained-release analgesia in the treatment of chronic pain [144]. With initial use, the 6- to 12-hour lag time from application to onset of action requires the use of short-acting opioids for analgesic coverage and for breakthrough pain; morphine, tapentadol, or oxycodone are preferred. Steady state is usually achieved in three to six days. With patch removal, a subcutaneous reservoir remains, and up to 24 hours is usually needed for drug clearance [16; 115].

Tramadol

Research efforts into mechanisms of pain relief during the 1990s focused on centrally mediated monoamine transmission and its influence on chronic and neuropathic pain. Clinical evidence demonstrated that increasing the extracellular concentrations of serotonin and norepinephrine in descending pain inhibitory pathways produced an analgesic effect. Norepinephrine is the primary monoamine contributor to pain signal attenuation and is especially useful in neuropathic pain. Combining an opioid agonist with a monoamine reuptake inhibitor was hypothesized to produce opioid-sparing effects, increased pain control, and decreased adverse effects. These efforts led to the development of tramadol and tapentadol [49].

Tramadol (Ultram, ConZip) is a synthetic codeine analog from the aminocyclohexanol structural group and a racemic compound. The positive enantiomer acts as a serotonin reuptake inhibitor, with 30% of total analgesic effect from weak mu opioid receptor agonism; the negative enantiomer inhibits norepinephrine reuptake [117]. Tramadol has greater efficacy in neuropathic than nociceptive pain. Monoamine reuptake inhibition accounts for tramadol's efficacy in neuropathic pain [117].

The primary metabolite, *O*-desmethyltramadol, has higher mu opioid receptor affinity and two to four times greater analgesic potency than the parent drug. Tramadol is as effective as morphine in mild-moderate pain. Its bioavailability is 68% following an oral dose and 100% following IM administration [145].

Tramadol has lower abuse potential than other opioids but is associated with the significant adverse drug reactions of serotonin syndrome and seizures. Dosage should not exceed 400 mg/day due to the seizure risk, and even doses less than 400 mg/day can increase seizure potential in patients with epilepsy or risk factors for seizure [117]. Seizure risk is elevated by concurrent use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), cyclobenzaprine and other tricyclic compounds, other opioids, neuroleptics, and certain other drugs. Tramadol should not be used within 14 days of monoamine oxidase inhibitors (MAOIs), as this increases risk of seizures or serotonin syndrome [16].

Tapentadol

Tapentadol (Nucynta) is a novel synthetic opioid structurally related to tramadol that was approved in 2009. It was intentionally designed to overcome the barriers to efficacy associated with tramadol, such as the potential risk for serotonin syndrome [49]. Tapentadol has 18 times less affinity for mu opioid receptor than morphine and is 5 times less potent than oxycodone (i.e., 50 mg tapentadol is equivalent to 10 mg oxycodone) [146; 147]. Tapentadol has an oral bioavailability of 32%, and plasma protein binding is 20%. Time to maximum serum concentration is achieved in 1.25 to 1.5 hours, and the half-life is 24 hours [103].

Tapentadol has no active metabolites and primarily undergoes hepatic metabolism via phase II conjugation. Tapentadol selectively inhibits norepinephrine reuptake with affinity and potency comparable to venlafaxine, which increases efficacy and avoids the potential risk for serotonin syndrome. In a study of patients with chronic pain receiving tapentadol for up to two years, 88% did not experience opioid withdrawal symptoms on abrupt withdrawal and symptoms were mild-to-moderate among those who did [148].

Analgesic tolerance develops at significantly lower rates with tapentadol than with morphine. It has a low risk for drug interactions, does not depend on metabolic activation for efficacy, and shows a lower incidence in adverse GI effects such as nausea, vomiting, and constipation relative to other opioids [49; 149].

A review of prolonged-release (PR) tapentadol concluded its broad analgesic efficacy, ease of initiating and titrating in opioid-naïve and opioid-experienced patients, favorable pharmacokinetic profile with few medication interactions, low abuse potential, and low risk of withdrawal after cessation may offer significant advantages over classic opioid analgesics. Tapentadol is not recommended in patients with severe renal or hepatic impairment, because studies are lacking in these patient populations [150].

Meperidine

Meperidine (Demerol, Meperitab) is a synthetic phenylpiperidine derivative with weak mu and kappa receptor agonist activity. It has roughly one-tenth the potency of morphine. The structural similarity to atropine is consistent with its original development as an anti-muscarinic agent. The effects are similar, but not identical, to morphine, with shorter analgesic duration and less antitussive and antidiarrheal efficacy. In equivalent analgesic doses, meperidine produces comparable sedation and respiratory depression and possibly greater euphoria than morphine, although some patients experience dysphoria. Pharmacologic differences from morphine include increased risk for tachycardia and dry mouth and less biliary tract spasm and miosis. Meperidine may significantly decrease blood pressure, especially when administered to elderly or hypovolemic patients [104; 123].

The short analgesic duration (2.5 to 3.5 hours) makes meperidine impractical for persistent pain, although it is a useful analgesic in labor and delivery and uniquely effective in treating post-operative shivering. Accumulation of the neurotoxic metabolite normeperidine contraindicates its use for longer than 48 hours or at doses of 600 mg or greater over 24 hours in any context. Normeperidine accumulation is especially likely in patients with impaired renal function. The neuroexcitatory properties of this metabolite can cause tremors, muscle twitches, delirium, or seizures; multifocal myoclonus develops before seizures and can serve as a warning sign. Normeperidine toxicity is not reversible with naloxone. Administration of meperidine to patients receiving MAOIs can lead to profound and possibly fatal autonomic instability [16; 110; 123]. Clinical use of meperidine has declined into virtual disuse in recent years [115].

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Propoxyphene

Propoxyphene (Darvon, Darvocet) was first marketed in 1957 to treat mild-to-moderate pain. Propoxyphene primarily binds to mu opioid receptors to produce mild analgesia, with potency one-half to one-third that of codeine [16]. Propoxyphene also became a popular drug of abuse. In 2010, the FDA requested the removal of propoxyphene from the U.S. market due to new data showing increased risk for serious abnormal heart rhythms with its use, even at therapeutic doses [151]. This drug is no longer available domestically.

Levo-Alpha-Acetylmethadol

Levo-alpha-acetylmethadol (LAAM) is a synthetic mu opioid receptor agonist closely related to methadone, but with a longer duration of action (48 to 72 hours). LAAM was originally developed by German chemists in 1948 and as early as 1952 was identified as an agent that could prevent opioid withdrawal symptoms for more than 72 hours. In 1993, the FDA approved LAAM for the treatment of opioid addiction, with the intent to build on the strengths and improve on the drawbacks of methadone [122; 152]. However, concerns over cardiovascular toxicity and subsequent under-utilization led to its withdrawal from the market in 2004 by the manufacturer, and LAAM is no longer commercially available in the United States [138].

PARTIAL AGONIST OPIOIDS

Partial agonists possess mu opioid receptor binding and activity, but to a lesser extent than full agonists such as morphine. Buprenorphine is the only commercially available partial agonist in the United States.

Buprenorphine

Buprenorphine (Belbuca, Suboxone, Subutex, Butrans) is a semi-synthetic opioid first derived from thebaine in 1966, initially as an alternative to methadone therapy for heroin addiction [153]. Injectable buprenorphine (Buprenex) was approved in 1981 for acute pain, and two sublingual formulations (Suboxone and Subutex) were approved for treating opioid addiction in 2002 [49]. The buprenorphine transdermal system was approved by the FDA in 2010 for the management of moderate-to-severe chronic pain in patients requiring continuous opioid analgesia for an extended time period. More recently, buprenorphine buccal film (Belbuca) was approved for the same indication. The transdermal and buccal products were developed to overcome the very low oral bioavailability resulting from substantial first-pass intestinal and hepatic metabolism [117].

The mu opioid receptor-binding kinetics of buprenorphine are unique. Receptor affinity is high, but buprenorphine associates and dissociates slowly (30 and 166 minutes, respectively) and incompletely (50%). This receptor saturation is particularly important with buprenorphine, because its high affinity and robust binding capacity make displacement by naloxone difficult or impossible. The relative resistance to naloxone antagonism requires higher doses for successful reversal [49].

The analgesic properties of buprenorphine mostly originate from mu opioid receptor interaction with high binding affinity and low efficacy, yielding partial agonist effects. Other contribution comes from activity as a nociceptin opioid peptide receptor partial/full agonist and kappa opioid receptor antagonist [117]. Prolonged analgesia can be achieved with buprenorphine from its highly lipophilic properties and prolonged receptor occupancy. It may have superior efficacy in neuropathic pain due to its pharmacologic profile and has also shown anti-hyperalgesic effects [117; 145]. A high-dose (15 mg) analgesic ceiling effect can occur, but this dose level is infrequent with analgesic use [122; 145]. Buprenorphine may act as a mu opioid receptor antagonist at high doses [117].

After application of the transdermal patch, plasma concentrations steadily increase, and the minimum effective analgesic dose is reached more rapidly with higher-dose patches. Steady state is reached after the third consecutive application. Bioavailability of the transdermal formulation is 60% compared with the IV route. Effective plasma levels occur within 12 to 24 hours and last for 72 hours. It takes 60 hours to reach maximum concentration. After patch removal, concentrations decrease by 50% in 12 hours, and then decline more gradually [103]. Transdermal buprenorphine has a maximum dose limited to 20 mcg per hour due to the potential for prolonged QTc wave interval at higher doses [16; 123].

Buprenorphine possesses a dose-ceiling effect for respiratory depression, reducing the likelihood of this potentially fatal consequence. Importantly, this applies only in the absence of co-ingested CNS or respiratory depressants. Side effects are similar to other opioids, but it is important to remember that as a result of its antagonist properties, buprenorphine can precipitate withdrawal symptoms in patients who are physically dependent on other commonly used opioids [110].

MIXED AGONIST/ANTAGONIST OPIOIDS

For more than 70 years, the ultimate goal of analgesic research has been the discovery of an opioid agent producing effective analgesia without respiratory depression or abuse/addiction potential [154]. Earlier efforts in this quest led to synthesis of the first mixed agonist-antagonist, *N*-allylmorphine (nalorphine), in 1942. Although nalorphine was a potent analgesic and antagonist to most morphine effects, dosing sufficient for analgesia produced severe psychotomimetic effects that made the drug unsuitable for clinical use. However, discovery and development of this opioid lay the groundwork for subsequent synthesis of several mixed agonist-antagonists that have entered clinical use [16; 155].

Available mixed agonist-antagonists act as mu receptor antagonists and kappa receptor agonists. Those in current clinical use share the characteristics of an analgesic ceiling effect, whereby dose escalation beyond a certain point will not increase analgesia but increases side effects. These agents have a greater likelihood of the side effects of dysphoria, delusions, and hallucinations than full mu agonists and an increased risk of triggering an opioid withdrawal crisis in patients with physiologic dependence to full mu agonists. Kappa receptor agonist activity contributes to the analgesic and side effect profile.

These drugs should be used with caution in any patient currently receiving opioid agonists [16; 115; 123]. Practice guidelines recommend against using mixed agonists/antagonists in cancer pain, and their absence from practice guidelines for chronic noncancer pain reflects discouragement for use in these patients as well [15; 156; 157]. However, several niche indications for pain have emerged.

Pentazocine

Pentazocine (Talwin) was the first opioid in this class to enter clinical use following the development of nalorphine; it was introduced to the U.S. market as an analgesic in 1967 [122]. Kappa opioid receptor activation accounts for the analgesic effects and potential side effects of dysphoria and psychotomimesis [125]. The analgesic potency is 25% to 50% of morphine. Moderate analgesia is produced by an oral dose of 50 mg; with doses greater than 70 mg, an analgesic and respiratory depression ceiling occurs. Pentazocine has lower abuse potential than morphine, but prolonged daily use can lead to physical dependence. Dysphoric and psychotic side effects are dose proportional and reversed with naloxone. Pentazocine can increase serum catecholamine levels. Clinical use is restricted by limited analgesia, antagonism of concurrent mu agonist opioids, and the potential for GI and cardiovascular adverse effects [155].

Butorphanol

Butorphanol (Stadol) is a morphinan congener with a pharmacologic profile similar to pentazocine. It is more suitable for acute than chronic pain. Side effects of drowsiness, weakness, sweating, sensation of floating, nausea, and psychotic-like effects are less frequent than with pentazocine. Physical dependence can develop from regular use [105]. Butorphanol was initially available as an injectable formulation (Stadol). More recently, a nasal spray (Stadol NS) became available, and the ensuing abuse and diversion of this product led to its designation as a Schedule IV controlled substance [122].

Butorphanol is a mu opioid receptor antagonist and kappa opioid receptor agonist, and the opioid receptor affinity ratio of 1:25:4 for mu, kappa, and delta receptors, respectively, indicates greater delta than mu opioid receptor affinity [158]. With parenteral administration, butorphanol has analgesic potency five to eight times greater than morphine. It has a rapid onset, with peak analgesia within 1 hour, plasma half-life of 2 to 3 hours, and elimination half-life of 4.5 to 5 hours. With oral administration, bioavailability is 17% that of a comparable IV dose. The intranasal formulation is commonly used in the treatment of migraine headache. The IV formulation is effective in moderate-to-severe pain and is typically used for postoperative pain and pain control during labor. With analgesia mediated by kappa and not mu receptor activation, butorphanol may be an effective analgesic option in patients with history of opioid use disorder [110]. At a dose of 10 mg IM, butorphanol induces respiratory depression similar to a comparable morphine dose, but the level of depression does not increase with dose escalation due to the ceiling effect [159; 160].

Nalbuphine

Nalbuphine (Nubain) is similar in structure to naloxone, with primary activity as a kappa opioid receptor agonist, a mu opioid receptor partial antagonist, and delta receptor activity. On a per-milligram basis, analgesic potency is comparable to morphine, and opioid antagonist potency is one-fourth that of nalorphine and 10 times that of pentazocine. Respiratory depression is similar to morphine at equianalgesic doses, does not increase at doses greater than 30 mg, and is reversed by naloxone. With IV administration, onset is 5 to 10 minutes, duration is 3 to 6 hours, and elimination half-life is roughly 5 hours.

The most common side effect is sedation. Nalbuphine produces less dysphoria than other mixed agonist-antagonists and may produce euphoria; hemodynamic parameters are unaffected. Nalbuphine can reverse the respiratory depression and pruritus produced by mu agonists while maintaining analgesia; in this context, it is co-administered epidurally [110; 161; 162; 163].

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OPIOID ANTAGONISTS

A fourth group of opioids, opioid antagonists, bind and inactivate opioid receptors. Naltrexone and naloxone have traditionally been used to reverse potentially fatal overdose from opioid receptor agonists such as morphine or heroin. Opioid agonist molecules on mu opioid receptor are displaced, agonist effects on mu opioid receptor are abruptly halted, and opioid-dependent patients rapidly experience full alertness, analgesic loss, and opioid withdrawal [164].

Clinical trials with low-dose naltrexone have found unexpected and paradoxical enhancement rather than blockade of analgesia when co-administered with morphine and other opioid agonists in postoperative pain or severe intractable pain. Other evidence suggests analgesic efficacy as monotherapy in Crohn disease, irritable bowel syndrome, and fibromyalgia [165]. These findings led to the development and introduction of the peripheral-acting mu receptor antagonists alvimopan, methylnaltrexone, and naloxegol for severe opioid-induced constipation [166; 167].

In addition to opioid-induced constipation, opioid antagonists are FDA-approved for the treatment of alcohol and opioid use disorder (naltrexone 50–100 mg/day oral) and opioid overdose (naloxone 0.4–1.0 mg/dose IV or IM). In pain medicine, the dose ranges of naltrexone and naloxone are substantially lower. Of the two, naltrexone is much more widely used, and published pain medicine studies have used dose ranges of 1–5 mg (termed "low-dose") or <1 mg in microgram amounts (termed "ultra-low-dose") [165]. For example, case studies have reported dramatic improvement in refractory pain with intrathecal administration of an opioid agonist combined with ultra-low-dose naloxone in the low nanogram range [168].

The mechanism of low-dose and ultra-low-dose opioid antagonists is not fully known and is the subject of investigation [165]. One explanation describes a sequential action, whereby binding and inhibition first occurs at excitatory receptors, followed by binding at inhibitory receptors. This decrease in excitation facilitates a broader clinical expression of inhibitory function, which potentiates analgesia and reduces adverse effects. For example, with opioid-induced hyperalgesia, ultra-low-dose naltrexone appears to act through excitatory blockade to promote analgesia and tolerability [169; 170].

Naloxone

Naloxone (Narcan) is an allyl-derivative of noroxymorphone first synthesized in 1960. It acts as a competitive antagonist with slightly higher affinity for mu receptors over kappa and delta receptors, and inhibits the entire range of pharmacologic effects produced by mu agonists. Naloxone is efficiently absorbed after oral administration, but extensive hepatic first-pass metabolism (>95%) and low bioavailability makes it unsuitable for oral use [120; 125]. Following IV or IM administration, peak plasma concentration occurs at 10 minutes, the duration of action is 1 to 4 hours, and the half-life is 30 to 81 minutes [165].

Naltrexone

Naltrexone (ReVia, Depade) has activity comparable to naloxone but with a longer duration of action and higher oral bioavailability (40%) [125]. Following oral administration of naltrexone, the peak plasma concentration occurs at 1 to 2 hours, the duration of action is up to 24 hours, and the half-life is up to 14 hours [165].

Methylnaltrexone

Methylnaltrexone bromide (Relistor) is a naltrexone derivative with high peripheral opioid receptor selectivity resulting from low lipid solubility and poor blood-brain barrier penetration into the CNS. Methylnaltrexone is indicated for opioid-induced constipation refractory to conventional therapies in patients with advanced illness receiving palliative care. It binds and antagonizes mu opioid receptors in the GI tract. With little oral bioavailability, methylnaltrexone is administered by subcutaneous injection [171].

Alvimopan

Alvimopan (Entereg) is a mu opioid receptor antagonist with limited CNS penetration due to its large molecular weight and polarity that facilitates selective GI mu opioid receptor antagonist activity. Alvimopan was developed to address the problem of bowel dysfunction following intestinal surgery and opioid use for postoperative pain. It is FDA-approved only to accelerate the time to upper and lower GI recovery after partial large or small bowel resection surgery with primary anastomosis [171]. Concerns over the risk of serious adverse cardiovascular events led the FDA in 2012 to restrict its use to a maximum of 15 capsules, a seven-day maximum duration, used only in hospitalized patients and only in hospitals with documented registration and completion of the Entereg Access Support and Education (EASE) program, a risk management program specific to alvimopan [172].

Naloxegol

Naloxegol (Movantik) is a polymer conjugate of naloxone administered orally once daily. It is FDA-approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain. The 25-mg dose appears similar in efficacy to the 12.5-mg dose, with greater side effects associated with the higher dose. In phase III trials, the most common side effects were abdominal pain (21%), diarrhea (9%), nausea (8%), flatulence (6%), vomiting (5%), headache (4%), and hyperhidrosis (3%) [171].

OTHER OPIOIDS IN CLINICAL USE

Diphenoxylate (Lomotil) and loperamide (Imodium) are meperidine congeners FDA-approved for the treatment of diarrhea. Both drugs bind intestinal opioid receptors to slow GI motility through action on intestinal circular and longitudinal muscles. At approved anti-diarrheal doses, both agents lack significant CNS effects [105].

PHARMACOKINETIC FACTORS IN OPIOID ANALGESIC RESPONSE

Pharmacokinetics is the process by which the body absorbs, distributes, metabolizes, and excretes a drug, and pharmacokinetic factors fundamentally influence the safety, efficacy, and tolerability of opioid analgesics. This is true with fatal toxicity, whereby rising serum opioid concentrations overwhelm a patient's physiologic capacity to clear the opioids through metabolism and elimination. Aside from high-dose ingestion, fatal and non-fatal toxicity results from interference with opioid metabolism and excretion from genetic factors, drug interactions, medical comorbidities, or opioid analgesic formulation and dosing. These risks can be mitigated by improved prescriber knowledge and skills.

ABSORPTION AND DISTRIBUTION

Most opioids, including morphine, oxycodone, hydromorphone, methadone, tramadol, tapentadol, fentanyl, sufentanil, buprenorphine, and codeine, possess high GI permeability and are completely absorbed from the GI tract following oral administration. However, fentanyl and buprenorphine, due to extensive hepatic first-pass metabolism, have very low oral bioavailability, rendering their oral use ineffective [1]. (This differs from sublingual and buccal administration.)

To produce analgesic action in the CNS after absorption, opioids must penetrate the blood-brain barrier; highly lipophilic opioids possess a more rapid onset due to greater ease of blood-brain barrier transport [1]. The basis for the widely variable duration of effect among opioids is complex, not always explainable by the rate of plasma clearance and terminal half-life. For example, at equivalent analgesic doses, morphine produces longer analgesia than fentanyl but has a shorter half-life. This may be explained by morphine's relatively low lipid solubility and slower diffusion out of CNS tissue [104].

METABOLISM AND ELIMINATION

Many drugs, including opioids, must undergo biotransformation to be readily eliminated from the body. Opioid analgesic molecules that produce CNS effects must be lipophilic to cross cell membranes in the blood-brain barrier, and metabolism is performed to convert lipophilic opioids into hydrophilic metabolic products for elimination. This is achieved through hepatic enzymes. The metabolic process ends when the opioid byproducts are sufficiently hydrophilic for urinary excretion [174]. Medications can be substrates at multiple cytochrome (CYP) isoenzymes, inducing one while inhibiting another.

Hepatic enzymes facilitate two forms of metabolism: phase I and phase II [174]. Phase I metabolism consists of modification of the drug molecular structure through chemical reactions such as oxidation, reduction, or hydrolysis. The predominant catalysts for phase I drug metabolism are found in the CYP450 enzymatic superfamily [130]. Phase I metabolism of some opioids produces active analgesic metabolites, as with conversions of codeine into morphine, hydrocodone into hydromorphone, and tramadol into *O*-desmethyltramadol [175]. The CYP system is comprised of more than 50 isoenzymes, but more than 90% of opioid metabolism involves the 3A4, 2D6, or 2C9 isoenzymes [145].

Phase II metabolism is a chemical reaction whereby a drug is conjugated with a chemical moiety (e.g., a glucuronide) to readily promote renal excretion. The most important Phase II conjugation reaction is glucuronidation, catalyzed by members of the uridine diphosphate glucuronosyltransferase (UGT) enzyme family. Within the UGT enzyme family, the most abundant enzyme involved in phase II opioid metabolism is UGT2B7. In most cases, the conjugated drug is rendered inactive and loses biologic activity. The exception is morphine; its conjugated metabolite, morphine-6-glucuronide, is analgesic. UGT2B7 is the primary enzyme that metabolizes morphine, hydromorphone, and oxymorphone [130].

Some opioids undergo both phase I and phase II metabolism; the breakdown products of both phases can be active or inactive. The process of metabolism ends when the molecule is sufficiently hydrophilic for efficient excretion [174].

The metabolic products of opioids differ in pharmacologic and clinical relevance. Some have analgesic activity, some are toxic with accumulation, and others are inactive. Active metabolites can bind to and activate opioid or other receptors, compete with co-administered drugs or their metabolites when metabolism involves a common pathway, or alter the activity of its CYP450 metabolic pathway.

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ADVERSE DRUG INTERACTIONS

One challenge in safe opioid analgesic prescribing is avoiding adverse drug interactions. Opioids have a narrow therapeutic index, potentially fatal concentration-dependent toxicity, and wide inter-individual variability. As discussed, many fatalities associated with opioid prescribing involve at least one other offending drug, and numerous reports of fatal pharmacokinetic adverse drug interactions with opioids have been published [130]. Elderly patients and patients with medical comorbidities typically require multiple medications, termed polypharmacy, which increases the risk of adverse drug interactions. Understanding the underlying cause of these interactions can mitigate a major toxicity risk when prescribing opioids [144].

Factors that interfere with opioid metabolism or excretion can cause opioids or metabolites to accumulate (leading to toxicity) or can accelerate their elimination (leading to analgesic failure). Conditions that can lead to delayed opioid metabolism include genetic predisposition (CYP450 isoenzyme polymorphism), hepatic and/or renal dysfunction, and drug-drug interactions [164]. Adverse opioid-drug interactions can involve pharmacokinetic or pharmacodynamic interactions, and while pharmacokinetic interactions involving CYP isoenzymes (phase I) are well characterized, those involving the UGT enzyme family (phase II) are less understood.

Among opioid analgesics, CYP metabolism occurs by either the CYP206 or CYP3A4 pathway. The propensity for drug interactions is higher for opioids metabolized by CYP3A4, and this is the pathway by which most opioids in general use are metabolized [103; 130; 174]. Thus, drugs and other compounds that inhibit or induce CYP3A4 activity contribute to opioid adverse drug interactions. CYP3A4 inducers include rifampin, St. John's wort, troglitazone, and phenytoin; inhibitors include telithromycin, itraconazole, ketoconazole, miconazole, voriconazole, ritonavir, lopinavir, erythromycin, clarithromycin, and grapefruit juice. Adverse opioid-drug interactions from enzyme induction mostly involve CYP3A4 and, to a lesser extent, CYP2B6.

Morphine

Morphine is believed to possess a low potential for adverse drug interactions, because UGT inhibition produces few relevant pharmacokinetic changes in morphine or its metabolites [130].

Codeine

Analgesia requires the conversion of roughly 10% of codeine via CYP2D6 into morphine, which is then converted to M3G and M6G by glucuronidation. Codeine is also metabolized by CYP3A4 to the inactive metabolite norcodeine [103].

CYP3A4 inducers speed the conversion of codeine to the inactive norcodeine and decrease conversion to morphine. Although codeine undergoes phase II metabolism to codeine-6-glucuronide, UGT2B7 inhibition or induction does not result in codeine adverse drug interactions [130].

Oxycodone

Oxycodone undergoes a complex hepatic metabolic process. CYP2D6 catalyzes oxycodone to oxymorphone (10% of metabolites), and UGT2B7 rapidly inactivates oxymorphone by conversion to oxymorphone-6-glucuronide; the analgesic contribution of oxymorphone is minimal. CYP3A4 catalyzes oxycodone to noroxycodone, the primary (90%), but inactive, metabolite. In addition, CYP2D6 converts noroxycodone to noroxymorphone. These metabolites have varying mu receptor potencies and affinities [99; 176].

Many adverse drug interactions have been reported between oxycodone and other CYP3A4 substrates. CYP3A4 inhibitors can substantially increase oxycodone serum levels, reflected in the "black box warning" to not use oxycodone with CYP3A4 inhibitors due to the elevated risk of serious adverse effects, including potentially fatal respiratory depression. CYP3A4 inhibitors may elevate plasma oxymorphone to increase opioid effects, while CYP3A4 inducers may substantially decrease oxycodone (and potentially oxymorphone) serum levels, leading to analgesic failure. In general, concurrent use of oxycodone with CYP3A4 inhibitors or inhibitors is likely to result in adverse drug interactions.

The clinical effects of CYP2D6-mediated drug interactions with oxycodone are mixed, because overall analgesic contribution from the active metabolite oxymorphone is minimal [130].

Oxymorphone

Oxymorphone undergoes hepatic metabolism by phase II conjugation via glucuronide UGT2B7. The absence of CYP450 involvement minimizes adverse drug interactions with CYP substrates [115].

Hydrocodone

Limited clinical data have been published on drug interactions with hydrocodone metabolism. The overall evidence suggests concurrent use of CYP2D6 inhibitors diminish conversion of hydrocodone into the active metabolite hydromorphone [130].

Hydromorphone

The metabolites of hydromorphone are not thought to contribute to its pharmacologic activity. Minimal CYP450 involvement indicates a lack of adverse drug interactions impacting its pharmacokinetics [16; 115].

Fentanyl

Fentanyl is metabolized primarily via hepatic CYP3A4 and is a weak CYP3A4 inhibitor. As such, many CYP3A4 substrates can interact with fentanyl. Elevated plasma fentanyl and decreased fentanyl clearance can result from coingestion of CYP3A4 inhibitors. CYP3A4 inducers can diminish fentanyl serum levels and analgesia and increase clearance. The adverse interactions between fentanyl and CYP3A4 inhibitors are potentially very serious, and a "black box warning" on all fentanyl products cautions against concurrent use of fentanyl and all CYP3A4 inhibitors because of the heightened risk of adverse effects, including fatal respiratory depression. CYP3A4 inducers may nullify fentanyl analgesia, and patients receiving fentanyl should avoid all CYP3A4 substrates [130].

Methadone

Methadone is associated with numerous potentially serious adverse drug interactions. CYP3A4 inhibitors can delay methadone clearance and potentially lead to toxicity. Methadone has been linked to the development of the ventricular arrhythmia torsades de pointes; additional reports suggest an association between methadone-induced torsades de pointes and CYP3A4 inhibition [130; 177].

CYP3A4 inducers can reduce plasma methadone levels, leading to analgesic failure and opioid withdrawal. CYP2B6 inhibitors can decrease methadone metabolism to increase side effect risk, while CYP2B6 inducers delay metabolism to diminish its therapeutic effects [130; 177].

Many members of specific drug classes adversely interact with methadone, and clinicians should carefully evaluate the interaction potential of any CYP3A4 or CYP2D6 inhibitor used with methadone [130; 177].

The complex pharmacology of methadone makes the drug hazardous when prescribed without extensive knowledge and experience. With a half-life (15 to 60 or more hours) longer than analgesia (4 to 8 hours), risks of accumulation and fatal overdose are increased, as when analgesia wears off and pain returns followed by re-dosing. Other factors that contribute to the risk of toxicity include [49]:

- Metabolism by numerous CYP isoenzymes, which elevates the risks of drug-drug interactions, delayed clearance, and increased serum concentrations of methadone to fatal levels
- Prolongation of QTc interval, which may increase risk of life-threatening cardiac arrhythmias
- P-glycoprotein (P-gp) substrate, elevating risk of drug interactions that accelerate methadone blood-brain barrier penetration

Methadone requires metabolism by at least five fully active CYP450 isoenzymes for its efficient breakdown and elimination. This makes it the opioid with greatest susceptibility to adverse drug interaction. Concurrent use of common medications such as benzodiazepines, antihistamines, antidepressants, and antiviral agents may result in inhibition of CYP450-mediated breakdown and clearance of methadone, increased plasma levels, and serious risk of oversedation and suppression of CNS respiratory centers [175].

Toxicity risks of methadone can be mitigated with gradual titration and dose adjustment. Opioid-naïve patients should be started at a low dose, usually 2.5 mg every eight hours. The dose may be titrated by 10% to 20% increments, not less than three to four days apart except under inpatient or closely supervised settings. Once-daily methadone is ineffective for chronic pain; dosing at least every eight hours is required. When rotating patients from another opioid to methadone, it is important to consult the latest product information for dose equivalence and conversion; do not use published equianalgesic tables [103; 175].

The increasing use of methadone treatment for chronic pain has led to high rates of fatal toxicity and concerns over its safe and appropriate use as an analgesic. Clinical practice guidelines have been developed to promote safer methadone prescribing for chronic pain [178]. The first step is careful patient assessment. From a thorough history, medical records review, physical examination, and possibly electrocardiography, stratify patients on risk for substance abuse, adverse reactions with other prescribed medications, and arrhythmia. Alternative opioids should be used in patients at high risk of QTc interval prolongation. If methadone is used, a low starting dose and slow titration are necessary, as are diligent monitoring and patient follow-up. All patients should receive education on methadone safety.

Levorphanol

No adverse interactions with CYP450 substrates have been noted with levorphanol. Interactions at glucuronidation enzyme sites are theoretically possible, but none have been substantiated [16].

Tramadol

CYP2D6 and CYP3A4 account for more than 70% of tramadol metabolism. CYP2D6 inhibitors reduce tramadol analgesia and concurrent use should be avoided. CYP3A4 inhibitors may increase exposure to tramadol, and their use should be avoided. CYP3A4 inducers can reduce plasma tramadol, and patients requiring CYP3A4-inducing medications should be monitored for inadequate analgesia [130].

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Tapentadol

Clinically relevant drug interactions are unlikely with tapentadol [179].

PHARMACODYNAMIC DRUG-DRUG INTERACTIONS

Pharmacodynamic drug-drug interactions are possible with all opioid analgesics. Drugs with hypoventilatory or CNS depressant properties, such as benzodiazepines, sedative-hypnotics, and antihistamines, can act synergistically with opioids to increase sedation and risk of potentially lethal respiratory depression [174].

Some pharmacodynamic adverse drug interactions with opioids can be clinically advantageous. For instance, ibuprofen co-administration with hydrocodone or oxycodone potentiates the analgesia of the opioids in laboratory-induced moderate-to-severe pain, producing a 2.5-fold and 4.6-fold shift in the effective dose, respectively. Aspirin and ketorolac have no effect on hydrocodone analgesia, and ibuprofen has no effect on fentanyl or morphine analgesia [180].

CDC GUIDELINES FOR OPIOID PRESCRIBING IN CHRONIC PAIN

In 2016, the CDC published opioid prescribing guidelines for chronic pain by primary care physicians, not applicable to active cancer treatment, palliative care, or end-of-life care [42]. The CDC guidelines are expected to have a significant effect on opioid prescribing. Release of the draft and final CDC guidelines provoked controversy and alarm from pain professionals and pain patient advocacy groups and serious concerns by the American Medical Association (AMA), the American Cancer Society (ACS), the American Academy of Pain Medicine (AAPM), and other prominent organizations [56; 57].

The public health issue of opioid analgesics is complex; the ideal is balancing opioid control and access. Overemphasis on access in the 1990s and early 2000s led to over-prescribing, increased addiction, and overdose; now, excessive control has the potential to lead to restricted access and undertreated and untreated chronic pain. The well-intentioned but narrow public health focus on curtailing opioid prescribing and patient access is consistent with the CDC's orientation and agenda, but it may not be the most helpful approach in patient care [5; 57].

The CDC guidelines were based on a systematic review that rejected opioid studies greater than one year in duration without randomized controlled design. This made the pool of evaluable studies essentially unchanged from a 2009 systematic review of opioid analgesics, but conclusions of the 2009 review markedly differed from the 2016 review [43].

It is also important to note that the NPS, a comprehensive action plan to decrease the burden of undertreated pain, was also released in 2016. The NPS was developed in response to the 2011 IOM mandate for system-wide transformation of pain care but was largely overshadowed by the CDC guideline release [58].

The following recommendations are reprinted from the CDC guidelines and represent a simple approach to opioid prescribing for chronic pain. While this may be helpful for primary care providers, it does not take into account many of the nuances of opioid use for chronic pain, including patient-specific response, side effects, comorbidities, and pharmacokinetics and pharmacodynamics. These issues will be discussed in detail later in this course.

WHEN TO INITIATE OR CONTINUE OPIOIDS

Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain [42]. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Before starting opioid therapy for chronic pain, clinicians should, for all patients:

- Establish treatment goals for pain and function.
- Consider how therapy will be discontinued if benefits do not outweigh risks.
- Continue opioid therapy only if clinically meaningful improvement in pain and function outweighs safety risks.

Before starting opioid therapy and periodically during the course of treatment, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

The American Society of Interventional Pain Physicians asserts that a robust agreement that is followed by all parties is essential in initiating and maintaining opioid therapy, as such agreements reduce overuse, misuse, abuse, and diversion.

(https://www.guideline.gov/summaries/summary/38257. Last accessed May 26, 2017.)

Level of Evidence: Fair (Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.)

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

When starting opioid therapy for chronic pain, clinicians should prescribe SA instead of ER or long-acting (LA) opioid formulations. When opioids are started, clinicians should prescribe the lowest effective dosage but use caution at any dosage. It is important to carefully reassess evidence of benefits and risks when increasing dosage to ≥50 mg MED/day. Prescribers should avoid or carefully justify increasing the dosage to ≥90 mg MED/day.

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids. It is important to prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

Clinicians should evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should also evaluate benefits and harms of continued therapy with patients at least every three months. If benefits do not outweigh harms of continued opioid therapy, clinicians should taper and discontinue opioids or optimize other therapies and work with patients to taper opioids to lower dosages.

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms and incorporate into the management plan strategies to mitigate risk. Offering a naloxone kit should be considered when factors are present that increase opioid overdose risk, including:

- History of overdose or substance use disorder
- Higher opioid dosages (≥50 mg MED/day)
- Concurrent benzodiazepine use

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. The patient's history of controlled substance prescriptions should be reviewed using state prescription drug monitoring program data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review prescription drug monitoring program data when starting opioid therapy for chronic pain, and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months.

When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy, and consider urine drug testing at least annually to assess for prescribed medications, other controlled prescription drugs, and illicit drugs. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorders.

According to the American Society of Interventional Pain Physicians, urine drug testing should be implemented from initiation of treatment with opioids along with subsequent adherence monitoring, in an in-office setting with immunoassay and confirmation for accuracy with chromatography in select cases, to identify patients who are noncompliant or abusing prescription drugs or illicit drugs, and urine drug testing may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

(https://www.guideline.gov/summaries/summary/38257. Last accessed May 26, 2017.)

Level of Evidence: Good (Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.)

CRITICAL RESPONSE TO CDC GUIDELINES

Experts have argued that the dose levels established in the CDC guideline are arbitrary. Millions of Americans currently receive 90 mg MED/day for needed pain control [56]. The true risk factors for toxicity and overdose include organ dysfunction, pain control, tolerance, drug interactions, psychiatric disorders, history of substance use disorder, genetic variation, and concurrent benzodiazepine/other CNS sedative use [6]. Critics have also asserted that the guideline neglects are the serious consequences from undertreated chronic pain [59].

In addition, the opioid dosing limits for acute pain were based on emergency department prescribing guidelines for non-traumatic, nonsurgical pain, to provide analgesia until the acute pain resolves or the patient sees his or her primary care provider [43]. As such, the recommendation is unlikely to be helpful in a chronic pain guideline.

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GENERAL RECOMMENDATIONS FOR ANALGESIC PRESCRIBING

As discussed, the CDC's opioid prescribing guidelines are strictly focused on curtailment and, as such, are less useful for guiding analgesic selection or patient matching [5]. Instead, this information may be obtained from practice guidelines from the FDA, the Federation of State Medical Boards, and the AAPM. These organizations state that opioid analgesics are generally not used as first-line analgesic therapy; non-drug and non-opioid drug alternatives should be considered first. Opioids may be initiated when benefits are likely to outweigh risks, when other approaches to analgesia are ineffective or unlikely to be effective, and with a treatment plan reasonably designed to mitigate the risks of addiction, toxicity, and other adverse effects [20; 181; 182].

Despite limited evidence for reliability and accuracy, screening for opioid use is recommended by the American Society of Interventional Pain Physicians, as it will identify opioid abusers and reduce opioid abuse.

(https://www.guideline.gov/summaries/summary/38257. Last accessed May 26, 2017.)

Level of Evidence: Limited (Evidence is insufficient to assess effects on health outcomes because of limited number of power studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.)

Opioid therapy should be presented as a time-limited trial to evaluate pain, functioning and quality of life benefits, and adverse effects. Opioid-naïve patients should be started at the lowest dose, with titration to effect. In general, it is best to begin opioid therapy with an SA formulation and rotate to an ER/LA formulation, if indicated. Opioid therapy may be continued beyond the trial period after careful evaluation of benefits versus adverse effects and/or potential risks [20; 182].

Fear of inducing respiratory depression has constrained opioid prescribing for patients with chronic pain, but this risk can be minimized by exercising caution and providing patient education regarding the risks of any concomitant use of CNS depressants, especially benzodiazepines and alcohol [20]. Caution should also be used with dosing and titration in patients with sleep apnea or end-stage respiratory disease.

Emerging data suggest an association of chronic opioid therapy with central sleep apnea, but the direction and details of this association are unclear. Patients on long-term opioid therapy are at risk for hypoxia if respiratory infections or acute asthmatic attacks supervene; patients should be advised that opioid dosage adjustments may be necessary in the event of any intercurrent illness that affects breathing.

Previous assumptions that patients on chronic opioid therapy will invariably develop analgesic tolerance (i.e., decreasing pain control with the same dosage over time) have also constrained effective opioid prescribing practices. Chronic pain unresponsive to opioid dose escalation may reflect tolerance, but it may also be the result of disease progression, non-opioid responsive pain syndromes, or opioid-induced hyperalgesia. Tolerance is not usually an impediment to long-term opioid therapy [20].

The most recent comprehensive guidelines for neuropathic pain were published by the Canadian Pain Society in 2014. Common causes of peripheral neuropathic pain include diabetic neuropathy; postherpetic neuralgia; post-thoracotomy, post-breast surgery, and post-back surgery pain; phantom limb pain; and complex regional pain syndrome [183]. ER opioid analgesics are recommended as second-line options for moderate-to-severe neuropathic pain.

Although there are few class-wide contraindications for the use of mu opioid agonist analgesics, contraindications to ER/LA opioid prescribing exist by formulation and specific opioid [181]. Contraindications to any use of opioid analgesics include [184]:

- Respiratory instability
- Acute psychiatric instability
- Uncontrolled suicide risk
- Active, untreated alcohol or substance use disorder
- True opioid allergy
- Current medication use with potential for dangerous drug interactions
- Active diversion
- Prolonged QTc (≥500 ms) (with methadone)
- Codeine (in pediatric patients)

Contraindications to long-term opioid analgesic therapy include [39; 185]:

- Primary headache
- Functional disorders
- Fibromyalgia syndrome (except tramadol)
- Chronic pain as prominent manifestation of a mental disorder (e.g., atypical depression, generalized anxiety disorder, post-traumatic stress disorder)

CLINICAL RELEVANCE OF AGE-RELATED PHYSIOLOGIC CHANGES	
Age-Related Change	**Clinical Relevance**
Pharmacokinetic Impact	
Reduced GI function and delayed absorption	Increased risk of opioid-related GI side effects Alteration of drug absorption (little clinical effect)
Altered distribution	Reduced distribution of water-soluble drugs Longer effective half-life of lipid-soluble drugs Increased potential for drug-drug interactions
Reduced hepatic metabolism	Reduced first-pass metabolism Oxidative reactions (phase I) may be reduced, prolonging half-life Conjugation (phase II metabolism) usually preserved Difficult to predict exact individual effects
Reduced renal excretion	Accumulation and prolonged effects of drugs and metabolites
Pharmacodynamic Impact	
Decreased receptor density, increased receptor affinity	Increased sensitivity to therapeutic and side effects
Source: [188]	*Table 3*

- Chronic pancreatitis, with the possible exception of brief (less than four weeks) treatment during an acute episode
- Chronic inflammatory bowel disease, with the possible exception of brief (less than four weeks) treatment during an acute episode
- Comorbid severe affective disorder and/or suicidality
- Current prescribed opioid abuse, diversion, and/or serious doubts over responsible use (e.g., unable to control opioid use, unwilling or unable to adhere to dosing schedule)
- Current or planned pregnancy

PATIENT FACTORS AND OPIOID ANALGESIC RESPONSE

Clinicians have long observed wide response variation in patients receiving opioids for pain. Patient factors, including age, medical comorbidity, and genetic differences, substantially contribute to this variation. Understanding how these factors influence opioid response can facilitate opioid selection and prescribing that mitigates side effects and toxicity while attaining adequate pain control.

AGE

By 2025, the number of adults 65 years of age and older in the United States is projected to increase 80% from 2010 estimates, comprising nearly 20% of the population. Understanding age-related physiologic changes and the complexity of pain management in elderly patients is essential for optimal efficacy, safety, and tolerability [49].

Independent of disease morbidity, aging elevates the risk of adverse events and associated opioid toxicity (***Table 3***). The elderly account for 49% of all hospitalizations due to medication adverse effects [186]. A variety of age-related physiologic changes account for this, including diminished gastric secretions and intestinal dysmotility; vitamin D deficiency, loss of appetite, and poor nutrition; and decreased bone density. Increased arterial thickening and rigidity elevate cardiac risk, while decreased lung elasticity may exacerbate respiratory disorders. Neurons become less stress-resilient. Reduced hepatic and renal blood flow diminish metabolism and filtration, increasing the risk for toxic substance accumulation [186]. Patients with dementia and/or cognitive deficits may have communication problems or confusion that render expression of pain severity, therapeutic response, and/or side effects difficult [187].

In older adults, heightened sensitivity to adverse effects results from physiologic changes, drug interactions, and drug-disease interactions [189]. Aging is associated with higher steady-state concentrations of water-soluble drugs and increased half-life of fat-soluble drugs. Consequently, opioid use in older adults may necessitate a lower than usual dose or longer dosage interval in order to maintain an appropriate balance between analgesia and side effect risk [190]. Other functional changes and comorbidities that impact opioid pharmacokinetics may also influence patient response and tolerability. Therefore, the selection and prescribed dosage of opioids in elderly patients must be considered carefully [187].

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Older adults are also more likely to be prescribed multiple medications for a variety of chronic and acute conditions. In some cases of multimorbidity and chronic conditions (e.g., hypertension), the use of multiple medications may be unavoidable if one is to follow best practice clinical guidelines; this is referred to as "appropriate polypharmacy." However, even when the prescription of multiple medications is warranted, it raises the risks of drug-drug interactions, compliance issues, and adverse effects.

Elderly adults are more likely than younger adults to experience significant chronic pain because of the higher prevalence of rheumatic diseases, orthopedic conditions, and other debilitating illnesses. In many cases, opioid therapy with optimum patient-treatment matching is the safest analgesic option for elderly patients compared with oral NSAIDs, acetaminophen, antidepressants, or anticonvulsants [49].

MEDICAL COMORBIDITIES

Comorbid medical or neuropsychiatric conditions can affect opioid response or tolerability by interfering with opioid metabolism, elimination, efficacy, and adherence. Many patients require polypharmacy, especially the elderly and patients with psychiatric illness, cancer, cardiovascular disease, diabetes, and other chronic illnesses. As discussed, polypharmacy elevates risks of drug interactions that reduce efficacy or increase toxicity [191].

Cardiovascular, cerebrovascular, and respiratory disease all impact susceptibility to respiratory depression, bradycardia, or hypotension. Neurologic or neuropsychiatric conditions such as dementia, brain injury, or psychiatric illness may render the patient more susceptible to adverse CNS effects from opioids, such as cognitive impairment or sedation [191]. The presence of significant cognitive or intellectual disabilities can accompany sensory or communication disorders to interfere with verbal or nonverbal communication of pain to healthcare providers. In these patients, chronic pain can manifest in behavioral challenges or gradual declines in function. Appropriate treatment can greatly improve patient quality of life and caregiver stress [71].

Hepatic Dysfunction

Opioid biotransformation occurs in the liver, and any significant impairment in hepatic function will delay the metabolism and prolong the effect of opioids and their metabolites. Generally, CYP-mediated metabolism is affected more than glucuronidation, although opioids solely metabolized by glucuronidation also show altered pharmacokinetics. Morphine clearance is reduced ≥25%, and hydromorphone plasma concentrations are increased four-fold [191]. As such, it is important to avoid using oxymorphone and tapentadol and to use hydromorphone and oxycodone with great caution in these patients. Fentanyl is the first-choice opioid in patients with serious liver disease. Buprenorphine is safe in patients with mild-to-moderate liver disease, and methadone can also be used safely [103]. All opioids should be used with extreme caution with lowest-dose initiation [191].

Renal Dysfunction

Renal impairment can interfere with clearance of opioids and metabolites, which may lead to serum concentrations rising to dangerous levels. Delayed morphine elimination can lead to respiratory depression, excitotoxicity, and/or neurotoxicity. In these patients, morphine, hydromorphone, tramadol, tapentadol, and codeine should be avoided. Oxymorphone and oxycodone may be used with great caution. Fentanyl should be considered as the opioid of first choice for patients with renal impairment, followed by buprenorphine and methadone [103]. All opioids should be started at a low dose and slowly titrated [191].

Cardiovascular Disease

In patients with heart failure, special care should be taken with methadone. Some patients prescribed methadone for chronic pain may be at increased risk for developing prolonged QT interval or may already have a congenital QT prolongation.

Tramadol is recommended ahead of NSAIDs for patients with significant cardiovascular risk, and the same can be argued for tapentadol. Fentanyl, morphine, or oxycodone should be considered for these patients, as none are significantly associated with QT prolongation [190].

GENETIC FACTORS

Morphine, oxycodone, hydromorphone, and fentanyl have comparable population level efficacy but widely variable analgesic efficacy and tolerability at the individual level; the same drug/dose may be toxic in some patients and have little or no effect in others. For example, up to 30% of patients with cancer-related pain show poor morphine response from inadequate analgesia or intolerability, but most achieve pain control with alternative opioids. Genetic factors account for at least 25% of this response variation to opioids [99; 192]. Genetic variations with greatest confirmation and relevance to opioid kinetics and dynamics include CYP450 enzymes, P-gp transporter ABCB1, catechol-O-methyltransferase (COMT) enzymes, and cytokine gene promoters (***Table 4***).

PRIMARY PHARMACOGENETIC INFLUENCES IN OPIOID ANALGESIC RESPONSE		
Site of Activity	**Genes of Interest**	**Function**
CYP450	*CYP2D6*	Involved in metabolism of several opioids analgesics, including: • Codeine to morphine • Oxycodone to oxymorphone • Tramadol to O-desmethyltramadol • Hydrocodone to hydromorphone
P-gp	*ABCB1/MDR1*	Decreased P-gp expression and activity can affect brain opioid levels and increase toxicity risk
COMT	*COMT Val158Met* variant	May increase dopaminergic stimulation due to dysfunctional COMT activity, which upregulates mu opioid receptor expression and increases morphine efficacy
Mu opioid receptor	*OPRM1*	Codes the expression of higher mu opioid receptor binding affinity of b-endorphin
Kappa opioid receptor	*MC1R*	Sex-specific increase in pain perception and analgesic response via the kappa opioid receptor
COMT = Catechol-O-methyltransferase, P-gp = P-glycoprotein.		
Source: [184; 192]		*Table 4*

ETHNIC/RACIAL DISTRIBUTION OF POLYMORPHIC *CYP2D6*			
Ethnicity/Race	**Poor Metabolism**	**Intermediate Metabolism**	**Ultra-Rapid Metabolism**
White	5% to 10%	2% to 11%	0.8% to 4.3%
Asian	1% to 2%	51%	0.9%
Black/African American	2% to 4%	30%	N/A
Hispanic	2.2% to 6.6%	N/A	1.7%
N/A = Not available.			
Source: [193; 194; 195]			*Table 5*

P-glycoprotein (P-gp) transporter ABCB1

The P-gp transporter ABCB1, encoded by the *ABCB1* gene, regulates the cerebrospinal fluid and serum levels of drugs passing the blood-brain barrier. *ABCB1* polymorphism alters P-gp transporter expression and activity at the blood-brain barrier to influence drug concentrations, CNS parent drug/metabolite ratios, and adverse effects. The impact of polymorphic *ABCB1* varies with the particular opioid in use. With morphine, it is associated with increased systemic and CNS exposure and accumulation; with fentanyl, increased respiratory depression; and with oxycodone, greater pain reduction and adverse effects due to higher plasma concentrations [193].

Cytochrome P450 Enzymes

As discussed, CYP enzymes influence the concentration of circulating opioids. Polymorphism of genes that encode CYP isoenzymes can affect opioid metabolism by determining isoenzyme activity level [194]. Polymorphic *CYP2D6* is the most important genetic determinant of opioid response [1].

Phenotypic variations due to *CYP2D6* polymorphism are classed into four functional groups: poor, intermediate, extensive, and ultra-rapid metabolizers [175]. In the general population, polymorphic *CYP2D6* results in ultra-rapid metabolism in 7%, poor metabolism in 10%, intermediate metabolism in 35%, and extensive metabolism in 48%. In white individuals, 77% to 92% are *CYP2D6* extensive metabolizers. However, racial differences are found in polymorphic *CYP2D6* distribution, with greater effects seen in certain groups (***Table 5***) [194].

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Inactive/Absent Activity (Poor Metabolizers)

In patients with *CYP2D6* polymorphism resulting in poor metabolism, the opioid cannot undergo metabolism and is eliminated unchanged. Absence of metabolic activity delays clearance and elevates plasma opioid concentration. This phenotype is hazardous and especially dangerous in opioid-naïve patients. Another effect is analgesic failure with pro-drugs, from the inability to convert to the active metabolite [175; 196].

Underactive Activity

In intermediate metabolizers, the isoenzyme functions at reduced activity level and the opioid is metabolized at a slower rate, delaying plasma clearance, elevating serum concentration, and increasing toxicity potential. In some patients, isoenzyme function is activated with high serum opioid concentration, but these patients have greater overall risk of adverse effects and require lower opioid dosing [175; 194].

Full Activity

The greatest proportion of the population has extensive (full) opioid metabolism ability. With isoenzyme activity fully functional, patients show expected opioid dose response and the expected rate of opioid metabolism [194; 197].

Overactive Activity

In overactive (ultra-rapid) metabolizers, accelerated opioid metabolism and clearance results in analgesic failure from serum concentrations not reaching analgesic threshold, leading to ongoing pain and frequent dose escalation to attain analgesia. Another effect is greatly reduced analgesic duration, as when an ER opioid normally providing 12 hours of analgesia is effective for only 4 hours [175; 194].

Mu Opioid Receptor-1 (OPRM1)

The mu opioid receptor is the primary site of action for opioid analgesics, encoded by the mu opioid receptor-1 (*OPRM1*) gene. The *OPRM1* polymorphism most consistently associated with opioid response is A118G, which results in higher mu opioid receptor binding affinity of beta-endorphins. Studies show a pattern of less analgesia (i.e., higher dose requirements for morphine, tramadol, and fentanyl) and fewer CNS and GI side effects in patients with this polymorphism, reflecting reduced mu opioid receptor sensitivity and higher drug concentrations required to displace beta-endorphin from the mu opioid receptor [193]. A study of genetic influences on oxycodone response also found variations in mu and delta opioid receptor genes that may explain differences in patient responses [198].

Catechol-O-Methyltransferase (COMT)

The COMT enzyme is responsible for inactivating catecholamines. The most widely studied variant is a nucleotide substitution that changes the amino acid from valine to methionine at codon 158 (*Val158Met*). This alteration reduces the enzymatic activity of COMT, and low COMT activity is associated with increased mu opioid receptor system sensitivity to morphine [184; 192].

Cytokines

Cytokines are vital for coordination of immune and inflammatory response and are broadly classed as pro-inflammatory or anti-inflammatory mediators. Polymorphic cytokine gene promoters are associated with greater pain severity and greater morphine dose requirements [184; 192].

Clinical Relevance

As discussed, there is patient-to-patient variability in the rate at which opioids are metabolized based on genetic phenotype. Patients who are poor or intermediate metabolizers achieve a therapeutic effect at low doses and are at higher risk of toxicity at usual doses of opioid. Patients who are rapid metabolizers require higher and more frequent opioid dosing in order to achieve and maintain plasma concentrations in the therapeutic range. Importantly, with opioid pro-drugs like codeine and tramadol, phenotypic influence on the pharmacokinetics of the primary analgesic metabolite is reversed [197; 199].

Following poor metabolic response to an opioid pro-drug or ultra-rapid metabolic response to a conventional opioid, patients may insist on the need for higher doses due to analgesic failure [195]. Clinicians should avoid assumptions of addiction, abuse, or drug seeking until further investigation clarifies the underlying cause of analgesic failure. This patient behavior may reflect a polymorphic-mediated pseudoaddiction. In patients who rapidly metabolize opioids and who develop physiologic dependence with long-term use, forced or arbitrary opioid reduction can be hazardous—serum opioid concentrations may drop too rapidly to a low or zero level and produce severe opioid withdrawal, pain rebound, and cardiovascular hyperactivity that, in older patients, carries some risk for cardiac arrest or stroke [175].

Codeine

As an inactive pro-drug that requires metabolism by CYP2D6 into morphine for analgesia, poor and intermediate metabolizers gain little to no analgesia from codeine. In contrast, ultra-rapid metabolizers can have dangerously high serum morphine levels with standard-dose codeine, because the codeine-to-morphine conversion progresses more rapidly and a higher overall proportion of codeine is converted to morphine. This can result in severe or life-threatening side effects [197].

Tramadol

Tramadol is also a pro-drug, and clinical response is significantly lower in poor metabolizers, who require at least 30% greater tramadol dosing than patients with normal CYP2D6 activity [145]. Concurrent use of CYP2D6 inhibitors further contributes to metabolic interference. Poor metabolizers show poor pain control and a four-fold need for rescue medication with tramadol, while ultra-rapid metabolizers have shown intoxication, serious adverse effects requiring hospitalization, respiratory depression requiring naloxone, and near-fatal cardiotoxicity [196].

Oxycodone

The biotransformation of oxycodone involves CYP2D6 and CYP3A4; the two isoenzymes are prominently linked by activity and metabolic byproduct [176]. As such, polymorphic *CYP2D6* significantly impacts oxycodone analgesia and toxicity. Ultra-rapid metabolizers experience significantly greater analgesic effect and toxicity, while poor metabolizers experience minimal therapeutic or side effects. Concurrent use of CYP3A4 inhibitors dramatically elevates analgesic efficacy and toxicity with oxycodone. This effect is further exaggerated in ultra-rapid metabolizers, who risk serious side effects and potentially fatal respiratory depression; an alternative analgesic should be considered in these patients [176].

Hydrocodone

Poor metabolizers with *CYP2D6* polymorphism have a 10- to 20-fold lower rate of hydrocodone clearance and reduced production of the active metabolite hydromorphone [115]. Evidence suggests that there is a heightened risk of side effects and toxicity if these patients concurrently ingest CYP3A4 inhibitors [196].

Methadone

The CYP3A4 and CYP2B6 isoenzymes primarily contribute to methadone metabolism. So, methadone should be used with caution in patients concurrently taking CYP3A4 or CYP2B6 inhibitors [196].

ANTICIPATING FACTORS THAT ALTER PATIENT RESPONSE TO OPIOIDS

Basic guidelines have been established to prevent opioid toxicity and overdose due to factors that alter opioid pharmacokinetics [175; 190; 199]. Genetic testing to identify polymorphisms relevant to opioid analgesics is not commercially available or affordable. Instead, providers should screen all patients for CYP450 polymorphism before prescribing an opioid by taking a medication history with an emphasis on side effects, therapeutic failure, beneficial effects, drug sensitivity requiring a low dose, and insensitivity requiring a high dose. For example, a history of inadequate response or marked side effects to codeine suggests that selecting an opioid not metabolized by CYP2D6 (e.g., tapentadol, morphine, fentanyl, oxymorphone) is warranted.

With suspected CYP450 polymorphism or in patients requiring several non-opioid medications that interact with CYP2D6, CYP3A4, CYP2C9, or CYP2C19 isoenzymes, prescribers should select an opioid with a metabolic pathway that mostly bypasses the CYP450 system. These include hydromorphone, oxymorphone, levorphanol, and tapentadol. Oxymorphone is perhaps the safest, as it lacks CYP450 metabolism and has no active or toxic metabolites.

All patients prescribed opioid analgesics should receive education on the dangers of co-ingesting benzodiazepines, antidepressants, and agents or drug classes that are known CYP450 enzyme inhibitors.

OPIOID SELECTION, INITIATION, AND MANAGEMENT

Analgesic response, safety, and tolerability are highly influenced by the complex interplay of opioid and patient factors. These factors should be considered before selecting an opioid agent and initiating treatment.

OPIOID RESPONSIVENESS

Opioid responsiveness is defined as the "degree of analgesia achieved as the opioid dose is titrated to an endpoint, defined either by intolerable side effects or the occurrence of acceptable analgesia" [200]. Poor pain response to opioids is the result of intolerable side effect(s), inadequate analgesia, or both, despite dose escalation. When poor analgesic response is identified, the clinician should consider using adjuvant analgesics, switching opioids, changing the route of administration, or using NMDA receptor antagonists [103].

RECENT OPIOID EXPOSURE

An essential safety factor in opioid selection is current opioid exposure. Many ER/LA opioid formulations and transmucosal immediate-release fentanyl are explicitly prohibited from use in opioid-naïve patients due to the high risk of severe, potentially fatal respiratory depression [201]. Patients should be identified as opioid-tolerant before considering the use of these particular formulations.

The term "opioid-tolerant" differs from "opioid tolerance." Opioid tolerance is the physiologic adaptation to opioid exposure over time that manifests in reduced drug effect [157; 202]. On the other hand, a patient is considered opioid-tolerant after continuous opioid use for at least one week of at least 60 mg/day oral morphine, 25 mcg/hour transdermal fentanyl, 30 mg/day oral oxycodone, 8 mg/day oral hydromorphone, 25 mg/day oral oxymorphone, or an equianalgesic dose of another opioid [181]. ER/LA opioid analgesic products and dose levels restricted to opioid-tolerant patients are shown in ***Table 6***.

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ER/LA OPIOID ANALGESIC PRODUCTS AND DOSES RESTRICTED TO OPIOID-TOLERANT PATIENTS		
Brand Name	**Generic Name**	**Doses Restricted to Opioid-Tolerant Patients**
Avinza	Morphine capsules	90 mg, 120 mg
Belbuca	Buprenorphine buccal film	>75 mcg film/day
Butrans	Transdermal buprenorphine	7.5, 10, 15, and 20 mcg/hr
Dolophine, Methadose	Methadone tablets	Refer to full prescribing information
Duragesic	Fentanyl transdermal system	All doses
Embeda	Morphine/naltrexone capsules	100 mg/4 mg
Exalgo	Hydromorphone tablets	All doses
Hysingla ER	Hydrocodone bitartrate tablets	Single-dose ≥80 mg
Kadian	Morphine capsules	100, 130, 150, and 200 mg
MorphaBond	Morphine tablets	100 mg
MS Contin	Morphine tablets	100 mg, 200 mg
Nucynta ER	Tapentadol tablets	No product-specific concerns
OxyContin	Oxycodone tablets	Single-dose >40 mg, daily dose >80 mg
Targiniq ER	Oxycodone/naloxone tablets	Single-dose >40 mg/20 mg, daily dose >80 mg/40 mg
Xtampza ER	Oxycodone capsules	Single-dose >40 mg, daily dose >80 mg
Zohydro ER	Hydrocodone bitartrate capsules	Single-dose >36 mg, daily dose >72 mg
ER = Extended-release.		
Source: [181; 203]		*Table 6*

ROUTES OF ADMINISTRATION AND FORMULATIONS

As discussed, opioids are available for many routes of administration, including oral, rectal, SC, IV, transdermal, transmucosal, and intraspinal. The oral route of administration is simple, cost-effective, and preferred, and SA and ER formulations are available for most oral opioids [103]. SA opioids are used to control pain until reaching a steady state.

SC, IV, rectal, transdermal, transmucosal, or intraspinal routes of administration are used when patients cannot take oral medications. IM administration is contraindicated, as it lacks any pharmacokinetic advantage and is painful. SC delivery is relatively easy, effective, and safe. IV is useful when pain is severe or pain levels have acutely increased. Transdermal fentanyl preparations are effective for patients unable to take oral medications who have stable pain control. Transmucosal fentanyl is similar to IV administration in its rapid onset and is used for acute breakthrough pain.

The intraspinal route of administration is either epidural or intrathecal. This is the most invasive mode of opioid delivery and requires specialist involvement, but it confers advantages in patients with significant dose-limiting adverse effects, because systemic exposure is circumvented. Intraspinal delivery allows adjuvant medications to be directly administered to the spinal cord [103].

ER/LA Opioid Formulations

Although SA opioids are effective for pain control in many clinical contexts, they are characterized by pharmacokinetic shortcomings that may interfere with achieving sustained analgesia. ER formulations were developed to circumvent these pharmacokinetic shortcomings. Transdermal formulations of fentanyl and buprenorphine avoid the extensive first-pass metabolism that limits bioavailability with oral opioids [1]. ER formulations also lack the acetaminophen or ibuprofen found in many SA codeine, hydrocodone, and oxycodone formulations. These non-opioid analgesics impose a daily dose ceiling because of toxicity risks [137].

Several high-potency oral opioids have been used for decades to treat moderate-to-severe pain, including morphine, oxycodone, hydromorphone, levorphanol, methadone, and oxymorphone [16]. Methadone and levorphanol are inherently long acting, while morphine, oxycodone, hydromorphone, and oxymorphone possess a short analgesic duration and plasma half-life that requires frequent administration to establish and maintain a satisfactory analgesic effect. Before the 1990s, high-potency opioids were primarily used in surgery and inpatient settings, because they required IV or IM administration [154]. Oral ER formulations of these opioids were introduced to fulfill the unmet need of outpatients with chronic or disabling pain who required continuous analgesia not achievable with SA formulations [204; 205].

The terminology used to describe delayed-release opioids can be confusing. Opioids formulated with a release-delaying mechanism have been designated as ER, continuous or controlled release (CR), or sustained-release (SR), but these terms lack specific definition. Methadone and levorphanol are termed LA opioids to distinguish their inherently longer analgesic duration from opioids reformulated with an ER mechanism [206]. Likewise, the original strong opioids with relatively brief analgesic duration have been termed immediate-release or IR, but SA is a more accurate designation. IR is better reserved for truly rapid-onset opioids such as transmucosal immediate-release fentanyl.

Absorption, distribution, and metabolism influence the duration and stability of opioid analgesia and are difficult to manipulate with SA opioids. ER formulations modify the kinetic behavior of the opioid without changing the pharmacodynamic characteristics in order to improve analgesia through prolonged plasma concentration, lower maximum and higher minimum concentration, reduced fluctuation in plasma concentration, and delayed time in reaching maximum concentration [207; 208]. These ER opioid kinetics are thought to allow pre-emptive pain control instead of attempting to control pain after it becomes established (i.e., "chasing the pain"). This reduces or eliminates gaps in analgesia when plasma levels decline before the next scheduled dosing; decreases sleep interruption, side effects, and early opioid withdrawal symptoms by improving adherence and decreasing dose frequency; and reduces abuse potential by decreasing reward and reinforcement from slower onset of effects [72; 154; 209].

Fluctuating analgesia levels achieved with SA opioids can result in a need to take the medications more frequently (for comfort). This can cause conditioned passive pill-taking behavior, which can discourage the patient from taking an active role in pain self-care. The enhanced analgesic coverage and adherence with ER opioids may improve assessment of changes in the underlying pain condition or the chronic pain state by reducing the confounding factor of analgesic fluctuation [137].

The theoretical advantages of ER over SA formulations have been difficult to demonstrate in randomized controlled trials. However, there have been some comparison trials that may give some insight into the basis for ER formulations. In one study, a patient adherence advantage was found with ER formulations versus SA opioids, which may translate into improved pain relief [206]. In patients with moderate or greater chronic pain, CR tramadol showed lower pain scores and higher patient and investigator efficacy ratings than SA tramadol [210]. In addition, the daily variations in pain control experienced with twice-daily morphine were not reported with once-daily dosing, and this correlated with stability in serum morphine concentrations [211].

Compared with three-times daily morphine, twice-daily morphine is superior in pain control, sleep quality, and physical and mental impairment. In one study, almost twice as many patients dropped out with three-times daily versus twice-daily morphine, with inadequate pain relief the primary reason [212]. Patients with moderate-to-severe cancer-related pain show significantly greater dropout rates with four-times daily oxycodone than with twice-daily oxycodone due to inadequate pain control and side effects [213]. Another study of patients with cancer pain reported significantly greater tiredness during initial titration with six-times daily morphine versus once-daily morphine [214].

A literature review found that ER formulations of morphine, oxymorphone, oxycodone, and tramadol promoted improvements in ability to fall asleep, sleep quality, sleep duration, and pain-related sleep disturbance compared with SA formulations [206]. Patients with osteoarthritis have shown significantly improved sleep quality scores with ER versus SA oxycodone and with once-daily compared with twice-daily morphine [215; 216].

The CDC recommends initiation of opioid therapy with an SA formulation, but no further discussion or guidance is given [28]. The FDA states that the use of ER/LA opioids is indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate [181]. To ensure that benefits outweigh risks and to reduce risks while preserving access to opioid analgesics, the FDA has implemented risk evaluation and mitigation strategies (REMS) for ER/LA opioid analgesics. The ER/LA REMS program consists of a core prescriber education component that stresses safe product use, patient safety information, and guidance on patient counseling. This REMS-compliant education is strongly encouraged but not mandatory [181].

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Contraindications to ER/LA Opioid Formulations

Class-wide contraindications to ER/LA opioids include [181]:

- Concurrent alcohol use (can cause rapid opioid release and potentially fatal respiratory depression)
- Mild pain, short-term, or acute pain
- Use as pre-emptive analgesia
- Postsurgical pain
- As-needed use for intermittent pain
- Paralytic ileus
- Acute or severe bronchial asthma or hypercapnia
- Significant respiratory depression, unless resuscitative equipment and respiration monitors are available

In addition to contraindications for all ER/LA opioids, there are some agent-specific contraindications. For example, dosages greater than 1,600 mg/day of morphine ER (Avinza) should be avoided due to the risk of severe liver toxicity from the fumaric acid excipient. Oxycodone/naloxone ER (Targiniq) should not be used in patients with moderate or severe hepatic impairment. Tapentadol ER (Nucynta) is contraindicated in the presence of current or past 14-day MAOI use.

With postoperative, acute, or chronic intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with SA hydrocodone, morphine, or oxycodone is more effective than ER formulations. SA opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [15; 207; 209].

Treatment of moderate-to-severe persistent pain in opioid-naïve patients should be initiated with an SA opioid, with subsequent upward or downward dose adjustment until reaching adequate and tolerable analgesia [28]. When satisfactory analgesia and dose stability are achieved, the patient should be switched to an ER formulation of the initial opioid (assuming patient tolerability) [15; 177].

When switching from SA to ER formulations, patients should be advised not to expect the relatively rapid onset of relief they may be used to with the SA opioid. Analgesic benefit will become evident over time, and taking a second tablet to speed the onset of pain relief may lead to delayed toxicity or overdose. These medications should be stored securely, never shared, never chewed or crushed, and properly disposed of when no longer needed, as they contain large amounts of opioid and are potentially lethal if ingested by someone without tolerance or tampered with to cause rapid release of the contents [137].

DOSING

In clinical practice, patients may require more frequent dosing intervals with LA/ER opioids than recommended in product labeling by the manufacturer. For example, the labeling for CR oxycodone recommends every-12-hour dosing, but some studies have found that patients need a dose interval of 7 to 8 hours and that the majority of such patients are prescribed CR oxycodone three to four times daily [217; 218; 219]. Other studies of patients with moderate-to-severe pain found the majority used CR morphine three to four times daily [220]. Transdermal fentanyl patch labeling recommends patch replacement every 72 hours, but in one study, close to 50% of patients required patch replacement every 24 or 48 hours [218; 220].

This disparity can be explained by how premarket drug evaluation studies obtain pharmacokinetic data used in postmarket product labeling. These data are usually obtained from phase I studies that evaluate kinetic behavior of the drug in younger, healthy volunteers free of medical and psychiatric comorbidity and other medication use. This eliminates most patient factors that alter the pharmacokinetics of the drug. Less often, analgesic pharmacokinetic data are obtained from clinical samples involving subjects with a given pain condition, free of other medical and psychiatric comorbidities and concurrent medication use. These tightly controlled conditions eliminate factors that could later confound postmarking clinical data, but this limits applicability of the results to typical patients in real-world settings. No single opioid dosing protocol can fit the characteristics of all patients to determine analgesic response, tolerability, and required dose frequency [221].

The FDA permits marketing of generic drugs when bioequivalence is shown. This parameter is met when serum levels of the active constituent fall within 80% to 125% of the original branded drug. The allowable variation in serum levels can be problematic in agents with a narrow therapeutic index. An added complexity is that FDA mainly relies on self-reported bioequivalence evaluation by the generic drug makers [221; 222].

DOSE TITRATION

Titration is the process of incremental dose change based on individual patient needs and responses. The dose is increased (escalated) or decreased (tapered) until a reasonable balance is reached between analgesia and tolerability. Gradual titration allows sufficient time to ensure that the patient obtains the fullest degree of analgesia possible at the current dosage before further escalation is considered [223]. Regardless of opioid or dose, titration should be individualized based on health and pain status, treatment goals, and previous opioid response. Side effects such as sedation or nausea can interfere with upward titration.

OPIOID ANALGESIC APPROXIMATE DOSE EQUIVALENTS			
Opioid Analgesic	**Oral Dose**	**Parenteral Dose**	**Morphine Equipotency Ratio, Oral**
Morphine	30 mg	10 mg	Reference opioid
Codeine	200 mg	100 mg	Not established
Fentanyl (transdermal)	Not applicable	100 mcg	Not applicable
Hydrocodone (Zohydro ER)	30–45 mg	Not applicable	1.5:1
Hydromorphone (Exalgo ER)	8 mg	2 mg	5:1
Levorphanol	4 mg	2 mg	Not established
Oxycodone (OxyContin ER)	20–30 mg	10–15 mg	2:1

Source: [123; 181] *Table 7*

Opioid titration is slower with ER than SA formulations. When transitioning from SA to ER formulations of the same opioid, the dose is based on the equivalent total daily dose [157].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends titration of long-acting opioids should be carried out with caution.

(https://www.guideline.gov/summaries/summary/38257. Last accessed May 26, 2017.)

Level of Evidence: Good (Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.)

OPIOID ROTATION OR SWITCHING

Pharmacologists formerly considered opioid analgesics interchangeable, on the basis of shared mu opioid receptor agonism, differing mainly by potency. In contrast, clinicians have long observed subtle but important pharmacologic differences in potency, efficacy, and tolerability [224]. It is now known that individual differences in mu opioid receptor expression and density contribute to this variation.

Opioid rotation exploits these pharmacologic differences and incomplete cross-tolerance among opioids and involves switching the current opioid or route of administration to improve efficiency and safety [173; 223]. Opioid rotation can be an effective strategy for overcoming analgesic failure, side effect intolerance, problematic drug interactions, opioid-induced hyperalgesia, change in clinical status, problems related to medication cost and/or availability, need for a different route of administration, and patient preference [173; 223; 225].

Equianalgesic-Dose Tables

Verbatim use of equianalgesic-dose tables for opioid rotation contributed to opioid analgesic deaths in the 2000s and prompted changes in opioid conversion methods to mitigate risk and improve safety [12]. These tables include calculations derived from single dosing in opioid-naïve patients and permit broad guidance only. To ensure safety, a new opioid should start 50% below the calculated comparable dose to compensate for variable opioid response and incomplete cross-tolerance. The new opioid is titrated using product-specific instructions, with SA opioids used for analgesic rescue in breakthrough pain until reaching up-titration [12; 20; 226].

Morphine is the reference against which other opioids are compared, and analgesic potency is calculated as dose equivalence to morphine (i.e., MED). ***Table 7*** shows a typical equianalgesic-dose table with figures validated for acute pain in opioid-naïve patients and conversions for opioid-tolerant patients [181].

Breakthrough Pain Management

Breakthrough pain has been defined as a sharply increased pain episode with otherwise stable, well-controlled pain. The incidence of breakthrough pain in patients with chronic cancer and noncancer pain is 50% to 90%, even with pain appropriately managed with around-the-clock opioid analgesic coverage [228; 229; 230]. Breakthrough pain types include spontaneous, incidental, and end-of-dose failure. It is important to minimize the use of medications to address breakthrough pain in patients with chronic pain by titrating the baseline opioid dose or using adjunctive agents. If necessary, a reasonable dose for breakthrough pain is 10% to 15% of the total daily opioid dose [184]. Transmucosal immediate-release fentanyl products may be considered if prevention and control of breakthrough pain is not achieved.

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Pharmacokinetic factors determine the options for breakthrough pain treatment. Analgesics for breakthrough pain are ideally selected according to the time it takes to reach maximum serum concentration. This period depends on the route of administration, usually attained by 1 hour with oral, 30 minutes with SC, and 6 minutes with IV routes [103].

Despite the self-limited duration (mean: 30 to 60 minutes), breakthrough pain is highly distressing to the patient and burdensome to families, caregivers, and healthcare systems. It is linked to decreased functional status, treatment dissatisfaction, and worse medical outcomes. Breakthrough pain may go unrecognized and is often undertreated due to lack of knowledge and undue concern regarding overmedicating [231]. Of patients with breakthrough pain, 60% describe pain intensity as severe but only half take medication to address it [117]. Breakthrough pain has an unpredictable onset and reaches peak pain intensity in 5 to 15 minutes, making SA morphine, hydromorphone, and oxycodone—with onsets of action 30 minutes after oral ingestion—ineffective [143].

IV fentanyl analgesia, with onset of action in 5 to 8 minutes and duration of 30 to 60 minutes, is ideal but not feasible for outpatient breakthrough pain management. Instead, transmucosal immediate-release fentanyl products overcome the limitations of SA opioids to deliver analgesia approaching the rapid onset of IV fentanyl [231]. Available products include [201]:

- Sublingual tablet (Abstral)
- Citrate oral transmucosal lozenge (Actiq)
- Buccal tablet (Fentora)
- Nasal spray (Lazanda)
- Buccal soluble film (Onsolis)
- Sublingual spray (Subsys)

Transmucosal immediate-release fentanyl products have been shown superior in pain reduction to placebo at all time points from 15 to 60 minutes and to SA oral morphine in the initial 45 minutes. Among these products, intranasal fentanyl spray is possibly superior to the buccal tablet and oral transmucosal lozenge in the first 30 minutes of dosing [143].

Transmucosal immediate-release fentanyl products are highly potent, rapid-acting opioids, and their use by opioid-naïve persons can be fatal at any dose. To ensure that benefits outweigh risks, the FDA enacted a class-wide REMS that emphasizes appropriate product prescribing and dispensing to opioid-tolerant patients only. It is also important to avoid the inappropriate conversion between one transmucosal immediate-release fentanyl product and another and to safeguard against accidental exposure to children and others. The FDA recommends prescribers, pharmacists, and patients be educated on the safe use and risks of misuse, abuse, addiction, and fatal overdose associated with these products. The diverse routes of administration of transmucosal immediate-release fentanyl products allow greater matching of product with patient preference, often determined by disease and breakthrough pain characteristics [201].

Although often used off-label, transmucosal immediate-release fentanyl medications are only approved for breakthrough pain in adults (18 years of age or older) with cancer who are already receiving, and are tolerant to, regular opioid therapy for underlying persistent cancer pain [143; 231]. The exception is Actiq and generic equivalents, which are approved starting at 16 years of age. Even highly opioid-tolerant patients should start at the lowest available dose. Patients may need to switch between formulations to find the best match, but prescribers should never attempt this without guidance from specific product prescribing information, available on the FDA website at https://www.TIRFREMSaccess.com. This website should be consulted for all information regarding transmucosal immediate-release fentanyl products, including new and updated information [201].

Analgesic Failure

Pain control and tolerability in long-term opioid therapy may be hindered by the development of analgesic tolerance, opioid-induced hyperalgesia, oral opioid malabsorption, or HPA-axis dysfunction. One way to gauge the adequacy of pain control is to consider whether the use of added opioids has resulted in improvements in functioning, physical capacity, psychologic well-being, family/social interactions, and healthcare resource use, which are weighed against unwanted effects, such as daytime sedation, mental confusion, constipation, and other side effects.

Tolerance

Opioid tolerance and opioid-induced hyperalgesia are both characterized by diminishing pain control. However, tolerance may reflect decreased opioid sensitivity, while opioid-induced hyperalgesia represents increased pain sensitivity [232]. Etiologically, opioid tolerance reflects an adaptation to drug exposure over time that diminishes drug effect, though pain can generally be controlled with dose escalation. Opioid-induced hyperalgesia reflects a paradoxical increase in pain that may worsen with opioid up-titration [233; 234].

Tolerance to opioids may develop in several ways. Short-term use inhibits the production and release of endogenous opioids (e.g., beta-endorphins), while long-term use may also inhibit mu-opioid receptor expression. Studies of long-term morphine use have found down-regulation in *POMC* gene expression and subsequent decrease in endorphin production; decreased mu opioid receptor density on beta-endorphin containing neurons in the hypothalamus; and mu opioid receptor uncoupling from ligand-gated voltage channels with decreased ion channel potency and efficacy [111]. Morphine analgesic tolerance may also result from increased production of the anti-opioid peptides that bind mu receptors to decrease opioid binding and activation of mu opioid receptors. These processes develop over time and correspond with patient requirements for increasing opioid dose to maintain analgesia [111].

Other mechanisms may contribute to the loss of opioid analgesia. Pharmacokinetic changes can accelerate opioid metabolism and elimination from up-regulation of enzymatic activity in the metabolic pathway for the opioid. With enzyme induction, plasma opioid concentration diminishes over time while dosing remains constant [233]. The addition of other medications can induce metabolizing enzymes, with accelerated breakdown and excretion of the opioid leading to loss of analgesia and the need for dose escalation to regain analgesia [235]. Pharmacodynamic processes that include activation of the NMDA receptor/nitric oxide cascade can also result in opioid hypoanalgesia. NMDA receptor or nitric oxide synthase blockade can prevent or reverse opioid tolerance [236; 237; 238].

Progression of the underlying pain condition can also increase pain intensity and require dose escalation to control the pain. This may be mistaken for pharmacologic tolerance [233]. In general, tolerance can be managed by opioid rotation, dose escalation, or adding a non-opioid analgesic [175].

Opioid-Induced Hyperalgesia

As noted, opioid-induced hyperalgesia is characterized by paradoxical pain amplification. Pain sensitivity is heightened in the absence of a new or exacerbated injury. Opioid-induced hyperalgesia should be suspected in the patient who reports an unusual or unexplained change in pain profile, a diffuse allodynia (i.e., pain from normally non-painful stimuli) not related to the original pain condition, or worsening pain in response to dose escalation [234; 239].

Opioid-induced hyperalgesia involves CNS and PNS sensitization that develops through multiple mechanisms, including NMDA receptor activation; increased spinal cord dynorphin levels that activate excitatory pro-nociceptive neuropeptides; and CNS glial cell activation [232; 233; 234; 240]. CNS pain facilitatory mechanisms contribute to hyperesthesia (i.e., exaggerated pain sensitivity) and allodynia. Pain abnormalities with opioid-induced hyperalgesia often reflect exacerbated pre-existing painful conditions, with pain intensity worse than before opioid therapy [232; 241]. However, patients often describe the pain as more diffuse, less defined in quality, and typically extending beyond the original painful areas. Many features of pain associated with opioid-induced hyperalgesia resemble the pain experienced during opioid withdrawal, and both share a common neurobiology [232].

The diagnosis of opioid-induced hyperalgesia is often made in association with an increase in the opioid dose. Pain reduction indicates opioid tolerance, while worsening pain indicates opioid-induced hyperalgesia. Conversely, reducing the opioid may alleviate opioid-induced hyperalgesia symptoms, although care should be taken to avoid inducing withdrawal symptoms, which can increase pain and cloud the clinical picture [232].

Opioid-induced hyperalgesia is managed by addressing the underlying mechanisms. Morphine has the highest risk of opioid-induced hyperalgesia and should be replaced, if appropriate, in these patients. Switching to an NMDA antagonist opioid (e.g., methadone, levorphanol) is one approach. Spinal dynorphin is a kappa opioid receptor agonist, and kappa receptor antagonism may reverse opioid-induced hyperalgesia. As such, the kappa receptor antagonist buprenorphine is uniquely helpful as an alternative opioid for opioid-induced hyperalgesia [232]. If neuropathic pain is the original condition, it will often preferentially respond to non-opioid analgesics such as amitriptyline or pregabalin, which can enhance analgesia and decrease opioid dosing [234].

The NMDA antagonist ketamine has been used successfully in outpatients with opioid-induced hyperalgesia and is perhaps the most effective agent [239]. There is also evidence that concurrent use of the opioid antagonists naltrexone or naloxone at ultra-low doses can prevent opioid-induced hyperalgesia and enhance analgesia [242].

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Oral Opioids and GI Malabsorption

Malabsorption may also contribute to analgesic failure. Possible causes of oral opioid failure were studied in 95 patients with intractable pain [19]. Patients were initially screened to assess pain and functional improvement with oral opioids; 21.1% had three or more failed oral opioid trials. Malabsorption symptoms of nausea and steatorrhea were identified in 100%, and undigested medication in the stool detected in 70%. Pain relief from IV hydromorphone was experienced by 75%. The researchers concluded that patients with intractable pain and oral opioid failure may have a GI condition that interferes with absorption. These patients require non-oral routes until the GI dysfunction is resolved [19].

Endocrinopathy

Some patients with severe chronic pain lack analgesic response from lower-dose opioids; their complaints of analgesic failure may be dismissed despite severe impairment and debilitation. It is crucial to consider an underlying endocrinopathy as a possible cause. In one study of 61 patients with refractory chronic pain, 80.3% showed at least one hormone abnormality and 11.5% showed severe pituitary-adrenal-gonadal deficiency [243].

Pain that is uncontrolled, intractable, or severe impacts the endocrine system. Pain is a potent stressor that initially elevates serum pituitary, adrenal, and gonadal hormones. Severe uncontrolled pain depletes serum hormone levels; this serves as a biomarker for endocrinopathies and indicates that enhanced analgesia and hormone replacement may be necessary. Adequate physiologic levels of specific hormones may be required for optimal analgesia, neuroprotection, and neurogenesis. Hormone replacement is not a substitute for opioids but can minimize dose requirements [243].

Patient Nonadherence

Many patients with chronic pain do not take their medication as prescribed or stop altogether. A review of 11 trials involving 2,473 patients found an overall discontinuation rate of 22.9%, including 11.4% with weak opioids and 34.1% with strong opioids [244]. Community-based studies have found that 21% to 38% of patients adhere to their prescribed opioid regimens [245; 246].

Treatment adherence is essential for optimal pain control, for quality of life improvement, and to reduce healthcare utilization and associated costs. Inconsistent adherence to strong opioid prescriptions is the most important risk factor for hospitalization in these patients [247]. Poor adherence is also linked to problematic side effects, depression, higher dosing frequency, and negative attitudes of relatives or partners toward the patient's need for opioids. Adherence may be improved by patient education regarding the pain condition, realistic treatment expectations, and perceived benefit from treatment. In addition, primary care providers can modify risk factors for poor adherence by decreasing the dose frequency and addressing treatment expectation and benefit, side effects, depression, and attitudes of relatives and partners [248]. A tailored approach to opioid selection and titration optimizes the balance between pain control and side effects, which often enhances therapy adherence [1].

OPIOID ANALGESIC SIDE EFFECTS AND MANAGEMENT

All opioid analgesics have the potential for serious adverse effects when prescribed without careful consideration of patient factors. Even when prescribed with due diligence, patients may experience side effects that, if not anticipated or managed properly, can promote treatment discontinuation or analgesic failure from intolerance of therapeutic dosages. Side effects are generally adverse (with the possible exception of sleep-promoting sedation) and result from specific opioid pharmacology, patient age, comorbidities, genetic polymorphisms, and impaired hepatic or renal function [103].

Upon treatment with opioids, most patients report their pain is less intense, less distressing, or gone entirely, while other sensory perceptions are unchanged. A minority of patients experience euphoria, but it is more common for pain-free volunteers without a history of substance use disorder to describe morphine as unpleasant. Except in cases of acute intoxication, opioids, even highly potent mu agonists, seldom induce the loss of motor coordination or slurred speech characteristic of calming or sedating drugs [104; 249].

Clinicians should anticipate and monitor common opioid side effects and discuss these effects with patients before opioids are initiated. Many side effects are time-limited and lessen or resolve following stable dosing. Tolerance to opioid effects tends to develop at different rates, ranked below in descending order [175]:

- Euphoria (most rapid)
- Sedation
- Nausea
- Analgesia
- Constipation (late, if ever)

SEDATION

Sedation is a dose-dependent and often time-limited side effect. Anticholinergic activity of some opioids may contribute to sedation and drowsiness, but alleviation of pain can itself promote relaxation and sleep. Excessive sedation can occur with higher-dose initiation or rapid dose escalation and may result in nonadherence or reduced quality of life [110].

Management approaches for opioid-induced sedation include reduction or elimination of nonessential sedating medication (e.g., benzodiazepines, antihistamines, some TCAs, muscle relaxants), opioid dose reduction, and/or opioid rotation [110].

PRURITUS

Opioid analgesics can cause pruritus, which may be severe and difficult to manage, highly distressing to the patient, and among the top reasons for discontinuation. Pruritus is often misdiagnosed as an opioid allergic reaction, but true allergic and anaphylactic reaction to opioids is rare (<1%) and results from activation of central mu opioid, dopamine, serotonin, prostaglandin, and histamine receptors. Reactions related to histamine activation have been reported, most often with morphine. These reactions include urticaria, bronchospasm, and hypotension. When pruritus does occur, it typically involves the face, nose, and torso, and intrathecal administration is most associated with intense itching. Histamine release is most common with morphine [104; 250].

The goal of treating opioid-associated pruritus is to ameliorate the symptom without reversing analgesia with opioid antagonists. Options include anti-histamines (e.g., diphenhydramine, hydroxyzine) or H2 blockers (e.g., ranitidine, cimetidine). Naloxone infusion may be considered if other treatments fail and itching is severe. Opioid rotation to a different synthesis class (natural, semisynthetic, or synthetic) may also be successful. Epidural kappa opioid receptor agonists nalbuphine or butorphanol can reverse pruritus from mu agonists while maintaining analgesia [110; 250; 251]. If a true opioid allergy is identified, the offending opioid should be replaced by an opioid from a different chemical class to avoid antibody recognition [128].

OPIOID-INDUCED CONSTIPATION AND BOWEL DYSFUNCTION

GI symptoms are among the most common side effects reported with opioid use. Providers should be alert to the character and extent of patient distress resulting from these effects and the potential for non-adherence to therapy. Opioid-induced bowel dysfunction takes various forms, including dry mouth, nausea, vomiting, gastric stasis, bloating, abdominal pain, and opioid-induced constipation. Opioid activation of mu and kappa receptors in the neuronal plexus of the gut wall increases intestinal wall and sphincter resting tone and reduces biliary, pancreatic, and intestinal secretions. This results in dysrhythmic, non-propulsive contractions (bowel spasm), delayed passage and increased viscosity of intestinal contents, and the onset of constipation. Spasm and colic can also result from increased biliary tract tone [105; 107].

The American Society of Interventional Pain Physicians asserts that constipation should be closely monitored in patients prescribed opioids and a bowel regimen be initiated as soon as deemed necessary.

(https://www.guideline.gov/summaries/summary/38257. Last accessed May 26, 2017.)

Level of Evidence: Good (Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.)

Up to 91% of patients taking opioids experience constipation, the most common opioid-induced bowel dysfunction symptom. Opioid-induced constipation, often in combination with chronic nausea, can cause considerable distress, greatly diminished quality of life, and opioid discontinuation by as many as 33% of patients [252]. Most patients require constipation management for the duration of opioid therapy because complete tolerance rarely develops [123].

In order to prevent opioid-induced constipation, a laxative bowel regimen and bowel management education should be provided to all patients prescribed an opioid. In the event of laxative or stool softener nonresponse, patients may try [123; 171]:

- Mild osmotic agents (70% sorbitol solution, lactulose, milk of magnesia)
- Polyethylene glycol
- Bulk-forming laxatives (psyllium) with proper liquid intake
- Mild cathartic laxatives (senna, bisacodyl)

Saline or tap water enemas may be necessary to avoid fecal impaction.

Opioid switching from a hydrophilic agent (e.g., morphine, oxycodone, hydromorphone) to a lipophilic opioid (e.g., fentanyl, buprenorphine, methadone) may be helpful, as there is greater GI opioid receptor activity with hydrophilic opioids. Peripherally acting mu opioid receptor antagonists are indicated when other opioid-induced constipation treatments fail, including methylnaltrexone (50% to 60% efficacy in severe refractory opioid-induced constipation) or subcutaneous naloxegol injections [171].

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NAUSEA AND VOMITING

Roughly 33% to 66% of patients receiving opioids experience nausea and vomiting, usually during initiation and titration. This often resolves by the first week of treatment, but can recur later with a significant dose increase. Nausea and vomiting results from reduced GI motility and constipation, delayed gastric emptying, and activation of opioid receptors, dopamine tracts, and other transmitters in the chemoreceptor trigger zone [123]. Some patients report a sharp exacerbation of nausea upon movement, suggesting a component of opioid-induced vestibular dysfunction [105].

Nausea and vomiting during opioid initiation should be controlled with antiemetics, and these agents should be available as needed after dosing is stabilized. Metoclopramide and domperidone are first-line options due to a mechanism that improves GI motility. Around-the-clock and/or transdermal prescribing may be considered, with extra doses for rescue. Extrapyramidal symptoms may occur, but are considered infrequent [123; 253].

Antihistamines block histamine receptors in the vomiting center and on vestibular afferents. They may be used when [123; 253]:

- Vestibular sensitivity mimics motion-induced nausea
- GI prokinetic agents are contraindicated due to bowel obstruction

Ondansetron and other serotonin receptor antagonists are also effective in treating nausea and vomiting. Chlorpromazine is likely to produce significant sedation; prochlorperazine has greater antiemetic potency. However, potential extrapyramidal symptoms and anticholinergic side effects limit the clinical use of these agents [123; 253].

RESPIRATORY DEPRESSION

Therapeutic doses of morphine depress all phases of respiratory activity, including the breathing rate, minute volume, and tidal exchange. Respiratory depression results from decreased brainstem sensitivity to carbon dioxide build-up and is the primary lethal side effect of opioids [120]. Patients are most vulnerable to respiratory depression in the first five days of opioid initiation, especially the first 24 hours. Risk factors include obesity, sleep apnea, and pre-existing respiratory disorders (e.g., acute asthma, respiratory infection). Respiratory depression is antagonized by pain, and patients with substantial pain relief following uncontrolled pain are also at risk. Coingestion of any CNS respiratory depressant, including benzodiazepines or alcohol, elevates the risk of pronounced respiratory depression and fatality [104; 254].

Opioid use at appropriate prescribed doses seldom results in significant respiratory depression, even in patients with end-stage chronic obstructive pulmonary disease or dyspnea from advanced-stage cancer [255]. Patients on stable-dose, long-term opioid therapy have low risk of respiratory depression, although concerns remain prevalent among clinicians and patients [123]. It is important to note that respiratory depression may occur with a change in opioid analgesic, rapid dose escalation, development of renal failure or a serious pulmonary condition, or a single, large, inappropriate dose [254].

Sedation always precedes respiratory depression. With fatal respiratory depression, the process begins with sedation followed by reduction and finally cessation of breathing over the course of 5 to 15 minutes. Respiratory depression is characterized by rising peripheral carbon dioxide pressure, falling peripheral oxygen, and decreasing respiratory rate [255]. While these laboratory markers directly measure ventilation and ventilatory drive, they are often only available in an inpatient setting. In the outpatient setting, breathing rate and/or oxygen saturation are surrogate measures of ventilatory drive. In these cases, severe respiratory depression is defined by a respiratory rate less than 8 to 10 breaths per minute and oxygen saturation of <85% for more than six minutes per hour [120].

Naloxone can reverse respiratory depression caused by most opioids (though it is ineffective with meperidine). The extent and duration of naloxone reversal is determined by the specific opioid and dose, route of administration, concurrent medication(s), underlying disease, pain and state of arousal, and genetic factors [120].

When indicated for reversal of opioid-induced respiratory depression, naloxone (1:10 dilution) titrated in small increments or given by infusion should be administered to improve respiratory function without reversing analgesia [255]. The patient should be monitored carefully until the respiratory depression episode resolves [123].

Naloxone should be administered cautiously by slow IV infusion in opioid-dependent patients because it can abruptly induce acute opioid withdrawal syndrome and precipitate severe uncontrollable pain. Given this potential for abrupt, overwhelming physiologic and emotional stress with naloxone intervention, its use in respiratory depression should be strictly limited to patients unresponsive to physical or verbal stimulation or patients with shallow respirations, respiratory rate less than seven breaths per minute, or pinpoint pupils [120]. The 30- to 81-minute duration of naloxone is less than most mu opioid agonists, and re-administration is usually required.

The unique properties of nalbuphine make it effective in reversing opioid-induced respiratory depression or pruritus while maintaining analgesia. Nalbuphine can be a good analgesic option for patients susceptible to severe respiratory depression, pruritus, or nausea and vomiting with standard opioids [110].

SEROTONIN SYNDROME

Serotonin syndrome results from overactivation of central and peripheral serotonin receptors, usually from concurrent use of multiple serotonergic agents. Serotonin syndrome can result from drugs that influence the reuptake, metabolism, synthesis, or release of serotonin; influence serotonin receptor activity; or interfere with CYP2D6 or CYP3A4 metabolism. The most commonly implicated agents are SSRIs, but other medications that may affect serotonin levels include serotonin-norepinephrine reuptake inhibitors, MAOIs, antipsychotics, analgesics, antiemetics, cough suppressants, and dietary supplements. In more severe cases, patients develop hyperthermia, autonomic instability, delirium, and muscle rigidity, with complications including seizure, rhabdomyolysis, arrhythmias, and respiratory arrest. Suspicion of serotonin syndrome requires urgent emergency management [256; 257].

Tramadol is the only opioid analgesic associated with serotonin syndrome. SSRIs inhibit CYP2D6, which decreases tramadol analgesic efficacy. Concurrent use of tramadol and paroxetine or venlafaxine has been reported to cause serotonin syndrome [256; 257]. Genetic susceptibility to serotonin syndrome has been identified and is influenced by a patient's ability to produce different ratios of positive and negative tramadol enantiomers [257].

NEONATAL ABSTINENCE SYNDROME

Teratogenic effects from opioid exposure during pregnancy have not been identified. However, chronic opioid use during pregnancy can result in physical dependence in utero and potentially life-threatening opioid withdrawal in the neonate at birth and for up to 12 days after [104].

If signs of neonatal abstinence syndrome are present, the neonate should be taken to intensive care for observation and further assessment. Opioid replacement may be necessary to stabilize the patient, reverse the syndrome, and reduce complications of withdrawal. Additional medications may be necessary to control seizures and other symptoms.

MORPHINE AND CARDIAC RISK

Morphine is commonly used for chest pain in patients with a suspected acute coronary syndrome, but data suggest morphine use in patients with unstable angina and non-ST segment elevation myocardial infarction may increase mortality. It should be used with great caution or avoided entirely in this patient group [258].

NEUROPSYCHIATRIC EFFECTS

Hallucinations are more strongly associated with mixed agonist/antagonist opioids and rarely occur with mu opioid agonists, with few exceptions. In fact, a review concluded that mu receptor agonist opioids were not only free of psychoses risk, but probably possesses antipsychotic activity yet to be characterized [259].

Other adverse CNS effects, including cognitive impairment, delirium, and generalized myoclonus, are associated with meperidine, morphine, or hydromorphone use in patients with renal impairment. In these patients, opioid metabolites accumulate to neurotoxic levels. The metabolites have anticholinergic activity, which can result in cognitive changes and delirium [123].

There is little research that sufficiently addresses brain response to chronic opioid therapy. Positron emission tomography and magnetic resonance imaging studies show changes in brain response to long-term opioid therapy in patients with chronic pain. However, it is unclear whether these neuroimaging findings are the result of the chronic pain or the opioid medication use [260].

Differential diagnosis is necessary in patients with suspected opioid-induced delirium to rule out dehydration, other CNS medications, sepsis, and hypercalcemia. Tactile hallucinations and myoclonus suggest opioid toxicity. Immediate delirium management consists of neuroleptics to control agitation and perceptual or delusional disturbances. Haloperidol is the first-line option; methotrimeprazine and chlorpromazine are alternative options, especially when sedation is beneficial. For resistant delirium, midazolam is preferred; lorazepam is used for comorbid anxiety. In cases of cognitive impairment in the absence of delirium, methylphenidate or modafinil may be used. These agents are not recommended with evidence of perceptual or delusional disturbances [123].

Opioid toxicity from accumulating neurotoxic metabolites may present with generalized myoclonus, sedation, confusion, or chronic nausea. This is generally resolved by opioid switching [123].

IMMUNOLOGIC CHANGES

The traditional view of opioids as immunosuppressive has been challenged by evidence showing a more complex role of opioid receptors in immune function. Different opioids or routes of administration act through different mechanisms to produce immunosuppressive, immunostimulatory, or dual immune effects. The impact of specific opioids on immune function probably result from a combination of direct effects on immunocytes and indirect effects on centrally mediated mechanisms, systemic production, and release of immunomodulatory mediators [261].

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The interaction between opioids and the immune system is complex. Trauma and severe pain alone are immunosuppressive, which is reversible by sufficient pain control [262]. Exogenous opioid drugs can induce immunosuppression, while endogenous opioids appear to promote immunoactivation.

Opioid therapy has been shown to inhibit humoral and cellular immune responses, including antibody production, lymphocyte activity, cytokine expression, and phagocytic activity. Potential underlying mechanisms include HPA modulation, sympathetic nervous system stimulation, and activation of mu opioid receptor on immune cells [263; 264]. Opioids vary by immune system interaction. Compared with morphine, tramadol produces greater enhancement in natural killer cell activity, lymphocyte proliferation, and interleukin-2 release, while buprenorphine produces a negligible effect on immune response [249].

ENDOCRINE EFFECTS

Opioid therapy can result in HPA suppression and hypopituitarism, clinically expressed as hypogonadism, impotence, infertility, and/or osteoporosis [265]. Opioid-induced hormone dysfunction has been observed in men and women with oral, transdermal, IV, and intrathecal administration [249].

Opioids appear to differ in degree of adverse effect on hormonal function. In one study, men receiving buprenorphine maintenance therapy for opioid addiction showed significantly higher plasma testosterone levels and less sexual dysfunction than those receiving methadone [266]. Although long-term opioid therapy produces a dose-dependent decrease in total and free testosterone level, serum hormone levels return to normal in both sexes shortly after opioid cessation. Not all men experience androgenic suppression with long-term opioid therapy; body mass index and smoking status are thought to increase the risk of opioid-induced hormonal dysfunction [249].

If a patient on opioid therapy complains of changes in libido or sexual dysfunction, treatment is empirical, with knowledge that multiple factors may be involved in the pathogenesis of sexual dysfunction. In these cases, non-opioid analgesics should be added to reduce or, if possible, discontinue the opioid. In men, testosterone replacement is indicated if serum testosterone is low and not contraindicated. Sildenafil or another phosphodiesterase type 5 inhibitor may be used for men experiencing sexual side effects [121; 123].

For women taking opioids with complaints of sexual side effects, dehydroepiandrosterone is the first-line option. This is because adrenal gland suppression is a greater contributor to female androgen deficiency. In younger women, oral contraceptives with a relatively androgenic progestin component may be used [121; 123].

ACETAMINOPHEN TOXICITY

Several codeine, hydrocodone, and oxycodone formulations include acetaminophen. In the United States, acetaminophen toxicity has replaced viral hepatitis as the most common cause of acute liver failure and is the second most common cause of liver failure requiring transplantation [227]. In 2009, the FDA imposed a daily dose ceiling for acetaminophen of 4,000 mg; however, doses less than 4,000 mg per day can produce subclinical liver toxicity. Concurrent alcohol use also increases the risk, and chronic alcohol use is a high risk factor for fatal acetaminophen toxicity [222; 225]. It is crucial to use caution when prescribing any opioid preparation containing acetaminophen to older patients or patients with hepatic or renal disease.

OPIOID USE DISORDERS

There is no adequately validated instrument to differentiate pain patients who are at risk of dependence from those who are not. Research suggests that patients, even alcoholics, with no history of opioid dependence are not at heightened risk of becoming addicted with short-term opioid exposure. However, those with a positive history of dependence would benefit from active recovery efforts while receiving such medications.

The Institute for Clinical Systems Improvement recommends that opioid prescribers should recognize the symptoms of opioid use disorder, understand the treatment options for opioid use disorder, and have a referral source available.

(https://www.guideline.gov/summaries/summary/50568. Last accessed May 26, 2017.)

Level of Evidence: Expert Opinion/Consensus Statement

Despite the rise in prescription opioid analgesic use and misuse, definitive data on the rate of dependence among patients administered opioids for acute pain does not yet exist. There is, however, agreement on how to minimize the risk of iatrogenic dependence. These steps include screening for risk potential based on a family history of substance abuse and the exploration of different delivery systems that adequately treat pain but minimize abuse potential. Although a pattern of aberrant behavior may be grounds for caution, a history of opioid misuse does not necessarily preclude a patient from successful treatment with an opioid. Screening for psychologic disorders is also advisable, including psychosomatic causes of pain.

CONCLUSION

Safety is the foundation of effective pain control with opioid prescribing. Safety risks are mitigated by understanding that most opioid analgesic overdoses involve co-ingested CNS sedatives or alcohol, with side effects, tolerability and analgesic response largely determined by comorbidities, drug interactions, and genetic variation.

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

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COURSE TEST - #95140 OPTIMIZING OPIOID SAFETY AND EFFICACY

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

This 15 credit activity must be completed by May 31, 2020.

1. Pseudoaddiction is defined as
- A) *a disproven concept that some drugs are inherently "addictive."*
- B) *diminished or lost analgesia and dose titration to regain pain relief.*
- C) *peripheral and central sensitization without detectable peripheral origin.*
- D) *an iatrogenic condition whereby patients display drug-seeking behaviors mimicking opioid use disorder but driven by intense need for pain relief.*

2. The increase in prescription overdose deaths reported by the CDC in 2014 was the result of
- A) *increased opioid prescribing.*
- B) *a change in reporting standards.*
- C) *an influx of illicit morphine from Mexico.*
- D) *increased patient misuse and diversion of opioids.*

3. In 2011, benzodiazepines were associated with what percentage of opioid analgesic fatalities?
- A) *3.1%*
- B) *13%*
- C) *31%*
- D) *73%*

4. The most common anatomic location of pain in U.S. adults is the
- A) *finger.*
- B) *shoulder.*
- C) *low back.*
- D) *headache or migraine.*

5. Which of the following statements regarding untreated or undertreated pain is TRUE?
- A) *Chronic pain is the leading medical cause of suicide.*
- B) *Failure to manage pain has serious physical, but not psychosocial, consequences.*
- C) *Poorly controlled moderate-to-severe chronic pain has no impact on risk of death.*
- D) *The negative impact of chronic pain on quality of life is comparable to terminal cancer.*

6. The presence of all of the following coping styles predicts the development of chronic pain, EXCEPT:
- A) *Acceptance*
- B) *Somatization*
- C) *Kinesophobia*
- D) *Catastrophizing*

7. The single most important and prevalent chronic pain comorbidity is
- A) *obesity.*
- B) *sleep impairment.*
- C) *major depressive disorder.*
- D) *post-traumatic stress disorder.*

8. All of the following groups are at risk for unrelieved pain due to stigma and bias, EXCEPT:
- A) *Men*
- B) *Children*
- C) *Military veterans*
- D) *Racial/ethnic minorities*

9. The three primary opioid receptor types are
- A) *mu, kappa, and delta.*
- B) *alpha, beta, and delta.*
- C) *mu, theta, and omega.*
- D) *mu, sigma, and gamma.*

10. The greatest factor that contributes to opioid analgesia is
- A) *the presence of inflammation.*
- B) *plasma concentration of the drug.*
- C) *concentration of the drug on the mu receptor.*
- D) *the intrinsic properties of the opioid (e.g., lipid solubility).*

Test questions continue on next page ➔

11. Which of the following is an alkaloid of raw opium with identified use in medicine?
A) *Narceine*
B) *Morphine*
C) *Narcotine*
D) *Hydromorphone*

12. Which of the following opioid analgesics is categorized as a mu opioid receptor full agonist?
A) *Fentanyl*
B) *Naloxone*
C) *Pentazocine*
D) *Buprenorphine*

13. The World Health Organization has designated which agent as the drug of choice for moderate-to-severe pain?
A) *Codeine*
B) *Morphine*
C) *Oxycodone*
D) *Acetaminophen*

14. Which of the following statements regarding hydromorphone is TRUE?
A) *It has a bioavailability of more than 90%.*
B) *It is 100 times more potent than morphine.*
C) *It should not be administered subcutaneously.*
D) *Its high water solubility permits very concentrated formulations.*

15. Codeine
A) *has high abuse potential.*
B) *is not associated with constipation.*
C) *is only available for oral administration.*
D) *is less likely to result in respiratory depression than morphine.*

16. How does oxycodone differ from morphine?
A) *It produces less dysphoria.*
B) *It is a partial, rather than a full, agonist.*
C) *It has greater plasma than CNS concentrations.*
D) *It is transported more slowly through the blood-brain barrier.*

17. The primary use of methadone in the United States over the last five decades has been
A) *for short-term analgesia of postsurgical pain.*
B) *to block the effects of heroin and other opioid drugs.*
C) *for the treatment of patients with opioid-induced hyperalgesia.*
D) *to obtain pain relief in patients with chronic pain refractory to other treatments.*

18. After removal of a fentanyl patch, what duration of time is necessary for drug clearance?
A) *2 to 4 hours*
B) *12 hours*
C) *up to 24 hours*
D) *more than 48 hours*

19. Due to the risk of seizure, tramadol dosage should not exceed
A) *100 mg/day.*
B) *400 mg/day.*
C) *500 mg/day.*
D) *800 mg/day.*

20. With butorphanol, peak analgesia is reached within
A) *30 seconds.*
B) *1 hour.*
C) *3 hours.*
D) *12 hours.*

21. Opioid antagonists are FDA-approved for the treatment of
A) *opioid overdose.*
B) *opioid-induced constipation.*
C) *alcohol and opioid use disorders.*
D) *All of the above*

22. All of the following opioids are completely absorbed from the GI tract following oral administration, EXCEPT:
A) *Morphine*
B) *Methadone*
C) *Pentazocine*
D) *Hydromorphone*

23. Which of the following is a CYP3A4 inhibitor?
A) *Rifampin*
B) *Phenytoin*
C) *St. John's wort*
D) *Grapefruit juice*

24. Which of the following is a pharmacologic property of methadone that increases the risk of toxicity?
A) *Shortened QTc interval*
B) *Longer half-life than analgesia*
C) *Lack of metabolism by CYP isoenzymes*
D) *None of the above*

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25. Which of the following opioids has the greatest susceptibility to adverse drug interaction?
A) *Fentanyl*
B) *Tramadol*
C) *Oxycodone*
D) *Methadone*

26. According to the CDC guidelines for opioid prescribing in chronic pain, before starting opioid therapy, clinicians should
A) *establish treatment goals.*
B) *consider how therapy will be discontinued if benefits do not outweigh risks.*
C) *discuss patient and clinical responsibilities for managing therapy with the patient.*
D) *All of the above*

27. According to the CDC guidelines, offering a naloxone kit should be considered when
A) *any opioid is prescribed at any dose.*
B) *benzodiazepines are used concurrently with opioids.*
C) *lower opioid dosages are prescribed (<50 mg MED/day).*
D) *a patient has no history of opioid use (i.e., is opioid-naïve).*

28. Opioid therapy should
A) *be presented as a time-limited trial.*
B) *should be initiated at the highest tolerable dose.*
C) *not be continued beyond the trial period regardless of benefits.*
D) *begin with an extended-release/long-acting (ER/LA) formulation.*

29. Which of the following is a contraindication to any use of opioid analgesics?
A) *Fibromyalgia*
B) *Planned pregnancy*
C) *Chronic pancreatitis*
D) *Respiratory instability*

30. In older patients prescribed opioids, age-related reduction in hepatic metabolism
A) *prolongs the drug half-life.*
B) *increases first-pass metabolism.*
C) *reduces distribution of water-soluble drugs.*
D) *results in increased opioid-related GI side effects.*

31. All of the following genetic variations have relevance to opioid kinetics and dynamics, EXCEPT:
A) *COMT enzymes*
B) *BRCA mutation*
C) *CYP450 enzymes*
D) *Cytokine gene promoters*

32. Of the following racial groups, which is most likely to have polymorphic *CYP2D6* resulting in intermediate (underactive) opioid metabolism?
A) *Asians*
B) *Whites*
C) *Hispanics*
D) *Black/African Americans*

33. In patients with suspected *CYP450* polymorphism or those requiring multiple medications that interact with CYP isoenzymes, perhaps the safest opioid is
A) *codeine.*
B) *tramadol.*
C) *hydrocodone.*
D) *oxymorphone.*

34. What route of administration is contraindicated for opioids because it is painful and lacks any pharmacokinetic advantage?
A) *Intravenous*
B) *Intramuscular*
C) *Subcutaneous*
D) *Transmucosal*

35. The FDA states that ER/LA opioids are indicated for
A) *treatment of severe acute pain in an inpatient setting.*
B) *use only in cases of failed treatment with another class of drugs.*
C) *patients with severe chronic pain who are at high risk for opioid misuse and/or diversion.*
D) *pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.*

36. Opioid rotation can be an effective strategy for overcoming
A) *analgesic failure.*
B) *opioid-induced hyperalgesia.*
C) *problems related to medication cost.*
D) *All of the above*

Test questions continue on next page ➔

37. Tolerance to which of the following opioid effects develops most rapidly?

A) Nausea
B) Euphoria
C) Analgesia
D) Constipation

38. The most common form of opioid-induced bowel dysfunction is

A) dry mouth.
B) constipation.
C) abdominal pain.
D) nausea/vomiting.

39. Which of the following is a risk factor for opioid-induced respiratory depression?

A) Narcolepsy
B) Underweight
C) Long-term opioid use
D) Coingestion of any CNS respiratory depressant

40. What is the only opioid analgesic associated with serotonin syndrome?

A) Codeine
B) Morphine
C) Tramadol
D) Oxycodone

Be sure to transfer your answers to the Answer Sheet insert located between pages 96–97.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

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MODERATE SEDATION

#40951 • 5 Credits

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Purpose: The purpose of this course is to provide physicians with the information necessary to perform moderate sedation safely and according to existing guidelines in order to facilitate better patient care.

Additional Approvals: ABIM, ABA, ABP

RISK MANAGEMENT

SALE!

#41471 • 5 Credits

By Mail – ~~$25~~ $16 • Online/eBook – $10

Mandate: CT, MA, PA, TX

Purpose: With patient safety as the priority, risk management should focus on the avoidance of medical errors, as they are, along with inadequate informed consent, the most common assertions in malpractice claims in the United States. The purpose of this course is to provide healthcare professionals with the information necessary to engage in risk management practices, including a variety of proven strategies to avoid malpractice.

Additional Approvals: ABIM, ABP

Special Approvals: This course meets the Texas requirement for 2 hours of ethics/professional responsibility education and meets the Connecticut, Massachusetts, and Pennsylvania requirement for risk management education.

MEDICAL ETHICS FOR PHYSICIANS

#47172 • 5 Credits

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Mandate: CT, MA, MI, NV, PA, TX

Purpose: The purpose of this course is to briefly review the history, theory, and practical issues of ethics as related to health care. Some states have felt that this subject is important enough to require all physicians to obtain continuing education credits in medical ethics.

Additional Approvals: ABIM, ABP

Special Approvals: This course meets the Michigan, Nevada, and Texas requirement for ethics/professional responsibility education and meets the Connecticut, Massachusetts, and Pennsylvania requirement for risk management education.

PNEUMONIA

#48541 • 10 Credits

By Mail – $35 • Online/eBook – $29

Purpose: The purpose of this course is to provide physicians with the information necessary to recognize, appropriately treat, and prevent pneumonia and its complications, thereby helping to alleviate a major clinical illness and important public health burden.

Additional Approvals: ABIM, ABA, ABP

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#48851 • 10 Credits

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Mandate: CA

Purpose: Without proper attention to risk factors, preventive measures, and early vigorous care and treatment, superficial areas of pressure injury to the skin can evolve into deep soft tissue necrosis and ulceration, from which life-threatening complications may ensue. The purpose of this course is to provide physicians, physician assistants, and nurse practitioners with the information necessary to prevent pressure ulcers, when possible, and to properly care for patients with pressure wounds.

Additional Approvals: ABIM

Special Approvals: This course meets the requirement for California physicians who must complete geriatric medicine education.

ISCHEMIC STROKE

#90282 • 10 Credits

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Purpose: The purpose of this course is to provide needed information about the roles of diagnosis and screening, evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.

Additional Approvals: ABIM, ABA

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Course Availability List *(Cont'd)*

A REVIEW OF INTERVENTIONAL RADIOLOGY
#90442 • 10 Credits
By Mail – $35 • Online/eBook – $29
Mandate: CA
Purpose: The purpose of this course is to provide information about a rapidly expanding field of radiological medicine. Knowledge of the basic procedures will assist physicians and nurses in preparing patients and their families for the many procedures performed in the radiology department.
Additional Approvals: ABIM, ABP
Special Approvals: This course fulfills the requirement for California physicians who hold a radiography supervisor and operator permit and are required to complete 10 credits of continuing education regarding the application of x-ray to the human body to renew their certification or permit.

COLORECTAL CANCER
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#90780 • 15 Credits
By Mail – $45 • Online/eBook – $39
Purpose: The purpose of this course is to provide healthcare professionals with information regarding the screening, diagnosis, and treatment of colorectal cancer in order to improve adherence to established guidelines and, by extension, patient outcomes.
Additional Approvals: ABIM

CARE OF THE PEDIATRIC TRAUMA PATIENT
#92071 • 15 Credits
By Mail – $45 • Online/eBook – $39
Purpose: As injury remains a leading cause of mortality and morbidity among children, the purpose of this course is to allow healthcare professionals to provide timely care to pediatric trauma patients and to assist parents and caregivers in recognizing measures that prevent this type of injury.
Additional Approvals: ABIM, ABA, ABP

MALE SEXUAL DYSFUNCTION
NEW!
#93770 • 10 Credits
By Mail – $46 • Online/eBook – $40
Purpose: Many men with sexual dysfunction complaints are reluctant to discuss concerns with healthcare and mental health providers. The purpose of this course is to provide healthcare professionals with the information necessary to identify and appropriately treat male sexual dysfunction.
Additional Approvals: ABIM

ANTIBIOTICS REVIEW
#95071 • 5 Credits
By Mail – $25 • Online/eBook – $19
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.
Additional Approvals: ABIM, ABP

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING
NEW!
#95150 • 3 Credits
By Mail – $18 • Online/eBook – $12
Mandate: CA, CT, MA, MI, NM, NY, OR
Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Additional Approvals: ABIM, ABA, ABP
Special Approvals: This course meets 3 hours of pain management education for California physicians.
This course meets the Connecticut requirement for 1 hour of risk management education.
This course meets the Massachusetts and Michigan requirement for 3 hours of pain management education.
This course meets 3 of the 5 hours of pain management education required by New Mexico.
This course is designed to meet the New York requirement for 3 hours of education in pain management, palliative care, and addiction every three years for those who are authorized to prescribe controlled substances.
This course meets 3 of the 7 hours of pain management education required by Oregon.

MEDICAL MARIJUANA AND OTHER CANNABINOIDS
#95170 • 5 Credits
By Mail – $25 • Online/eBook – $19
Mandate: OR
Purpose: The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.
Additional Approvals: ABIM, ABP
Special Approvals: This course meets 5 of the 7 hours of continuing education in pain management as required by the State of Oregon.

ALZHEIMER DISEASE
#96152 • 15 Credits
By Mail – $66 • Online/eBook – $60
Mandate: CA
Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.
Additional Approvals: ABIM
Special Approvals: This course meets the requirement for California physicians who must complete geriatric medicine education.

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Course Availability List *(Cont'd)*

ANXIETY DISORDERS

#96180 • 15 Credits

By Mail – $45 • Online/eBook – $39

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.

Additional Approvals: ABIM, ABP

BORDERLINE PERSONALITY DISORDER

#96220 • 15 Credits

NEW!

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide health and mental health professionals with the information necessary to assess and treat patients with borderline personality disorder effectively and safely, while minimizing their own stress level and clinic disruption these patients are capable of producing.

Additional Approvals: ABIM, ABP

HUMAN TRAFFICKING AND EXPLOITATION

#96311 • 5 Credits

NEW!

By Mail – $25 • Online/eBook – $19

Mandate: MI

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

Additional Approvals: ABIM, ABP

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

MENTAL HEALTH ISSUES COMMON TO VETERANS AND THEIR FAMILIES

#96340 • 2 Credits

NEW!

By Mail – $16 • Online/eBook – $10

Mandate: CT

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of military service on patient health as well as the skills necessary to effectively identify and intervene for these patients.

Additional Approvals: ABIM

Special Approvals: This course meets the Connecticut requirement for 2 hours of education on mental health conditions common to veterans and family members of veterans.

SUICIDE ASSESSMENT AND PREVENTION

#96440 • 6 Credits

NEW!

By Mail – $30 • Online/eBook – $24

Mandate: CT, NV, WA

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Additional Approvals: ABIM, ABP

Special Approvals: This course meets the Connecticut requirement for 2 hours of education on mental health conditions common to veterans and family members of veterans.
This course is approved by the Nevada State Board of Medical Examiners to fulfill 2 hours of education on suicide prevention and awareness.
This course is approved by the state of Washington Department of Health to fulfill the requirement for suicide prevention training, approval number TRNG.TG.60715375-SUIC.

ASSESSMENT AND MANAGEMENT OF PAIN AT THE END OF LIFE

#97141 • 2 Credits

By Mail – $16 • Online/eBook – $10

Mandate: CA, MA, NJ

Purpose: Because pain is frequently encountered in the palliative and hospice care environments, a knowledge of appropriate diagnosis and alleviation is vital to all members of the interdisciplinary team. The purpose of this course is to provide an overview of the assessment and management of pain in the end of life, focusing on the components integral to providing optimum care.

Additional Approvals: ABIM, ABA

Special Approvals: This course fulfills 1 hour of education on the appropriate care of the terminally ill for California-licensed physicians who must complete 12 hours of pain management and the appropriate care of the terminally ill.
This course meets the New Jersey and Massachusetts requirement for end-of-life education.

CULTURAL MEANINGS OF DEATH AND DYING

#97361 • 5 Credits

By Mail – $25 • Online/eBook – $19

Mandate: CT, NJ

Purpose: With the ever-increasing multicultural diversity in the landscape of the United States, culturally competent and sensitive practice is essential for practitioners. The purpose of this course is to increase clinicians' knowledge and awareness of the impact of culture on issues of death and dying in order to improve the provision of care and patients' quality of life.

Additional Approvals: ABIM, ABA

Special Approvals: This course meets the Connecticut and New Jersey requirement for cultural competency education.

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Course Availability List *(Cont'd)*

CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT

#97532 • 2 Credits

By Mail – $16 • Online/eBook – $10

Mandate: NY

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.

Additional Approvals: ABIM, ABP

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.

INFECTION CONTROL: THE NEW YORK REQUIREMENT

#98641 • 5 Credits

By Mail – $25 • Online/eBook – $19

Mandate: NY

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.

Additional Approvals: ABIM

Special Approvals: This course is approved by the New York State Department of Health to fulfill the requirement for 3 hours of infection control training as mandated by Chapter 786 of the Laws of 1992. Provider #TP02078.

SLEEP DISORDERS

#98881 • 10 Credits

By Mail – $35 • Online/eBook – $29

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to identify and effectively treat sleep disorders, thereby improving patients' quality of life and preventing possible complications.

Additional Approvals: ABIM, ABA, ABP

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of a course constitutes permission to share the completion data with ACCME.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit. Please see individual course details.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity in the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program (MOCA)®, known as MOCA 2.0®. Please see individual course details.

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What You Should Know About…

Prescription Opioids

This page is perforated for easy removal.

Patient Education Handout
A service for patients

WHAT are opioids

Prescription opioids are powerful pain-reducing medications that include prescription oxycodone (OxyContin, Percodan, Percocet), hydrocodone (Vicodin, Lortab, Lorcet), and morphine (Kadian, Avinza, MS Contin), among others, and have both benefits as well as potentially serious risks. Although they are very effective pain relievers, these medications are classified as narcotics and can be dangerous when abused. When used properly, opioids have long been known to help the severe pain that follows surgery and to alleviate the suffering of people with advanced cancer. More recently, morphine and similar drugs have been used to treat chronic pain not caused by cancer. For many people, they have been remarkably helpful; for others, it either hasn't worked or has created problems over time.

Taken as directed, opioids can manage pain effectively when used for a short amount of time. With long-term use, people need to be screened and monitored, because a fraction of those treated will develop an addiction disorder, abuse the drugs, or give them to others. Long-term daily use of opioids leads to physical dependence, which is not to be confused with addiction disorder. An addiction disorder occurs in about 5% of people who take these pain relievers as directed over the period of one year. An addiction disorder can be treated, but like those who misuse or illegally distribute prescription drugs, the prescriber needs to be vigilant to identify and address these problems. That is why everyone who uses prescription opioids needs to be screened and closely monitored.

WHO is prescribed opioids

Opioids are commonly prescribed because they are effective in relieving many types of pain. Opioids may be used short-term to manage pain associated with surgery, labor pain, breakthrough pain (defined as pain that arises despite the use of long-term pain relief medication), and intermittent pain (arising only every once in a while).

As noted, long-term opioid use may be necessary for some patients with chronic, severe pain. This type of opioid therapy is only prescribed if the expected benefits for your pain and function are expected to outweigh the risks. It is important to work with your healthcare provider to make sure you are getting the safest, most effective care.

WHAT are the risks and side effects of opioid use

Prescription opioids carry serious risks of addiction and overdose, especially with prolonged use. In one study, 25% of patients receiving opioids from a primary care provider struggled with addiction. An opioid overdose, often marked by slowed breathing, can cause sudden death. The use of prescription opioids can have a number of side effects as well, even when taken as directed:

- Tolerance—meaning you might need to take more of a medication for the same pain relief
- Physical dependence—meaning you have symptoms of withdrawal when a medication is stopped
- Increased sensitivity to pain
- Constipation
- Nausea and vomiting
- Dry mouth
- Sleepiness
- Dizziness
- Confusion
- Depression
- Low levels of testosterone that can result in lower sex drive, energy, and strength
- Itching and sweating

WHAT factors increase the risk of opioid side effects

The risks are greater if certain factors are present. This includes:

- History of drug misuse, substance use disorder, or overdose
- Mental health conditions (such as depression or anxiety)
- Sleep apnea
- Older age (65 years or older)
- Pregnancy

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In addition, the use of alcohol and certain other medications can increase the risk of slowed breathing and overdose. So, you should always avoid alcohol while taking prescription opioids. Also, unless specifically advised by your healthcare provider, medications to avoid include:

- Benzodiazepines (such as Xanax or Valium)
- Muscle relaxants (such as Soma or Flexeril)
- Hypnotics (such as Ambien or Lunesta)
- Other prescription opioids

Do not take medicine unless it was prescribed for you. Do not stop taking your medicine without talking to your healthcare provider. Do not cut, break, chew, crush, dissolve, snort, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.

WHO should I contact if I have side effects

Call 911 or your local emergency service right away if:

- You take too much medicine
- You have trouble breathing or shortness of breath
- A child has taken one of your opioids

Talk to your healthcare provider:

- If the dose you are taking does not control your pain
- About any side effects you may be having
- About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements

HOW can I dispose of unneeded opioids

In some cases, you may have some opioids left after your pain resolves. In these cases, you should dispose of the drugs safely. It is important never to share your medication with others.

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. Any personal information should be obscured or destroyed. Certain medicines, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), should be flushed down the toilet instead of thrown in the trash. Only flush prescription drugs down the toilet if the label or accompanying patient information specifically instructs doing so.

This information is reprinted from material provided by the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration.

This handout is provided to you by NetCE and your healthcare provider. For more information, please consult your physician.

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	94180	Viral Sexually Transmitted Infections / 5 Credits	$20
	98930	Irritable Bowel Syndrome / 10 Credits	$40
	95140	Optimizing Opioid Safety and Efficacy / 15 Credits	$60

Additional Courses Available by Mail

Payment must accompany this form. To order by phone, please have your credit card ready.

✓	Course #	Course Title / Credits	Price
☐	40951	Moderate Sedation / 5	$26
☐	41471	Risk Management / 5	$16
☐	47172	Medical Ethics for Physicians / 5	$26
☐	48541	Pneumonia / 10	$35
☐	48851	Pressure Ulcers: Pathogenesis and Management / 10	$35
☐	90282	Ischemic Stroke / 10	$46
☐	90442	A Review of Interventional Radiology / 10	$35
☐	90780	Colorectal Cancer / 15	$45
☐	92071	Care of the Pediatric Trauma Patient / 15	$45
☐	93770	Male Sexual Dysfunction / 10	$46
☐	95071	Antibiotics Review / 5	$25
☐	95150	Responsible and Effective Opioid Prescribing / 3	$18
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☐	97361	Cultural Meanings of Death and Dying / 5	$25
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Grand Total

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Answer Sheet

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Please note the following:

- In accordance with changes to the *AMA PRA Category 1 Credit*™ system, physicians must complete and pass a post-test to receive credit.
- A passing grade of at least 70% must be achieved on each course test in order to receive credit.
- Darken only one circle per question.
- Use pen or pencil; please refrain from using markers.
- **Information on the Customer Information form must be completed**.
- **Include the completed and signed mandatory Evaluation.** Your postmark or fascimile date will be used as your completion date.

#94180 VIRAL SEXUALLY TRANSMITTED INFECTIONS—5 CREDITS

Please refer to pages 25–26.

Expiration Date: 06/30/20

May be taken individually for $20

	A	B	C	D		A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍	11.	❍	❍	❍	❍	16.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍	12.	❍	❍	❍	❍	17.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍	13.	❍	❍	❍	❍	18.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍	14.	❍	❍	❍	❍	19.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍	15.	❍	❍	❍	❍	20.	❍	❍	❍	❍

#98930 IRRITABLE BOWEL SYNDROME—10 CREDITS

Please refer to pages 57–59.

Expiration Date: 11/30/19

May be taken individually for $40

	A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	11.	❍	❍	❍	❍	21.	❍	❍	❍	❍
2.	❍	❍	❍	❍	12.	❍	❍	❍	❍	22.	❍	❍	❍	❍
3.	❍	❍	❍	❍	13.	❍	❍	❍	❍	23.	❍	❍	❍	❍
4.	❍	❍	❍	❍	14.	❍	❍	❍	❍	24.	❍	❍	❍	❍
5.	❍	❍	❍	❍	15.	❍	❍	❍	❍	25.	❍	❍	❍	❍
6.	❍	❍	❍	❍	16.	❍	❍	❍	❍	26.	❍	❍	❍	❍
7.	❍	❍	❍	❍	17.	❍	❍	❍	❍	27.	❍	❍	❍	❍
8.	❍	❍	❍	❍	18.	❍	❍	❍	❍	28.	❍	❍	❍	❍
9.	❍	❍	❍	❍	19.	❍	❍	❍	❍	29.	❍	❍	❍	❍
10.	❍	❍	❍	❍	20.	❍	❍	❍	❍	30.	❍	❍	❍	❍

#95140 OPTIMIZING OPIOID SAFETY AND EFFICACY—15 CREDITS

Please refer to pages 103–106.

Expiration Date: 05/31/20

May be taken individually for $60

	A	B	C	D		A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	11.	❍	❍	❍	❍	21.	❍	❍	❍	❍	31.	❍	❍	❍	❍
2.	❍	❍	❍	❍	12.	❍	❍	❍	❍	22.	❍	❍	❍	❍	32.	❍	❍	❍	❍
3.	❍	❍	❍	❍	13.	❍	❍	❍	❍	23.	❍	❍	❍	❍	33.	❍	❍	❍	❍
4.	❍	❍	❍	❍	14.	❍	❍	❍	❍	24.	❍	❍	❍	❍	34.	❍	❍	❍	❍
5.	❍	❍	❍	❍	15.	❍	❍	❍	❍	25.	❍	❍	❍	❍	35.	❍	❍	❍	❍
6.	❍	❍	❍	❍	16.	❍	❍	❍	❍	26.	❍	❍	❍	❍	36.	❍	❍	❍	❍
7.	❍	❍	❍	❍	17.	❍	❍	❍	❍	27.	❍	❍	❍	❍	37.	❍	❍	❍	❍
8.	❍	❍	❍	❍	18.	❍	❍	❍	❍	28.	❍	❍	❍	❍	38.	❍	❍	❍	❍
9.	❍	❍	❍	❍	19.	❍	❍	❍	❍	29.	❍	❍	❍	❍	39.	❍	❍	❍	❍
10.	❍	❍	❍	❍	20.	❍	❍	❍	❍	30.	❍	❍	❍	❍	40.	❍	❍	❍	❍

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Evaluation

(Completion of this form is mandatory)

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To receive continuing education credit, completion of this Evaluation is mandatory.

Please read the following questions and choose the most appropriate answer for each course completed.

1. Was the course content new or review?
2. How much time did you spend on this activity, including the questions?
   (Physicians should only claim credit commensurate with the extent of their participation in the activity.)
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing this course, did you identify the necessity for education on the topic to improve your professional practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
11. Are you more confident in your ability to provide patient care after completing this course?
12. Do you plan to make changes in your practice as a result of this course content?
13. May we contact you later regarding planned changes in your practice and changes in treatment or health status of your patients as a result of this activity?

#94180
Viral STIs
5 Credits

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

#98930
Irritable Bowel Syndrome
10 Credits

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

#95140
Optimizing Opioid Safety and Efficacy
15 Credits

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

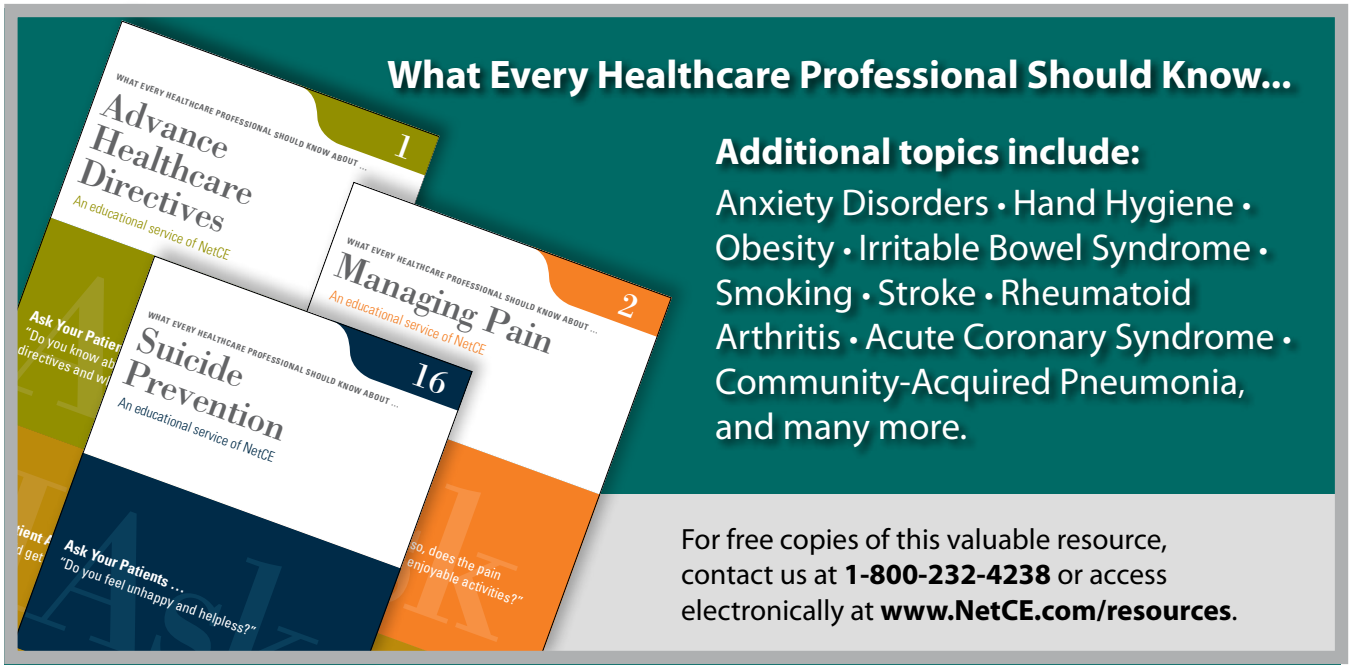
#94180 Viral Sexually Transmitted Infections — What change(s) do you plan to make in your practice? _____

#98930 Irritable Bowel Syndrome — What change(s) do you plan to make in your practice? _____

#95140 Optimizing Opioid Safety and Efficacy — What change(s) do you plan to make in your practice? _____

Signature _____

Signature required to receive continuing education credit.



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