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CONTINUING EDUCATION FOR TEXAS PHARMACISTS 2024

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Review of Texas Pharmacy Law for Pharmacists

This course meets the Texas requirement for 1 hour of education on Texas pharmacy laws.

Audience
This course is designed for pharmacists licensed to practice in Texas.

Course Objective
The purpose of this course is to review Texas State Board of Pharmacy laws and rules to ensure compliance with the continuing education requirement to complete at least one contact hour on Texas pharmacy laws or rules during each renewal period.

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

1. Review pharmacist training and continuing education requirements.
2. Identify appropriate prescription dispensing practices.
3. Discuss pharmacy record management and retention requirements.
4. Explain pharmacy technician regulations.
5. Describe controlled substance laws that impact the practice of pharmacy.

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

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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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INTRODUCTION

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Every state has an agency that functions to protect the health, safety, and welfare of patients. To protect patients, the Texas State Board of Pharmacy has a set of laws and regulations that pharmacy personnel must follow.

There are times when state laws differ from federal laws. When this happens, ALWAYS go with the stricter law. Usually, the stricter law is the state law. So, most of the time, you'll follow the state law.

Think about it this way when considering which law is stricter: if you are complying with the state law, and that automatically makes you compliant with the federal law, then you know the state law is stricter. You will see examples of this throughout this review.

PHARMACIST LICENSURE AND EDUCATION REQUIREMENTS

REFLECTION

What do you need to do to maintain your pharmacist license in Texas? How do you meet these requirements? What special requirements do you have to follow if you are an immunizing pharmacist or a preceptor in Texas?

GENERAL REQUIREMENTS TO MAINTAIN PHARMACIST LICENSURE

Pharmacists who are licensed with the Texas State Board of Pharmacy will need to renew their pharmacist license every two years [1; 2]. Keep in mind that licenses expire on the last day of the assigned expiration month [2].

When you renew, you must report that you've completed **30 hours of continuing education (CE)** [3]. Of those 30 hours, 1 hour must be related to Texas-specific pharmacy laws and/or rules, which this course is designed to help you meet. The remaining 29 hours can be on any subject and can consist of any special CE requirements, if applicable (e.g., immunization, sterile compounding, preceptorship) [4; 5]. In addition, all pharmacists must complete a Texas Health and Human Services Commission (HHSC)-approved human trafficking prevention training course [4; 6]. Note that while this is a training requirement and not a CE requirement, some courses may offer CE credit. If the course you take provides CE credit, it may count towards your CE hour requirement. You can find HHSC-approved human trafficking courses, including at least one course that is available without charge (a requirement of the statute) on the HHSC Health Care Practitioner Human Trafficking Training website [6].

Newly licensed pharmacists don't need to complete the full 30-hour CE requirement during their initial license period. However, newly licensed pharmacists must complete an HHSC-approved human trafficking training course during their initial renewal period. Additionally, within the first 12 months of licensure, newly licensed pharmacists must obtain at least two CE credit hours related to prescribing and monitoring controlled substances [7].

You'll need to keep copies of the certificates (either hard copy or electronic) for your continuing education activities for at least **three years from the date that you report the hours on a license renewal application** [3]. This means that if you took a course in January 2024, but submitted your renewal application in September 2024, you would need to maintain this record until September 2027 (not January 2027). You must present CE certificates if the Board requests them.

Any program with a primary focus covering the topics specified above that is offered by an Accreditation Council for Pharmacy Education (ACPE)-accredited provider can be used to help meet these continuing education requirements [4].

Pharmacists can receive three credit hours for attending a full, public Texas State Board of Pharmacy Board Meeting in its entirety. A maximum of six credit hours are allowed for attending board meetings during a license period. Proof of attendance will be provided as a certificate from the Texas State Board of Pharmacy, which will serve as the CE certificate [3].

STERILE COMPOUNDING EDUCATION REQUIREMENTS

Pharmacists who prepare sterile compounds or supervise pharmacy technicians that prepare sterile compounds must initially complete a single course on sterile compounding of at least **20 hours of instruction and experience**. This training can be obtained through completion of a recognized course from an accredited college of pharmacy, or a course sponsored by an ACPE-accredited provider. Pharmacists must also complete a structured on-the-job didactic and experiential training program at the pharmacy where the sterile compounding takes place. The training should include the facility's specific sterile compounding processes and procedures. This training cannot be transferred to another pharmacy unless the pharmacies are under the same ownership and use the same training program. After the initial training, moving forward upon license renewal, pharmacists must complete at least **two hours of CE credit** on sterile compounding if the pharmacist is engaged in compounding low- or medium-risk sterile preparations, or f**our hours of CE credit** if the pharmacist is engaged in compounding high-risk sterile preparations [8].

Note that with non-sterile compounding, although the Board states that there must be initial training and continuing education "appropriate for the type of compounding done," the type of initial training and number of hours of initial and ongoing training haven't been specified as they have with sterile compounding. Follow your company's policies and procedures around initial and ongoing training for non-sterile compounding [9].

CASE STUDY: ROBERT

Robert has been a Texas licensed pharmacist for the past five years. He just renewed his license last year, so it's due for renewal in another year. He recently moved across the state and started a new job working in a hospital pharmacy that performs high-risk sterile compounding. Even though he was performing sterile compounding at his old job, he knows that he is going to have to get additional training at the new hospital he will be working at. He is also aware that he will have to complete four hours of CE on sterile compounding before renewing his license next year, since he's involved in preparing high-risk sterile compounds.

IMMUNIZATION ADMINISTRATION EDUCATION REQUIREMENTS

Pharmacists may administer immunizations under a written protocol with a physician. Notification of immunization must be provided within 24 hours of administering the vaccine to the protocol physician, and within 14 days to the patient's primary care physician [10].

According to state law, immunizations other than the flu vaccine may be administered to patients 14 years of age and older. The flu vaccine may be administered to patients age 7 and older. Immunizations can be administered to patients under the age of 14 (or under the age of seven for the flu vaccine) upon referral from a physician who has a relationship with the patient [10].

In order to give immunizations, there are several requirements for pharmacists [3; 10]:

- You must have completed an initial course from an ACPE-accredited provider which requires documentation of CPR certification and is a minimum of 20 hours of immunization-related content which includes hands-on training and requires testing with a passing score. You must keep documentation of initial course completion.
- You must complete three hours of continuing education related to immunizations every two years.
- You must maintain current CPR certification. Courses offered by the American Red Cross, American Heart Association, or their equivalent are recognized.
  - CPR courses are recognized as approved CE programs to be counted towards your continuing education requirements. Proof of completion of a CPR course issued by the American Red Cross, American Heart Association, or its equivalent, shall serve as the CE certificate.

- Pharmacists may receive credit for one contact hour upon completion of a **Basic** CPR course once during a license period.
- Pharmacists may receive credit for 12 contact hours upon **initial** advanced cardiovascular life support (ACLS) or pediatric advanced life support (PALS) certification once during a license period.
- Pharmacists may receive credit for four contact hours upon **recertification** in ACLS or PALS once during a license period.

It's also important to be aware that in Texas, it is required by law to cleanse your hands with an alcohol-based waterless antiseptic hand rub or wash your hands with soap and water before preparing to give a vaccine and between each patient contact. Texas law does not require you to wear gloves, but if gloves are worn, you must change them between patients [10].

COVID-19 Considerations

During the COVID-19 public health emergency, the federal government, under the Public Health Readiness and Emergency Preparedness (PREP) Act, authorized qualified pharmacists to order and administer, and pharmacy technicians and pharmacy interns to administer, influenza and COVID-19 vaccines to any patient age 3 and older. Although the public health emergency has ended, this authority under the PREP Act has been extended through December 2024 [11]. If you are providing immunizations during the public health emergency under the PREP Act, make sure you are following both the federal requirements and your state's requirements for reporting and recordkeeping.

CASE STUDY: KRISTINE

Kristine recently became licensed to practice pharmacy in Texas after moving to the state. She is going to be practicing in a community pharmacy where she will be providing immunizations. She was an immunizer in the state she moved from and has already gone through the 20-hour certificate program. She also has current CPR certification. However, she notes that she is going to have to complete three hours of CE related to immunization every two years, a requirement she didn't have in the state she was previously practicing in.

PRECEPTOR EDUCATION REQUIREMENTS

If you want to become a pharmacist preceptor, you must be approved and certified by the Board of Pharmacy. To become a preceptor, you must meet the following requirements [12]:

- Your Texas pharmacist license must be current and active
- You must have either one year of experience as a licensed pharmacist, OR six months of residency training if the pharmacy resident is completing a residency program
- You must have completed three hours of preceptor training within the previous two years (for initial certification) or within your current license renewal period. This training must be:
  - Developed by a Texas college/school or pharmacy, or
  - Approved by a committee comprised of the Texas college/schools of pharmacy, or
  - Approved by the Board

Once approved by the Texas State Board of Pharmacy, you will be able to print a preceptor certificate from the Board's website [13]. As a preceptor, you are responsible for supervising the activities of pharmacist-interns. Keep in mind that you may only supervise one pharmacist-intern at any given time (1:1 ratio), and the pharmacist-intern is not counted towards the pharmacy technician ratio (discussed later). The exception to the 1:1 ratio is if you are precepting pharmacy students as part of a Texas college/school of pharmacy program (e.g., students on IPPE or APPE rotations); there is no ratio requirement in this scenario [12].

DRUG THERAPY MANAGEMENT EDUCATION REQUIREMENTS

Pharmacists in Texas may engage in drug therapy management as delegated by a supervising physician and authorized through a written protocol. The Texas State Board of Pharmacy defines drug therapy management as [14]:

- The performance of specific acts by pharmacists as authorized by a physician through written protocol. Drug therapy management does not include the selection of drug products not prescribed by the physician, unless the drug product is named in the physician-initiated protocol or the physician initiated record of deviation from a standing protocol. Drug therapy management may include the following:
  - Collecting and reviewing patient drug use histories;
  - Ordering or performing routine drug therapy related patient assessment procedures including temperature, pulse, and respiration;
  - Ordering drug therapy related laboratory tests;
  - Implementing or modifying drug therapy following diagnosis, initial patient assessment, and ordering of drug therapy by a physician as detailed in the protocol; or
  - Any other drug therapy related act delegated by a physician.

In order to initially engage in drug therapy management, pharmacists must have completed at least six hours of CE related to drug therapy offered by an ACPE-accredited provider within the last year (or have been engaging in drug therapy management as allowed under previous laws or rules). This six-hour CE requirement must be met each year if pharmacists want to continue to participate in drug therapy management [14].

PHARMACIST STANDARDS

CASE STUDY: KRISTINE

At Kristine's old pharmacy, she only supervised one to two technicians at a time. Her new pharmacy is much busier, with multiple pharmacists and technicians on duty at any given time.

What rules related to overseeing pharmacy staff should Kristine familiarize herself with? What duties can and cannot be performed by pharmacy technicians in Texas?

IDENTIFICATION

All pharmacy staff (pharmacists, technicians, trainees, and pharmacist-interns) must **wear an ID badge** when working. The badge should include your name and title [15].

The Texas State Board of Pharmacy also requires that you maintain at the pharmacy and make available to the public on request, proof that each pharmacist, pharmacist-intern, pharmacy technician, and pharmacy technician trainee holds the appropriate license or registration [16]. In addition, the pharmacist-in-charge must display their license so that it is visible to the public.

The **license for the pharmacy** must also be posted so that it is visible to the public [16].

Be aware that you'll need to notify the Board **within 10 days of a change in your name, address, or place of employment**. You must also make sure that your name is removed from the pharmacy license of your previous employer and added to the new employer's pharmacy license [17; 18].

PATIENT COUNSELING

REFLECTION

What are the rules in Texas about counseling patients? What information should be discussed during counseling? What type of documentation is needed?

OBRA stands for the Omnibus Budget Reconciliation Act of 1990. This act plays a role in patients receiving counseling on new prescriptions and refills of medications. OBRA '90 required states to establish standards for patient counseling and stated that pharmacists must offer to counsel patients. The Texas State Board of Pharmacy is stricter than OBRA '90 in that it mandates counseling for all patients getting new prescriptions [19].

Keep in mind that requirements for counseling differ based on your practice setting. If you work in a hospital or institution, you do not have to counsel inpatients [19].

If you work in a **community pharmacy**, you must counsel the patient or their agent on **all new prescriptions**. A new prescription is defined as a prescription that hasn't been dispensed by the pharmacy to the patient in the same dosage form and strength within the last year [19].

For new prescriptions, a non-pharmacist staff member (such as a technician) CANNOT ask if a patient requests counseling, because counseling is required. You must also provide counseling if the patient requests it or has questions. Only pharmacists can provide drug information, counsel, or answer questions for patients about their medications [19].

As part of patient counseling, the Texas State Board of Pharmacy states that you should include information that you feel is needed to optimize therapy for the particular prescription drug or device. This might include [19]:

- Name and description of drug
- Dosage form, dose, route of administration, duration of therapy
- Special directions or precautions for use
- Common severe side effects or interactions, including how to avoid these or what to do if they occur
- Techniques for self-monitoring
- Storage requirements
- Refill information
- What to do if a dose is missed

Written information (either in hard-copy or electronic format, such as by email, if requested by the patient) must also be provided at the time of verbal counseling for reinforcement. This info must be in simple language and easy for patients to read (no smaller than 10-point Times New Roman font). For compounded meds, the major active ingredient(s) should determine what written information is provided [19].

If a prescription is delivered to a patient's home, the information that would otherwise be given orally must be given to the patient in writing. Either on the prescription container or on a separate sheet of paper, you must provide the pharmacy's phone number along with this statement (in English and Spanish) [19]:

> "Written information about this prescription has been provided for you. Please read this information before you take the medication. If you have questions concerning this prescription, a pharmacist is available during normal business hours to answer these questions at (insert the pharmacy's local and toll-free telephone numbers [if prescriptions are routinely delivered outside the area covered by the pharmacy's local telephone service])."

There is one exception when written information may not need to be provided. If you are dispensing a new drug and written information is not yet available, you are not required to give this info. However, you must inform the patient of this, document that the info was not provided, and if the prescription is refilled you must provide this written information to the patient once it's available [19].

You must also **document the initials or other identification code of the pharmacist who provided counseling**. This documentation may be either on the original hard-copy prescription, in the pharmacy's data processing system, or in an electronic or hard-copy logbook. If a patient refuses counseling, you must document that refusal [19].

Every community pharmacy must have an area which is suitable for patient counseling. The area must be easily accessible to both patients and pharmacists, must not allow patients to have access to prescription drugs, and must be designed to maintain the confidentiality and privacy of the pharmacist/patient communication. Other patients or pharmacy staff should not be able to overhear the conversations occurring at the counseling area. Community pharmacies must also make available to patients, either in hard-copy or electronic format, a drug information reference book or leaflets that are designed for patients [19].

CASE STUDY: KRISTINE

Kristine is excited about getting to know her new patients. She sees that her new pharmacy has a system in place where they specially mark all new prescriptions so that any staff member can easily identify that counseling is needed. For new prescriptions, the technicians immediately direct patients to the counseling window. When Kristine completes the counseling, she documents her initials in the pharmacy's electronic logbook.

PATIENT MEDICATION RECORDS

All pharmacies in Texas must maintain a system for keeping information on patients whenever new or refill prescriptions are dispensed, known as a patient medication record (or patient profile). You and all other pharmacy personnel must make a reasonable effort to obtain, record, and maintain patient information. **All patient records or profiles must be maintained for at least two years from the date of the last entry** [20; 21].

Patient medication records in community settings must include [20; 21]:

- Patient name, address, and phone number
- Patient's age or date of birth
- Patient's gender
- A list of the patient's medications (both Rx and OTC), including all orders dispensed by the pharmacy in the last two years and including any other drugs currently being used by the patient
- Any known drug allergies or drug reactions
- Any known disease states
- Any pharmacist comments relevant to the patient's drug therapy

Patient medication records in hospital settings must include [20; 21]:

- Patient name and room number or identification number
- Gender and date of birth or age
- Weight and height
- Known drug sensitivities and allergies to drugs and/or food
- Primary diagnoses and chronic conditions
- Primary physician
- Other drugs the patient is receiving, in addition to current medication order information (date of distribution; drug name, strength, and dosage form; and directions for use)

PROSPECTIVE DRUG REVIEW

You must review the patient profile before any prescription is dispensed. At a minimum, you must identify any clinically significant [19; 22]:

- Allergies
- Contraindications
- Inappropriate doses or routes of administration
- Inappropriate directions for use
- Duplicate therapy
- Drug-drug, drug-food, or drug-disease interactions
- Adverse drug reactions
- Inappropriate use, including overuse or underuse
- Clinical laboratory or clinical monitoring methods to evaluate drug effectiveness, side effects, toxicity, or adverse effects, and appropriateness to continued use of the drug in its current regimen (hospital setting only)

If you recognize any problem during the review, you must take steps to resolve the problem, such as by consulting with the prescriber. Document your findings by including the date the prescriber was consulted, name of the person you spoke with, any relevant information, and your initials [19; 22].

SUPERVISING PHARMACY STAFF

As a pharmacist, you may be responsible for overseeing **pharmacy technicians** or **pharmacy technician trainees**. Be familiar with the Texas State Board of Pharmacy requirements for these staff members.

Pharmacy Technician Registration

REFLECTION

You are working with a pharmacy technician trainee who is wondering what she needs to do to become registered as a pharmacy technician. What would you tell the technician-in-training? How long can the pharmacy technician trainee work as a technician-in-training before needing to become registered as a pharmacy technician?

Individuals interested in working as a pharmacy technician in Texas must first **register with the Board of Pharmacy** before they begin working in a pharmacy. He or she must meet several requirements to be eligible for pharmacy technician registration [23; 24]:

- Have a high school or equivalent diploma or be working toward one for no more than two years
- Complete the Board application and pay the required fee
- Submit fingerprints in order for the Board to access the individual's criminal history, AND
- Pass the Pharmacy Technician Certification Board (PTCB)'s Pharmacy Technician Certification Exam (PTCE) or the National Healthcareer Association (NHA)'s Exam for the Certification of Pharmacy Technicians (ExCPT)

Technicians who are waiting to take and pass one of the national certification exams can still work in a pharmacy. But they must first apply for registration as a pharmacy technician trainee. This registration as a trainee is only good for two years, and it's NOT renewable. This means that **pharmacy technician trainees can't work as a technician-in-training for more than two years**. To work in the pharmacy after that time, they must have passed one of the Board-approved national certification exams AND have obtained pharmacy technician registration from the Board. Maintaining national certification is completely voluntary. The Texas State Board of Pharmacy only requires that technicians be nationally certified for their initial registration, not to maintain their certification [25]. However, registration with the Board must be maintained at all times that a pharmacy technician will be working in a pharmacy [23].

Pharmacy Technician Training Requirements

Both technicians and technician trainees must complete **initial "on-the-job" training** when they start working at your pharmacy. This training must be outlined in a training manual. The training must include how technicians will be supervised, clarify technician duties, and instruct technicians on basic areas of pharmacy practice. Technicians and trainees must also complete **continuing in-service education and training** to supplement the initial training. Documentation of the training must be kept on file at the pharmacy [26].

A written record of initial and in-service training of pharmacy technicians and pharmacy technician trainees must be maintained at the pharmacy and should include the following information [26]:

- Name of person receiving the training
- Date(s) of training
- General description of topics covered
- Statement certifying that the individual is competent to perform duties assigned
- Name of person supervising the training
- Signatures of person receiving the training and the pharmacist-in-charge, or other pharmacist designated by the pharmacist-in-charge as responsible for training

Additional training, including ongoing continuing education, is required for pharmacy technicians and pharmacy technician trainees engaged in non-sterile or sterile compounding. The pharmacist-in-charge is responsible for determining that all personnel engaged in compounding possess the education, training, and proficiency needed. Training activities should be documented and covered by standard operating procedures [8; 9].

Initial training for pharmacy technicians and pharmacy technician trainees who will be involved in sterile compounding must include either a single 40-hour course offered by an ACPE-accredited provider which provides a combination of instruction and experience, OR a training program accredited by ASHP. Pharmacy technicians and pharmacy technician trainees must also complete a structured, on-the-job didactic and experiential training program. All pharmacy personnel engaged in sterile compounding, including pharmacy technicians and pharmacy technician trainees, must pass written and skills testing initially and every 12 months for low- and medium-risk level compounding, or every six months for high-risk level compounding [8].

Pharmacy Technician Continuing Education Requirements

Once a pharmacy technician has registered with the Texas State Board of Pharmacy as a pharmacy technician, they will need to renew their pharmacy technician registration **every two years**. In order to renew their license, pharmacy technicians must complete and report 20 contact hours of approved continuing education obtained during the renewal period in pharmacy-related subjects. Up to five hours may be earned during in-service education and training from their employer.

One hour must be related to Texas pharmacy laws or rules. Like pharmacists, all pharmacy technicians are also required to complete an HHSC-approved human trafficking prevention training course. Although this is a training requirement and not a CE requirement, if the course taken provides CE credit, it may count towards the technician's total 20 hours. Even pharmacy technicians in their initial renewal period must complete this human trafficking training requirement [27; 28].

Like pharmacists, for the first renewal, technicians don't need to complete the required CE hours. Also, like pharmacists, technicians need to keep copies of the certificates (either hard copy or electronic) for CE activities for at least three years from the date of reporting the hours on a renewal application [27].

As mentioned for pharmacists, during each renewal period, pharmacy technicians who are engaged in sterile compounding need to complete at least two hours of CE related to sterile compounding if they are compounding low- or medium-risk sterile compounds, or four hours of CE if they are compounding high-risk compounds [8].

Keep in mind that pharmacy technician trainees do not have any continuing education requirements.

What Pharmacy Technicians May Do

In Texas, pharmacy technicians are allowed to perform many tasks while assisting the pharmacist. But any activities a pharmacy technician performs must be done under the direct supervision of the pharmacist. Ultimately, the pharmacist is the one responsible for all activities that occur inside the pharmacy.

Examples of duties a registered pharmacy technician is allowed to do [15]:

- Access and restock automated medication supply systems after proper training
- Affix labels to prescription containers
- Bulk compound or batch preparation
- Compound non-sterile and sterile preparations
- Distribute routine orders for stock supplies to patient care areas
- Enter prescription data into the pharmacy computer system
- Fill medication carts
- Initiate and receive refill authorization requests
- Load unlabeled drugs into an automated dispensing system
- Prepackage and label prepackaged drugs
- Prepare and package drug orders, including counting pills, measuring liquids, and placing them in containers
- Reconstitute medications
- Remove stock bottles from the shelf to help prepare prescriptions

The type of activities a pharmacy technician assists with will also depend on the practice setting. Depending on the specific activity, there may be additional Board requirements the technician will have to meet.

For example, the Board allows certain technicians who work in a hospital to check the work of another technician. This is often referred to as "tech-check-tech." But there are a few requirements before a technician can check another technician's work. The Board must approve the tech-check-tech process for your pharmacy. Then, a technician can only check the work of another technician for orders related to filling floor stock and unit-dose distribution [15].

What Pharmacy Technicians May NOT Do

Tasks that require the professional judgment of a pharmacist must be left to the pharmacist. The Texas Board of Pharmacy recognizes this, and says that pharmacy technicians may NOT [15]:

- Counsel patients
- Interpret prescription drug orders
- Perform a drug regimen review
- Receive oral prescription orders for controlled substances
- Transfer controlled substance prescription orders to and from other pharmacies
- Verify that controlled substances listed on invoices are received

In addition, **only a pharmacist may perform the final check of a completed prescription**.

PHARMACY STANDARDS

There are other rules and regulations that the pharmacy as a whole must follow. Some of these rules will depend on your practice setting.

TECHNICIAN-TO-PHARMACIST RATIO

REFLECTION

If you work in a community pharmacy, what is the pharmacist to pharmacy technician and pharmacy technician trainee ratio? Does a pharmacist-intern count towards this ratio?

Texas limits the number of pharmacy technicians and pharmacy technician trainees that a pharmacist can supervise at one time **in community pharmacies**. This ratio does not apply to institutional pharmacies [15].

A pharmacist is not allowed to supervise more than six pharmacy technicians at any given time. No more than three technicians can be pharmacy technician trainees (in other words, the ratio of pharmacists to pharmacy technician trainees may not exceed 1:3) [15].

As previously mentioned, a **pharmacist may only supervise one pharmacist-intern at any given time**. The pharmacist-intern is not counted as a technician in the ratio of pharmacists to technicians [15].

CASE STUDY: KRISTINE

In her new job, Kristine normally works with one other pharmacist, an intern, and six technicians during the week. On Tuesday, Kristine's partner calls in sick and she's unable to get a covering pharmacist right away.

In this case, as long as the number of pharmacy technician trainees does not exceed three, Kristine would still be operating within the ratios set by the Texas State Board of Pharmacy.

GENERIC SUBSTITUTION

If a prescription is written for a brand-name drug and there is a less expensive generically equivalent or interchangeable biological product available, you may substitute it. This is true unless the patient OR prescriber requests otherwise [29].

For the prescriber to request the brand name to be dispensed, they must write in their own handwriting, "**Brand Medically Necessary**" or "**Brand Necessary**" on the face of written prescriptions. You may get a prescription drug order that has check boxes or other notations that indicate "substitution instructions." This type of method to indicate "no substitution" is not valid in Texas [29].

If the prescription order is called in or electronically transmitted, the prescriber must clearly indicate if the brand is necessary. If a prescription reimbursed by Medicaid is verbally called in to the pharmacy and the prescriber clearly indicates that brand name is necessary, the prescriber must also mail or fax a written prescription to the pharmacy with the appropriate notation within 30 days [29].

Texas recognizes the Food and Drug Administration (FDA)'s Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) and the Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book) to determine which meds can be substituted. This means that if a drug product is therapeutically equivalent and has an "A-rating" in the Orange Book, then a generic can be substituted. And if a biological product is listed as interchangeable, it can be substituted for the reference product. An additional requirement for biological products which have an interchangeable biological product approved by the FDA is that within three business days of dispensing the product, information on the specific product dispensed (including name and manufacturer or NDC number) must be communicated to the prescriber. This communication can be made electronically, or via fax or phone, or via other "prevailing means." It can also be made through documentation into an interoperable electronic medical records system, through electronic prescribing technology, or a pharmacy benefit management system or a pharmacy record that a pharmacist reasonably concludes is electronically accessible by the prescribing practitioner [29].

Keep in mind that in Texas, pharmacists may dispense, without prior approval from the prescribing practitioner, a dosage form of a drug product that's different from that prescribed, such as a tablet instead of a capsule or liquid instead of tablets, provided that the patient consents to the dosage form substitution and that the dosage form dispensed [29]:

- Contains the identical amount of the active ingredients as the dosage form prescribed;
- Is not an enteric-coated or time release product; and
- Does not alter desired clinical outcomes

Patients must be notified when a generic or interchangeable biological product is substituted, and they have the right to request the brand-name drug instead. In addition, if a generically equivalent drug or interchangeable biologic is dispensed, the label must include the statement "Substituted for Brand Prescribed" or "Substituted for [Brand Name]" where [Brand Name] is the actual name of the brand name product prescribed [29].

DISPENSING REQUIREMENTS FOR PRESCRIPTIONS

Earlier in this course, you learned that state law will sometimes be stricter than federal law. This is true in Texas for many of the rules about dispensing prescriptions.

Prescription Expiration Dates/Refills

Texas has limits on how long prescriptions are valid. **Noncontrolled prescriptions cannot be filled or refilled more than one year from the date the original prescription was written**. Keep in mind that this includes prescriptions written by the prescriber, but never filled [15].

If a prescription is written for a smaller quantity of a noncontrolled drug with refills, you may dispense up to a 90-day supply of the prescription. However, you may only do this if the [15]:

- Total amount dispensed does not exceed the total amount prescribed (including refills);
- Patient is at least 18 years old;
- Patient consents and the prescriber is notified electronically or by telephone;

- Prescriber has NOT specified that dispensing the smaller amount with refills is medically necessary; and
- Prescription isn't for a psychotropic drug used to treat mental or psychiatric conditions.

Transferring Prescriptions

Texas requires that the transfer of original prescription information must be completed **within four business hours of the request**.

A patient is allowed to transfer noncontrolled prescriptions that have refills from one pharmacy to another. These can be transferred up to the number of originally authorized refills. Transfers for noncontrolled drugs can be communicated by pharmacists, pharmacist-interns, or pharmacy technicians to another pharmacist, pharmacist-intern, or pharmacy technician [15].

The rules for transferring controlled substances in Schedules III through V are a little stricter. Prescriptions for controlled substances can be transferred between pharmacies, but **only one time, and the remaining refills must be dispensed by the new pharmacy**. Make sure patients who transfer prescriptions for controlled substances realize that they cannot transfer these prescriptions again. The exception is if pharmacies share a real-time, online database. In this case, the prescription can be transferred up to the maximum refills allowed by law and the prescriber's authorization. Also be aware that transfers for controlled substances can be communicated by pharmacists or pharmacy-interns to another pharmacist or pharmacy-intern. Pharmacy technicians cannot transfer controlled substance prescriptions [15].

The person transferring the prescription must [15]:

- Write "void" on the face of the transferred prescription or invalidate it in the electronic record
- Record the following:
  - Name and address of the receiving pharmacy
  - DEA number of the receiving pharmacy for controlled substances
  - Name of the person transferring the information and the name of the person receiving the transfer
  - Date of transfer

The person receiving the transferred prescription must [15]:

- Write "transfer" on the face of the prescription or note this in the electronic record
- Record the following:
  - Original date of issue
  - Date of original dispensing
  - Original Rx number and original number of refills
  - Number of valid refills remaining
  - Dates and locations of previous refills for controlled substances
  - Name and address of transferring pharmacy
    - If transferring pharmacy is different from the pharmacy that originally dispensed the Rx, the name and address of that pharmacy is also needed
  - DEA number of the transferring pharmacy for controlled substances
    - If transferring pharmacy is different from the pharmacy that originally dispensed the controlled substance Rx, the DEA number of that pharmacy is also needed
  - Name of person transferring the Rx

Pharmacies may also perform a one-time transfer of electronically prescribed Schedule II through V controlled substances for initial filling [30; 31]. But this can only be done if both pharmacies are set up to forward and receive electronic controlled substance prescriptions. If this is not the case, the prescriber should be contacted to retract the electronic controlled substance prescription and resend to the pharmacy requested by the patient [15].

Emergency Prescriptions

CASE STUDY: KRISTINE

Kristine is working at the pharmacy on a Saturday when a patient comes in just before closing time. The patient tells Kristine that he is out of refills on his lisinopril and metformin. He thought he had enough pills to get him through the weekend, but he was wrong. What should Kristine do?

There will be times when a patient runs out of refills on a prescription that must be taken with little or no interruption. In most cases, you can dispense a one-time emergency refill when a patient is out of medication AND the prescriber can't be contacted. In these cases, the law says that you can give up to a **72-hour supply of medication**. This includes all medications **except Schedule II controlled substances**. You must notify the patient that prescriber authorization is required and that the emergency refill is being done without prescriber authorization. You must also notify the prescriber of the emergency fill as soon as reasonably possible [15].

If the prescription was originally filled at another pharmacy, you can provide the patient with a 72-hour emergency supply if there are no refills remaining or if the other pharmacy can't be contacted for a transfer. However, the patient must have their prescription bottle (or other documentation that contains enough information to safely fill the prescription).

There's one exception to this 72-hour emergency supply and that is if the prescription requiring an emergency supply is for insulin or insulin-related supplies. In this case, the quantity of the emergency refill may not exceed the lesser of a 30-day supply or the smallest available package [15].

Schedule II controlled substances are not included in this 72-hour rule. However, per federal and state law, emergency prescriptions of Schedule II controlled substances are allowed in certain situations. Prescribers can call in an emergency prescription for a Schedule II controlled substance with a quantity needed to cover the emergency period. "Emergency prescription" in this context means that the immediate administration of a drug is necessary for proper treatment of the patient, that no alternative treatment is available, and it's not possible for the prescriber to provide a written prescription at the time. Prescribers must then, within seven days, send an electronic prescription, or if exempt from the e-prescribing controlled substances mandate (discussed later), deliver a written, signed prescription (either in person or by mail). The written prescription must have written on its face "Authorization for Emergency Dispensing" and the date of the oral order. For electronic prescriptions, the pharmacist must annotate the record with the original authorization and date of the oral order. If a written or electronic prescription isn't received within seven days, the local DEA diversion field office must be notified [32; 33].

In the event of a disaster, a pharmacist may be able to dispense up to a 30-day supply of a medication (other than a Schedule II prescription) without the authorization of a prescriber under specific circumstances, such as the governor has declared a state of emergency and the executive director of the Board of Pharmacy has notified pharmacies that pharmacists may dispense up to a 30-day supply of prescription drugs [15].

CASE STUDY: KRISTINE

Kristine decides that it is appropriate for her to go ahead and dispense a one-time 72-hour supply of lisinopril and metformin for this patient. Kristine knows that these meds are needed, and that interruption of therapy could result in undesirable health consequences.

Kristine writes out a new prescription for the emergency supply and leaves a voicemail for the patient's prescriber to let him know an emergency supply has been dispensed. Kristine informs the patient that she is providing this emergency refill without prescriber authorization, and that any additional refills need to be authorized by his prescriber. She recommends that the patient reach out to his prescriber on Monday to find out if he needs to be seen before the prescriber can authorize additional refills.

Handling Prescriptions from Other States and Countries

CASE STUDY: KRISTINE

Kristine gets a prescription for metoprolol tartrate from a prescriber whose office address is in Mexico. What should she do?

Pharmacists can accept prescriptions issued by prescribers licensed in other states, but there are specific rules for controlled substances. For Schedule III through V prescriptions from out-of-state practitioners, the prescription can be filled if it is issued by a physician, dentist, veterinarian, or podiatrist who is legally authorized to prescribe controlled substances in the state they practice (controlled substance prescriptions from out-of-state nurse practitioners or physician assistants may not be filled). However, in order to fill prescriptions from out-of-state prescribers for Schedule II prescriptions, your pharmacy must have a plan approved by and on file with the Board which allows the activity [15; 34].

Prescriptions from prescribers licensed in Canada or Mexico in a health field that is recognized by the state of Texas as one that is legally authorized to prescribe drugs (e.g., physician, dentist, veterinarian, or podiatrist), may also be filled under certain circumstances. The prescription cannot be for a controlled substance, and it must be an original, written prescription with a manual signature [15].

The Texas State Board of Pharmacy provides a helpful quick reference guide for determining if you could dispense out-of-state prescriptions [35].

LABELING REQUIREMENTS FOR PRESCRIPTIONS

According to federal law, certain information must be included on the labels of dispensed prescriptions. Texas has a few additional requirements for the information that must be on the label of dispensed medications.

Community pharmacy prescription labels must include [15]:

- The name, address, and telephone number of the pharmacy
- The prescription number
- The date the prescription was dispensed
- The dispensing pharmacist's initials (not required to be on the label if the identity of the pharmacist is maintained in the dispensing system)
- The name of the patient (or if it's for an animal, the species of the animal and the name of the owner)
- The name of the prescriber
- The directions for use
- The drug name, amount dispensed, and strength

- The generic and brand name of the medication and a note if generic substitution occurred
- Beyond-use date
- Appropriate ancillary instructions, such as storage instructions or cautionary statements
- Disposal statement (explained below)

The beyond-use date should be the expiration date provided by the manufacturer of the drug if the drug is dispensed in its original packaging. If the drug is repackaged, the beyond-use date should be the expiration date provided by the manufacturer, OR the date that is one year from the date the drug is dispensed, whichever comes first. In addition, compounded medications must include a statement that the drug has been compounded (an auxiliary label can meet this requirement). This statement should also be included in the written drug information that is required to be provided to patients in the outpatient setting [15].

The pharmacy must also provide a disposal statement to the patient, either on the prescription label or on the written information accompanying the prescription. The statement must say: "Do not flush unused medications or pour down a sink or drain." But this statement isn't required for drugs that the FDA recommends flushing for disposal, such as some controlled substances. Examples of meds that FDA recommends flushing include fentanyl (*Duragesic*, etc), morphine (*MS Contin*, etc), oxycodone (*OxyContin*, *Percocet*, etc) and others [36].

In the hospital setting, the label must also include a beyond-use date. But many of the other labeling requirements listed above aren't mandated.

CASE STUDY: GEORGE

George works full-time in a hospital pharmacy and part-time in a community pharmacy. What differences should he expect to see in the labeling of drugs in these two settings?

Recordkeeping

Pharmacies in Texas are required to maintain records of all prescriptions and dispensed medications. For prescriptions, the pharmacy must keep the original prescription or an electronic image of it for at least two years from the date it was last filled. Inventory records should also be kept for two years from the date of the inventory or record.

Additionally, in community pharmacies, a daily hard copy printout of all prescriptions dispensed and refilled should be produced within 72 hours and reviewed within seven days. Each individual pharmacist who dispenses or refills a prescription shall verify that the data indicated on the daily hard copy printout is correct, by dating and signing the document. Alternatively, the pharmacy can keep a logbook with each individual pharmacist signing (or electronically signing) a statement each day attesting that the information entered into the dispensing system has been reviewed and is correct. The hard copy printouts or logbook must be maintained for two years from the date of dispensing.

Patient Privacy

Another example of when Texas law is stricter than federal law can be seen with privacy laws. The federal Health Insurance Portability and Accountability Act (HIPAA) was created to protect a patient's health information. The Texas Medical Records Privacy Act (TMRPA) adds additional safeguards on top of HIPAA for protected health information (PHI). For example, TMRPA requires that covered entities, such as pharmacies, provide employee training on both federal and state laws related to the protection of PHI [37]. This training should be specific to the employee's responsibilities and the pharmacy's course of business. Each new employee must complete this training within 90 days after the hire date [37]. Employees must also be trained anytime there is a change in Texas or federal law that affects their duties by no later than the first anniversary of the date the change in law takes effect [37]. Contact your supervisor for more information on where to get this required state/employer-specific training.

Texas law also expands the definition of "covered entities" beyond the HIPAA definition [37]. In addition to healthcare providers, plans, and medical clearinghouses defined in federal law, Texas law broadened this to include any person, business, or organization that touches PHI in any way. Another more stringent state requirement is that patients must be given their electronic health records within 15 business days of their written request [37]. This is shorter than the 30-day federal requirement. Financial penalties related to inappropriate disclosure of PHI in Texas may also be higher compared to federal penalties. Make sure you are familiar with the Texas-specific laws for maintaining patient privacy. You can find more information about the various health information privacy laws that have been passed in Texas on the Attorney General of Texas' website [38].

CONTROLLED SUBSTANCES

Many Texas controlled substance laws are similar to federal law. For example, the number of refills allowed for controlled substance prescriptions in Schedule III or IV is the same as federal law (max of five refills within six months). However, there are some differences to be aware of. For instance, while federal law specifies that prescriptions for Schedule III or IV meds must not be refilled more than five times or more than six months after the date of issue, it doesn't specify this requirement for Schedule V prescriptions, while Texas law does. In other words, Texas law also requires that prescriptions for Schedule V prescriptions not be refilled more than five times and not be refilled beyond six months past the date of issue.

Classifications of Controlled Substances

Texas classifies controlled substances into **five schedules, just like federal law**. Practically all controlled substances are in the same schedules as federal law. For example, fentanyl is a Schedule II product. Buprenorphine is a Schedule III controlled substance. And diazepam is a Schedule IV controlled substance [39].

One difference is that Texas requires a prescription for codeine-containing Schedule V medications. Federal law allows some of these meds to be sold over the counter as long as they don't exceed certain quantities. In Texas, codeine-containing cough meds or any other products containing codeine or dihydrocodeine must have a prescription to be dispensed. Treat these Schedule V products like pregabalin (*Lyrica*), diphenoxylate/atropine (*Lomotil*), and other Schedule V prescription controlled substances [33].

Electronic Prescribing of Controlled Substances

The Texas Health and Safety Code requires prescriptions for controlled substances to be issued electronically [33; 40]. There are some exceptions to this, such as prescriptions issued by veterinarians, prescriptions ordered in an emergency, or cases where a prescriber has applied for a waiver from the Texas Medical Board due to exceptional circumstances prohibiting e-prescribing implementation [41]. Keep in mind that pharmacists who receive an otherwise valid written, oral, or faxed controlled substance prescription after the implementation date do not have to verify that the prescription is exempt from the requirement of e-prescribing.

Schedule II Prescriptions

CASE STUDY: KRISTINE

Kristine has been working in Texas for about three weeks when she is faced with a partial fill of a Schedule II prescription situation. The patient has requested to fill only a few pills at a time. Is Kristine able to fulfill the patient's request based on Texas state law? Why or why not?

As mentioned above, all controlled substance prescriptions, including Schedule II prescriptions, are required to be sent electronically unless the prescriber is exempted from the requirement. If the prescriber is exempted, the only other acceptable format for a Schedule II prescription outside of an emergency is for it to be written on an "official Texas prescription form" that the prescriber orders from the Texas State Board of Pharmacy [40]. A Schedule II med must be filled within 30 days after the date the prescription was issued [40].

There is generally no days' supply limit set by the Board for a Schedule II prescription. However, for opioids for the treatment of acute pain, a prescriber may not issue a prescription for an opioid in an amount that exceeds a 10-day supply [40]. While pharmacists won't be subject to penalties for dispensing a prescription that exceeds this limit, it's important to remember that pharmacists have a corresponding responsibility to ensure the prescription is for a legitimate medical purpose in the usual course of professional practice [40].

Additionally, there is a days' supply limit when prescribers issue multiple Schedule II prescriptions. Prescribers can issue multiple prescriptions for the same Schedule II drug on the same day, but only up to a 90-day supply (in total for all prescriptions) [40]. The prescriber must include the date each prescription was written AND the earliest date each prescription can be filled. In this case, the prescription must be dispensed within 30 days of the earliest fill date noted on each prescription (not necessarily the date of issue) [40].

Texas allows for partial filling of Schedule II controlled substances in accordance with federal law [33]. According to federal law, partial filling of Schedule II controlled substance prescriptions is allowed at the request of the prescribing practitioner or patient as long as the total quantity dispensed in all partial fillings doesn't exceed the total quantity prescribed. In addition, remaining portions of a partially filled Schedule II prescription cannot be filled beyond 30 days after the date the prescription was written [33; 42]. If a Schedule II prescription is partially filled due to a pharmacy stock issue, DEA regulations specify that the remainder must be dispensed within 72 hours, otherwise the remaining quantity is voided, and the prescriber must be notified [32].

Pharmacists who dispense Schedule II controlled substances must provide patients with a written notice on the safe disposal of controlled substances, unless the pharmacy is able to accept the drugs back for safe disposal (e.g., pharmacies that are authorized collectors or pharmacies that provide at no cost a mail-in pouch for patients to dispose of drugs) [40]. This written notice must include information on locations where Schedule II drugs are accepted for safe disposal or provide a web address of a website specified by the Board, such as the DEA's Drug Disposal information website, that has a searchable database of locations where Schedule II prescriptions can be accepted for safe disposal [40; 43]. The written notice can be provided in an electronic form, but only if the patient or patient's agent requests this and the request is documented [40].

Prescribing Authority

In addition to limits on Schedule II prescriptions, Texas restricts who can write controlled substance prescriptions.

Like most states, Texas allows doctors, dentists, veterinarians, and podiatrists to write controlled substance prescriptions. However, it also allows other prescribers, such as nurse practitioners, optometrists, and physician assistants to order scheduled drugs, but with limits. For example, nurse practitioners and physician assistants can write for Schedule III, IV, and V meds. But the prescription, including refills, cannot exceed a 90-day supply. Nurse practitioners and physician assistants

can only write for Schedule II prescriptions in the hospital setting, including for patients receiving services in the emergency department. They may also write Schedule II prescriptions for patients with a terminal illness receiving hospice care [35; 44].

Controlled Substance Inventory

REFLECTION

How often does your pharmacy perform a full inventory of all the medications on the shelves? How does this frequency differ when comparing controlled substances to noncontrolled substances? How does it differ from federal pharmacy law? When must the inventories occur?

Under federal law, controlled substances must be inventoried every two years. This is another area where Texas law is stricter than federal law regarding scheduled medications. **Pharmacies in Texas must inventory controlled substances every year**. This coincides with the annual inventory requirement for noncontrolled drugs as well. However, inventory records for Schedule II drugs must be maintained separately from other controlled substances, and inventory records for Schedule III, IV, and V drugs must be maintained separately from noncontrolled drugs or be readily retrievable [15].

Inventory must occur on May 1st annually, or on the pharmacy's regular general physical inventory date (determined by the pharmacy). Both the person taking the inventory and the pharmacist-in-charge must sign and date the records and have the document notarized within three days of the inventory being completed. This inventory must be filed separately from all other records and be available at the pharmacy for inspection for **at least two years** [15].

Texas Prescription Monitoring Program

Pharmacies must report all outpatient controlled substance prescriptions to the Texas Prescription Monitoring Program no later than the next business day after filling the prescription [45]. Pharmacists may delegate access to the Texas Prescription Monitoring Program to registered pharmacy technicians, but pharmacy technicians must register as a separate user [46]. Additionally, pharmacists dispensing an outpatient prescription for an opioid, benzodiazepine, barbiturate, or carisoprodol will be required to check the patient's Prescription Monitoring Program history before dispensing [47]. Exceptions to this requirement include prescriptions issued by veterinarians or if it's clearly noted on a prescription that the patient has a diagnosis of cancer or sickle cell disease or that the patient is in hospice care [47].

THE BOTTOM LINE

This course covered a few highlights of the Texas pharmacy laws and rules. It is important to keep current on matters that impact you as a pharmacist, and to meet all requirements of the Texas State Board of Pharmacy. Meeting these requirements will help avoid potential violations from the Texas State Board of Pharmacy, the Texas Department of Public Safety, or other regulatory agencies. Staying current on state laws and rules will not only help you and your pharmacy, but your patients as well.

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COURSE TEST - #81090 REVIEW OF TEXAS PHARMACY LAW FOR PHARMACISTS

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 1 contact hour activity must be completed by December 31, 2025.

1. What would you tell a colleague about the human trafficking education requirement?
- A) *This is a training requirement, not a CE requirement.*
- B) *It's necessary to obtain 1 credit hour on the topic each year.*
- C) *This requirement doesn't apply during the initial license period.*
- D) *It's necessary to obtain 2 credit hours on the topic each license renewal period.*

2. John works at a hospital pharmacy full-time where he participates in low- and medium-risk sterile compounding. He does not participate in high-risk compounding. At least how many CE credit hours must he obtain on the topic of sterile compounding during his license renewal period?
- A) *1*
- B) *2*
- C) *4*
- D) *7*

3. What does the Texas State Board of Pharmacy require to be posted for public viewing in a community pharmacy?
- A) *The pharmacy license*
- B) *The licenses for all staff pharmacists*
- C) *Pharmacist-intern certificates of registration*
- D) *Pharmacy technician certificates of registration*

4. What should you keep in mind about Texas State Board of Pharmacy counseling requirements for community pharmacies?
- A) *Patients may not refuse counseling.*
- B) *Counseling is required for all prescription refills.*
- C) *Written information should also be provided at the time of verbal counseling.*
- D) *Oral counseling is mandated even when the prescription is delivered to the patient's home.*

5. For at least how long do patient medication records need to be maintained after the date of last entry in order to be compliant with the Texas State Board of Pharmacy's rules?
- A) *6 months*
- B) *12 months*
- C) *2 years*
- D) *3 years*

6. Laura is a new pharmacy technician trainee who started working in a hospital pharmacy two weeks ago. As a pharmacy technician trainee, what should Laura keep in mind?
- A) *She needs to get 5 CE credit hours every year.*
- B) *She will have to renew her pharmacy technician trainee registration every 2 years.*
- C) *She cannot begin training on sterile compounding until she becomes registered as a pharmacy technician.*
- D) *She must pass a Board-approved national certification exam before she can be eligible to register as a pharmacy technician.*

7. Which duty may a registered pharmacy technician perform in Texas?
- A) *Complete a drug regimen review on a refilled prescription*
- B) *Process a request from a patient to refill their prescription*
- C) *Transfer a controlled substance prescription to another pharmacy*
- D) *Take an oral prescription order for a controlled substance over the phone*

8. Which prescription issued by a physician in Mexico can you fill in Texas?
- A) *Written and manually signed prescription for lisinopril*
- B) *Written and manually signed prescription for hydrocodone*
- C) *Verbally called-in prescription for lisinopril*
- D) *Verbally called-in prescription for hydrocodone*

Test questions continue on next page ➞

9. According to state or federal law, what is a requirement when providing a partial fill of a Schedule II prescription that is requested by the patient?

A) Texas law does not allow for partial filling of Schedule II prescriptions.

B) Texas law only allows for partial fills of Schedule II prescriptions when requested by the prescriber.

C) Federal law states that remaining portions can continue to be filled for up to 30 days after the date of issue.

D) Federal law requires that partial fill requests from patients always be filled within 72 hours, otherwise the remaining quantity is void.

10. How often must pharmacy inventories be performed in Texas?

A) Annually for both noncontrolled and controlled substances

B) Biennially for both noncontrolled and controlled substances

C) Annually for noncontrolled substances and biennially for controlled substances

D) Biennially for noncontrolled substances and annually for controlled substances

Antidepressant-Associated Sexual Dysfunction

This course meets the Texas requirement for drug therapy management education.

Audience
This course is designed for health and mental health professionals involved in the care of patients who have been prescribed antidepressants.

Course Objective
The purpose of this course is to provide needed information about the relationship between antidepressants and sexual dysfunction and the resultant impact on treatment efficacy and adherence so healthcare professionals may select the best possible treatment plan.

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

1. Outline the demographics and etiology of antidepressant-associated sexual dysfunction.
2. Describe the approach to managing sexual side effects of antidepressant use in men.
3. Discuss potential sexual side effects of antidepressant use in women.
4. Evaluate the impact of post-treatment enduring sexual dysfunction in patients who were prescribed antidepressants.

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

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

Division Planner
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Senior Director of Development and Academic Affairs
Sarah Campbell

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

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Designations of Credit
This activity was planned by and for the healthcare team, and learners will receive 1 Interprofessional Continuing Education (IPCE) credit for learning and change.

NetCE designates this activity for 1 hour ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-22-022-H01-P.

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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

Before the 1980s, reports of antidepressant-associated sexual dysfunction were rare, mainly due to under-reporting, lack of patient assessment and discussion, and the widespread assumption that persons with mental health problems were asexual and/or lacked sexual desire [1; 2]. Since then, research has established that sexual side effects are associated with all commercially available antidepressants, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and dual serotonergic/noradrenergic reuptake inhibitors (SNRIs). Among antidepressants, SSRIs/SNRIs show the highest rates of sexual dysfunction, including impaired sexual motivation, desire, arousal, and orgasm affecting men and women. Prescribers dramatically underestimate the prevalence and patient burden of sexual side effects and other adverse effects from antidepressants and other medications [3]. Comparison of spontaneous patient reporting with systematic inquiry has led to estimated sexual side effect rates that differ by ≥ 60% [1; 2]. SSRIs account for most antidepressant prescriptions, and primary care providers should have a good understanding of the risk and patient impact of sexual side effects and management of this iatrogenic condition.

DEMOGRAPHICS AND ETIOLOGY OF ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

In 2015–2018, 13.2% of adults 18 years of age and older used antidepressant medications in the past 30 days [4]. Antidepressants are among the most widely prescribed drugs in the United States, and SSRIs/SNRIs account for roughly 85% of these prescriptions [5; 6]. An estimated 1 in 6 American women have been prescribed antidepressants, the result of women seeking care for depression at higher rates than men and being twice as likely to be prescribed antidepressants for the same complaint [6; 7]. Side effects largely contribute to the 31% to 60% non-adherence rate with antidepressants. Sexual side effects are the most frequent antidepressant side effect reported by primary care patients [8]. In a study involving 2,163 adults who had undergone at least eight weeks of treatment with antidepressants, 79% showed some degree of sexual dysfunction [51].

In both men and women, antidepressant-induced sexual side effects largely result from increased serotonin (5-HT) neurotransmission via reuptake blockade of serotonin transporters. Antidepressants that primarily increase dopamine and norepinephrine neurotransmission produce markedly fewer sexual side effects. SSRI/SNRI-induced sexual side effects are likely mediated by inhibitory actions on dopamine signaling

LIKELIHOOD OF SEXUAL SIDE EFFECTS WITH SPECIFIC ANTIDEPRESSANTS[a]		
Agent	**Percent of Male Patients Affected**	**Percent of Female Patients Affected**
Desire Dysfunction		
Citalopram	84.11%	70.78%
Fluoxetine	86.18%	74.39%
Paroxetine	73.65%	72.89%
Sertraline	84.15%	71.92%
Venlafaxine	80.62%	72.00%
Arousal Dysfunction		
Paroxetine	64.51%	83.96%
Sertraline	67.05%	82.00%
Venlafaxine	75.00%	77.71%
Orgasm Dysfunction		
Citalopram	74.05%	39.47%
Fluoxetine	77.23%	40.36%
Paroxetine	80.23%	44.84%
Sertraline	71.64%	44.22%
Venlafaxine	82.14%	44.85%
[a]These figures are based on data that did not record the duration of, or distress from, sexual side effects.		
Source: [15]		*Table 1*

in sex brain circuits and can be decreased by simultaneously increasing norepinephrine and dopamine neurotransmission but not by increasing norepinephrine alone. This provides the rationale for treatment using bupropion and other agents that simultaneously increase norepinephrine and dopamine signaling. It also suggests the theoretic basis for developing novel antidepressants that increase 5-HT and dopamine signaling. These findings are clinically relevant for patients who develop sexual side effects but also attain substantial clinical improvement or remission of depression with serotonergic agents. All reasonable options to mitigate the antidepressant-induced sexual side effect should be explored before lowering the dose or switching effective antidepressant therapies [9; 10]. Serotonergic antidepressants produce the highest rates of sexual side effects, but a multifactorial etiology is more likely than a specific monotransmitter action. Other possible mechanisms for SSRI/SNRI-induced sexual side effects include decreased dopaminergic transmission, cholinergic and alpha-adrenergic blockade, inhibition of nitric oxide synthase 1, and prolactin elevation [11; 12].

The association between major depressive disorder and sexual dysfunction is bidirectional. Estimated prevalence rates of antidepressant-induced sexual side effects are very high for several antidepressants, but estimation of true prevalence is complicated by the high prevalence of sexual dysfunction in all patients with mood disorders and by the under-reporting of sexual side effects. Baseline sexual functioning should be assessed with validated rating scales at the same time depression is evaluated [10; 13].

The American Psychiatric Association recommends that men and women who are taking antidepressants be asked whether sexual side effects are occurring with these medications.

(http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed October 27, 2022.)

Strength of Recommendation: I (Recommended with substantial clinical confidence)

As discussed, the prevalence of sexual side effects in antidepressant use is highest for SSRIs and venlafaxine. TCAs and MAOIs have moderate rates of sexual side effects, and low rates are noted with bupropion, trazodone, nefazodone, mirtazapine, agomelatine, and vilazodone. Perhaps the lowest rate is associated with moclobemide, a reversible MAOI [1; 14].

Women often require considerably more time to climax than men, which can make SSRI-induced delayed orgasm unwanted in women but a desired effect in men. A meta-analysis of sexual side effect rates with SSRIs and venlafaxine reported that orgasm and desire dysfunction are more common in men, while arousal dysfunction is more common in women (***Table 1***) [15].

MANAGEMENT

As noted, switching medications to an antidepressant with fewer sexual side effects has been considered highly undesirable and should be avoided, if possible, in patients showing an otherwise positive therapeutic response. However, it may be an option of select patients. A 2019 study analyzed the effects of switching agents on participants with well-treated depressive symptoms but SSRI-associated sexual dysfunction. The patients were directly switched from an SSRI (citalopram, paroxetine, or sertraline) to vortioxetine or escitalopram [50]. Both groups maintained antidepressant efficacy after eight weeks, but patients switched to vortioxetine experienced greater improvements in treatment-emergent sexual dysfunction. The authors concluded that vortioxetine was a safe and effective option for adults with SSRI-induced sexual dysfunction [50].

If low sexual response or libido is a known problem prior to the initiation of antidepressant therapy, selection of an effective agent with the lowest rate of sexual side effects is recommended. Another strategy is antidepressant dose reduction, on the basis of a dose-response relationship in sexual side effects. Although common as a first-line approach and suggested by the American Psychiatric Association, this may precipitate symptomatic relapse and should be avoided in most patients with serious depression [16; 17; 18]. Taking a drug holiday by stopping the antidepressant for a few days has also been suggested [19]. This may be feasible with fluoxetine, owing to its long half-life, but it is not advised with other antidepressants, as patients can experience discontinuation symptoms, disruption of therapeutic effect, and worsening of depression symptoms [18].

Adding medications with mechanisms that offset the SSRI/SNRI side effects is a valid approach. 5-HT receptor antagonists or agonists or dopamine agonists are most commonly used for this purpose. Several trials have found favorable response with the 5-HT2 and 5-HT3 receptor antagonist mirtazapine, which broadly improves sexual side effects but can cause weight gain; the 5-HT2A antagonist cyproheptadine, which alleviates SSRI-induced orgasm disruption but can cause sedation; the 5-HT1A agonist buspirone; and the norepinephrine and dopamine agonist bupropion, which has the greatest evidence support and most extensive use for this indication [20; 21; 22; 23; 24].

MALE SEXUAL DYSFUNCTION

The incidence of male sexual dysfunction is much higher with SSRIs/SNRIs and much lower with antidepressants with primary adrenergic or dopaminergic mechanism. Ejaculatory delay is highly prevalent with serotonergic antidepressants. However, as noted, this can be a desired instead of adverse effect in men with premature ejaculation. In fact, the SSRI dapoxetine has become first-line therapy in the treatment of premature ejaculation [25; 26]. Certain antidepressants, particularly trazodone, may rarely cause priapism (prolonged and painful erection) [46].

Trazodone

The antidepressant trazodone inhibits central nervous system 5-HT uptake and increases central dopamine transmission without peripheral norepinephrine reuptake inhibition. While efficacy in erectile dysfunction has been inconsistent in controlled trials, trazodone may be effective in treating SSRI-induced sexual dysfunction [27; 28].

S-Adenosyl-L-methionine

Men with SSRI/SNRI-induced sexual dysfunction were randomized to daily S-adenosyl-l-methionine (SAMe) or placebo for six weeks, while maintaining their SSRI/SNRI. Controlling for baseline sexual dysfunction severity and depression improvement from baseline, significantly greater reduction in arousal and erectile dysfunction was found with SAMe versus placebo. SAMe is used for mild-to-moderate depression, and the authors state improvements in male sexual dysfunction were likely independent of an antidepressant effect [29].

FEMALE SEXUAL DYSFUNCTION

Up to 96% of women taking antidepressants report at least one sexual side effect, with 20% to 50% qualifying as a distinct clinical problem [30; 31]. Antidepressants can prominently affect female sexual functioning and cause decreased libido, problems with arousal, and anorgasmia at prevalence rates as high as 80% [32].

Drugs that increase 5-HT negatively impact female sexual behavior, while decreases in 5-HT apparently facilitate sexual behavior facilitation. In particular, 5-HT1A receptor agonists inhibit sexual behavior, while 5-HT2 or 5-HT3 receptors may exert a positive influence. There is substantial evidence to support a role for 5-HT in the modulation of female consummatory sexual experience, but studies on the role of 5-HT in other elements of female sexuality, such as desire, motivation, and sexual appetite, are much fewer [33].

Exercise

Exercise may improve antidepressant-related genital arousal problems. Because exercise increases genital arousal in healthy women most likely by increasing sympathetic nervous system (SNS) activity, a clinical trial measured the impact of exercise on genital arousal in 47 women taking antidepressants (68% SSRIs) and reporting antidepressant-related sexual arousal problems. Measures of genital and SNS arousal while watching an erotic film were compared when preceded by no exercise or 20 minutes of exercise 5 or 15 minutes before the film. Exercise prior to sexual stimuli was associated with increased genital arousal in both groups. Women reporting more severe sexual dysfunction had greater increases in genital arousal post-exercise. For women taking SSRIs, genital arousal was linked to SNS activity [34].

Bupropion

Adding bupropion 300 mg/day to a current SSRI regimen seems to improve sexual function in women experiencing sexual side effects [35]. Treatment of SSRI-induced female sexual dysfunction with adjunctive bupropion 300 mg/day for 12 weeks was studied in 218 women (25 to 45 years of age). Compared to placebo, the bupropion group showed greater improvement in mean total Female Sexual Function Index (FSFI) score (17.2 vs. 25.9) and in all FSFI domain scales. The bupropion group showed greatest increase from baseline in FSFI scores for desire (86.4%) and lubrication (69.2%) domains [36].

Testosterone

A randomized controlled trial evaluated transdermal testosterone therapy 300 mcg/day in 44 women (35 to 55 years of age) with SSRI/SNRI-emergent libido loss [37]. After 12 weeks, the increase in frequency of satisfactory sexual events and reduction in sexual distress were significantly greater with transdermal testosterone than placebo. No women withdrew because of androgenic adverse events. No improvement was found on the primary measure of sexual function, possibly from poor sensitivity in the study's measuring instrument. The researchers concluded that transdermal testosterone therapy benefits some women with SSRI/SNRI-associated libido loss [37].

Interesting results were found in a comparison of premenopausal women with major depressive disorder and a premenopausal, non-depressed control group. Before successful antidepressant treatment, mean total testosterone and bioavailable testosterone were significantly lower in the treatment group relative to controls. Following antidepressant treatment, these parameters significantly increased from baseline levels and were comparable to controls. The authors state the significant increase in testosterone to normal levels following antidepressant therapy suggests that testosterone may be involved in the etiology of depression for some women [38].

Sublingual Testosterone Plus Buspirone or Sildenafil

Androgen receptor gene polymorphism, encoded by the nucleotides cysteine, adenine, and guanine, may influence the effect of testosterone on female sexual functioning and treatment. In one study, 21 pre- and postmenopausal women with SSRI-induced sexual dysfunction received daily sublingual testosterone 0.5 mg, plus buspirone 10 mg or sildenafil 50 mg. Women using low-dose SSRIs showed marked improvement in sexual function from both treatments relative to placebo. Sublingual testosterone combined with sildenafil or buspirone may be beneficial in subgroups of women with SSRI-induced sexual dysfunction [39].

Bremelanotide and Flibanserin

Beginning in 2015, two medications have been approved for the treatment of hypoactive sexual desire disorder in premenopausal women—bremelanotide and flibanserin. Flibanserin is a mixed 5-HT1A agonist/5-HT2A antagonist, while bremelanotide is a synthetic heptapeptide with strong binding affinity and agonist action with melanocortin receptor 4. There is some evidence that flibanserin may be safely added to a stable SSRI or SNRI treatment regimen in premenopausal women with remitted or mild depression [49]. However, the efficacy of addressing SSRI/SNRI-associated sexual dysfunction was not analyzed. It is important to note that these medications are specifically approved to treat low female sexual desire not the result of the effects of a medication, so their use in the management of antidepressant-associated sexual dysfunction is off-label.

Saffron

Saffron (*Crocus sativus* L.) has shown beneficial aphrodisiac effects, but little is known of its efficacy in the management of medication-induced sexual dysfunction. A random controlled trial evaluated saffron 30 mg/day in 38 women with SSRI-induced sexual dysfunction, stabilized on fluoxetine for major depression. After four weeks of treatment, the saffron group had significantly greater improvement in total FSFI score and arousal, lubrication, and pain domains, but not desire, satisfaction, or orgasm domains. Side effects were similar between the two groups. Saffron may safely and effectively improve some fluoxetine-induced sexual problems, including arousal, lubrication, and pain [40].

Maca Root

Maca root (*Lepidium meyenii*) has been suggested as an option for the management of antidepressant-related sexual side effects in postmenopausal women. In one small study, women given maca root were approximately twice as likely as the placebo group to experience remission of sexual side effects [52].

POST-TREATMENT ENDURING SEXUAL DYSFUNCTION

Post-SSRI sexual dysfunction is little known in the broader medical community and, when reported, has been partially attributed to psychologic factors [12]. However, the adverse impact from antidepressant-induced sexual side effects and post-SSRI sexual dysfunction may be worse than the condition for which treatment has been sought [41].

In the first review of post-SSRI sexual dysfunction in 2008, Bahrick and Harris challenged conventional wisdom that sexual side effects resolve with SSRI cessation, stating that research literature had failed to include systematic follow-up to support this assumption [42]. This emerging problem is supported by a convergence of case reports, consumer reports, and robust evidence from efficacy studies of healthy men documenting SSRI-induced delayed ejaculation persisting long after SSRI cessation. Internet drug consumer sites may provide a database of this qualitative information not captured within research paradigms or existing post-market pharmacovigilance mechanisms [42].

In 2014, the broader category of post-treatment enduring sexual dysfunction (PTESD) was investigated and 120 cases (mean age: 30.9 years) were identified. Highest rates occurred with SSRI agents (11.2% to 15.5%), venlafaxine (7.8%), isotretinoin (6.0%), and finasteride (5.2%). Women comprised 20% of SSRI cases, and all of the isotretinoin and finasteride cases occurred in men. PTESD occurred following medication exposure of 3 to 5,840 days, and a common feature was sexual side effect onset after medication was discontinued. The consequences of PTESD were severe, including several well-documented cases of suicide. The longest case was 18 years, from a brief exposure to fluoxetine at 18 years of age [43].

In a data report from 2017 including 300 cases of enduring sexual dysfunction, the highest rates of PTESD occurred with isotretinoin (18%), escitalopram (14%), citalopram (13.7%), and paroxetine (13.3%) [48]. The duration of the treatment ranged from a single dose to more than 16 years. The report also found that many cases of sexual dysfunction appeared or became worse when treatment came to an end. Subjects consistently reported difficulty maintaining romantic relationships and 30% reported that their work had been affected [48].

PTESD symptoms can include the entire spectrum of male and female sexual dysfunction, but the triad of penile or clitoral anesthesia, loss of libido, and loss of function is the core characteristic of PTESD, across all identified drug classes and agents [43; 44; 48]. Pleasureless orgasm has also been reported [45; 48].

Efforts to manage PTESD have involved serotonin and dopamine system modulation with the 5HT-1 agonist buspirone, the 5HT-2 and 5HT-3 antagonists trazodone and mirtazapine, and dopamine agonists (e.g., pramipexole, cabergoline, bupropion, dexamphetamine). Phosphodiesterase type 5 inhibitors, testosterone, ketamine, donepezil, and metformin have all been tried for PTESD. However, none of these have helped. This treatment-refractory characteristic may reflect epigenetic changes in PTESD [43]. Additional research into the underlying etiology of persistent sexual dysfunction following antidepressant cessation will hopefully give insight into an effective treatment.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Discussions of depression and sexuality can be sensitive, and removing possible language barriers using professional interpreters is recommended for patients for whom English is not their first language. 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

Identifying and adhering to an effective antidepressant regimen can be challenging, and the presence of sexual side effects makes the task even more difficult. These side effects are relatively common, particularly with SSRIs/SNRIs, but they may be under-reported and undertreated as a result of the stigma surrounding mental health care and patients' and healthcare providers' reluctance to discuss sexual topics. This course has briefly outlined the demographics of antidepressant-associated sexual dysfunction and gender-specific manifestations. Enriching one's knowledge of sexual side effects and approaches to management will improve patients' adherence to antidepressant therapy and overall quality of life.

COURSE TEST - #95082 ANTIDEPRESSANT-ASSOCIATED SEXUAL DYSFUNCTION

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 1 Hour activity must be completed by October 31, 2025.

1. What is the most commonly prescribed class of antidepressants?
- A) *Atypical agents*
- B) *Tricyclic antidepressants (TCAs)*
- C) *Monoamine oxidase inhibitors (MAOIs)*
- D) *Selective serotonin reuptake inhibitors (SSRIs) and noradrenergic/serotonergic reuptake inhibitors (SNRIs)*

2. What is the most frequent antidepressant side effect reported by primary care patients?
- A) *Insomnia*
- B) *Weight gain*
- C) *Sexual dysfunction*
- D) *Fatigue and drowsiness*

3. In both men and women, antidepressant-induced sexual side effects largely result from
- A) *blocked oxytocin production.*
- B) *inhibition of the activity of the enzyme monoamine oxidase.*
- C) *increased serotonin (5-HT) neurotransmission via reuptake blockade of serotonin transporters.*
- D) *blocked serotonin and norepinephrine transporters, which results in an elevation of the extracellular concentrations of these neurotransmitters.*

4. Which of the following medications has perhaps the lowest rate of sexual side effects of all antidepressants?
- A) *Citalopram*
- B) *Venlafaxine*
- C) *Agomelatine*
- D) *Moclobemide*

5. Which of the following side effects is more common in women prescribed paroxetine than men?
- A) *Desire dysfunction*
- B) *Arousal dysfunction*
- C) *Orgasm dysfunction*
- D) *All of the above*

6. All of the following are preferred approaches to the management of antidepressant-induced sexual dysfunction, EXCEPT:
- A) *Antidepressant dose reduction*
- B) *Adding medications with mechanisms that offset the side effect*
- C) *Taking a drug holiday, particularly if the agents has a long half-life*
- D) *Switching medications to an antidepressant with fewer sexual side effects in patients showing an otherwise positive therapeutic response*

7. The incidence of male sexual dysfunction is higher with
- A) *SSRIs/SNRIs.*
- B) *monoamine oxidase inhibitors (MAOIs).*
- C) *antidepressants with primary adrenergic mechanism.*
- D) *antidepressants with primary dopaminergic mechanism.*

8. What percentage of women taking an antidepressant report at least one sexual side effect?
- A) *2%*
- B) *31%*
- C) *67%*
- D) *96%*

9. Adding which of the following medications to a current SSRI regimen appears to improve sexual function in women experiencing sexual side effects?
- A) *Sertraline*
- B) *Sildenafil*
- C) *Buspirone*
- D) *Bupropion*

10. All of the following are core characteristics of post-treatment enduring sexual dysfunction, EXCEPT:
- A) *Loss of libido*
- B) *Delayed orgasm*
- C) *Loss of sexual function*
- D) *Penile or clitoral anesthesia*

Responsible and Effective Opioid Prescribing

This course meets the Texas requirement for 2 hours of controlled substance education.
This course meets the Louisiana requirement for 3 hours of controlled substance education.

Audience
This course is designed for pharmacy and other healthcare professionals who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Course Objective
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.

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

1. Apply epidemiologic trends in opioid use and misuse to current practice so at-risk patient populations can be more easily identified, assessed, and treated.
2. Create comprehensive treatment plans for patients with pain that address patient needs as well as drug diversion prevention.
3. Evaluate behaviors that may indicate drug seeking or diverting as well as approaches for patients suspected of misusing opioids.
4. Identify state and federal laws governing the proper prescription and monitoring of controlled substances.
5. Describe the available treatment modalities for opioid use disorder.

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

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

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

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INTRODUCTION

Pain is the leading reason for seeking medical care, and pain management is a large part of many healthcare professionals' practice. Opioid analgesics are approved by the U.S. Food and Drug Administration (FDA) for moderate and severe pain and are broadly accepted in acute pain, cancer pain, and end-of-life care, but are controversial in chronic noncancer pain. In response to the long-standing neglect of severe pain, indications for opioid analgesic prescribing were expanded in the 1990s, followed by inappropriate prescribing and increasing abuse, addiction, diversion, and overdose through the 2000s. In tandem with the continued under-treatment of pain, these practice patterns led to needless suffering from uncontrolled pain, opioid analgesic addiction, and overdose. Opioid analgesic prescribing and associated overdose peaked in 2011 with both now in multi-year decline.

Patients show substantial opioid response variations in analgesia and tolerability and may exhibit a range of psychologic, emotional, and behavioral responses that reflect inadequate pain control, an emerging opioid use problem, or both. Clinician delivery of best possible care to patients with pain requires appreciation of the complexities of opioid prescribing and the dual risks of inadequate pain control and inappropriate use, drug diversion, or overdose. A foundation for appropriate opioid prescribing is the understanding of factual data that clarify the prevalence, causality, and prevention of serious safety concerns with opioid prescribing.

SCOPE OF THE PROBLEM

Inappropriate opioid analgesic prescribing for pain is defined as the non-prescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness of opioids [1]. Appropriate opioid prescribing is essential to achieve pain control; to minimize patient risk of abuse, addiction, and fatal toxicity; and to minimize societal harms from diversion. The foundation of appropriate opioid prescribing is thorough patient assessment, treatment planning, and follow-up and monitoring. Essential for proper patient assessment and treatment planning is comprehension of the clinical concepts of opioid abuse and addiction, their behavioral manifestations in patients with pain, and how these potentially problematic behavioral responses to opioids both resemble and differ from physical dependence and pseudodependence. Prescriber knowledge deficit has been identified as a key obstacle to appropriate opioid prescribing and, along with gaps in policy, treatment, attitudes, and research, contributes to widespread inadequate treatment of pain [2].

The extent of opioid analgesic use in the United States in the 2000s was unprecedented in the country's history and unparalleled anywhere in the world. Before 1990, physicians in the United States were skeptical of prescribing opioids for chronic noncancer pain. In 2019, 22.1% of adults used a prescription opioid such as oxycodone and hydrocodone for chronic pain, and sales of opioid analgesics totaled approximately $7 billion in 2016 [3; 4].

Worldwide consumption of opioid analgesics has increased dramatically in the past few decades, with the United States driving a substantial proportion of this increase. For example, the 1990 global consumption of hydrocodone was 4 tons (3,628 kg), compared with the 2009 consumption of 39 tons (35,380 kg); 99% of this was consumed in the United States. Similarly, 3 tons (2,722 kg) of oxycodone were consumed globally in 1990, versus 77 tons (69,853 kg) in 2009, of which 62 tons (56,245 kg or 81%) were consumed in the United States [5]. With only 4.23% of the world's population, the United States annually consumes more than 80% of all opioid supplies, including [6; 7]:

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

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

Between 1992 and 2003, the U.S. population increased 14%, while persons abusing opioid analgesics increased 94% and first-time non-medical opioid analgesic users 12 to 17 years of age increased 542% [8]. It is interesting to note that while opioid prescribing has increased precipitously among adults in the United States, the rate remained low and steady for children between 1996 and 2012 [9]. A study using data from 2005 to 2015 showed opioid prescribing in 57 million visits from adolescents and young adults, representing a prescribing rate of nearly 15% in emergency departments and nearly 3% in outpatient clinical settings [10]. During the course of the study, emergency department prescribing decreased slightly while outpatient clinical setting prescribing remained the same [10]. To assist in monitoring the public health problem associated with prescribed opioids, numerous governmental, non-profit, and private sector agencies and organizations are involved in collecting, reporting, and analyzing data on the abuse, addiction, fatal overdose, and treatment admissions related to opioid analgesics.

Before it was halted in 2011, the Drug Abuse Warning Network (DAWN) provided estimates of the health consequences of nonmedical use of individual drugs, including opioid medications [11]. DAWN indicates that opioid abuse is a growing problem in the United States. In 2005 and 2011, hydrocodone and its combinations accounted for 51,225 and 97,183 emergency department visits, respectively. Oxycodone and its combinations resulted in 42,810 visits to the emergency department in 2005; this number increased to 175,229 visits in 2011 [12; 13]. Visits for nonmedical use of all opioids increased from 217,594 to 420,040 during the six-year period. In 2016–2017, there were 127,101 nonmedical opioid emergency department visits [14]. While this number is an improvement from previous years, nonmedical use accounts for 47.6% of all emergency department visits related to opioids [14].

PAIN MANAGEMENT APPROACHES

Healthcare professionals should know the best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with non-opioid therapy or nonpharmacologic pain therapy without adequate pain relief, are considered to be candidates for a trial of opioid therapy [3; 15]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [16].

In 2016, the CDC issued updated guidance on the prescription of opioids for chronic pain [3]. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. In addition, the CDC further updated guidance against the misapplication of this guideline in 2019, noting that some policies and practices attributed to the guideline were inconsistent with the recommendations [17].

While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published an updated guideline in 2022 [18]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [18]. It is important to remember that inappropriately limiting necessary opioid medications to address patients' pain can be damaging and should be avoided. A central tenet of the updated 2022 guideline is that acute, subacute, and chronic pain needs to be appropriately and effectively treated regardless of whether opioids are part of a treatment regimen [18].

ACUTE PAIN

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 in a quantity no greater than that needed for the expected duration of severe pain. In most cases, three days or less will be sufficient; more than seven days will rarely be needed [3]. Payers and health systems should not use the 2022 guideline to set rigid standards related to dosage or duration of opioid therapy. The guideline is not a replacement for clinical judgment or individualized, patient-centered care [19].

With postoperative, acute, or intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with short-acting hydrocodone, morphine, and oxycodone is more effective than extended-release formulations. Short-acting opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [20; 21; 22].

CHRONIC PAIN

Nonpharmacologic therapy and non-opioid pharmacologic therapy are the preferred first-line therapies for chronic pain [18]. Several nonpharmacologic approaches are therapeutic complements to pain-relieving medication, lessening the need for higher doses and perhaps minimizing side effects. These interventions can help decrease pain or distress that may be contributing to the pain sensation. Approaches include palliative radiotherapy, complementary/alternative methods, manipulative and body-based methods, and cognitive/behavioral techniques. The choice of a specific nonpharmacologic intervention is based on the patient's preference, which, in turn, is usually based on a successful experience in the past.

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [23]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient [18].

Opioid therapy for chronic pain should be presented as a trial for a pre-defined period (e.g., ≤30 days). The goals of treatment should be established with all patients prior to the initiation of opioid therapy, including reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [1; 18]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies. Opioid therapy should not be initiated without consideration by the clinician and patient of an exit strategy to be used if opioid therapy is unsuccessful [18].

In patients who are opioid-naïve, start at the lowest possible dose and titrate to effect. Dosages for patients who are opioid-tolerant should always be individualized and titrated by efficacy and tolerability [1; 18]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting opioid formulations [18].

The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression. Prescribers should carefully reassess evidence of benefits and risks when increasing the dosage to ≥50 mg morphine equivalent dose (MED) per day. Decisions to titrate dose to ≥90 mg MED/day should be avoided or carefully justified [17; 18].

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioids and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [18; 24].

PALLIATIVE CARE AND PAIN AT THE END OF LIFE

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [25]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [25; 26; 27; 28].

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [29]. This reluctance is related to a variety of attitudes and beliefs [25; 29]:

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

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [30]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction [26]. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [25]. It is also helpful to note the difference between addiction and physical dependence.

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

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

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

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [25; 27; 29; 31]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [29; 31]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [29; 31].

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

Strong opioids are used for severe pain at the end of life [26; 27]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [32]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. For patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [27]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [27].

CREATING A TREATMENT PLAN AND ASSESSMENT OF ADDICTION RISK

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring program (PDMP), and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses (***Table 1***) [33; 34]. Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations [18; 35].

Before deciding to prescribe an opioid analgesic, clinicians should perform and document a detailed patient assessment that includes [1]:

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

If substance abuse is active, in remission, or in the patient's history, consult an addiction specialist before starting opioids [1]. In active substance abuse, do not prescribe opioids until the patient is engaged in treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly those that are extended-release or long-acting), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental exposure by children [18; 24].

Screening and assessment tools can help guide patient stratification according to risk level and inform the appropriate degree of structure and monitoring in the treatment plan. It should be noted that despite widespread endorsement of screening tools used to help determine patient risk level, most tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [33; 34].

RISK ASSESSMENT TOOLS

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a five-item, patient-administered assessment to help predict aberrant drug-related behavior. The ORT is also used to establish patient risk level through categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychologic disorders, and other risk factors [36].

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) is a patient-administered, 24-item screen with questions addressing history of alcohol/substance use, psychologic status, mood, cravings, and stress. Like the ORT, the SOAPP-R helps assess risk level of aberrant drug-related behaviors and the appropriate extent of monitoring [36; 37].

Screening Instrument or Substance Abuse Potential (SISAP)

The Screening Instrument or Substance Abuse Potential (SISAP) tool is a self-administered, five-item questionnaire addressing history developed used to predict the risk of opioid misuse. The SISAP is used to identify patients with a history of alcohol/substance abuse and improve pain management by facilitating focus on the appropriate use of opioid analgesics and therapeutic outcomes in the majority of patients who are

RISK STRATIFICATION FOR PATIENTS PRESCRIBED OPIOIDS
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing, including MRI, physical examination, and interventional diagnostic techniques
With or without mild psychologic comorbidity
With or without minor medical comorbidity
No or well-defined and controlled personal or family history of alcoholism or substance abuse
Age 45 years or older
High levels of pain acceptance and active coping strategies
High motivation and willingness to participate in multimodal therapy and attempting to function at normal levels
Medium Risk
Significant pain problems with objective signs and symptoms confirmed by radiologic evaluation, physical examination, or diagnostic interventions
Moderate psychologic problems, well controlled by therapy
Moderate coexisting medical disorders that are well controlled by medical therapy and are not affected by chronic opioid therapy (e.g., central sleep apnea)
Develops mild tolerance but not hyperalgesia without physical dependence or addiction
History of personal or family history of alcoholism or substance abuse
Pain involving more than three regions of the body
Defined pathology with moderate levels of pain acceptance and coping strategies
Willing to participate in multimodal therapy, attempting to function in normal daily life
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of alcoholism or drug misuse, abuse, addiction, diversion, dependency, tolerance, or hyperalgesia
Major psychologic disorders
Age younger than 45 years
HIV-related pain
High levels of pain exacerbation and low levels of coping strategies
Unwilling to participate in multimodal therapy, not functioning close to a near normal lifestyle
HIV = human immunodeficiency syndrome, MRI = magnetic resonance imaging.
Source: [33; 34] *Table 1*

not at risk of opioid abuse, while carefully monitoring those who may be at greater risk [36].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consisted of four questions designed to help clinicians determine the likelihood that a patient was misusing or abusing alcohol. These same four questions were modified to create the CAGE-AID (adapted to include drugs), revised to assess the likelihood of current substance abuse [38].

Diagnosis, Intractability, Risk, and Efficacy (DIRE) Score

The Diagnosis, Intractability, Risk, and Efficacy (DIRE) risk assessment score is a clinician-rated questionnaire that is used to predict patient compliance with long-term opioid therapy [36; 39]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [1]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications.

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

PERIODIC REVIEW AND MONITORING

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [1].

This can include input from family members and/or the state PDMP. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the "5 A's" [1; 40]:

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

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [41; 42]:

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

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [1]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

Involvement of Family

Family members of the patient can provide the clinician with valuable information that better informs decision making regarding continuing opioid therapy. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [41; 42]:

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

Assessment Tools

VIGIL

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

- Verification: Is this a responsible opioid user?
- Identification: Is the identity of this patient verifiable?
- Generalization: Do we agree on mutual responsibilities and expectations?
- Interpretation: Do I feel comfortable allowing this person to have controlled substances?
- Legalization: Am I acting legally and responsibly?
- The foundation of VIGIL is a collaborative physician/pharmacist relationship [43].

Current Opioid Misuse Measure (COMM)

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients being treated for chronic pain. Unlike the ORT and the SOAPP-R, the COMM identifies aberrant behaviors associated with opioid misuse in patients already receiving long-term opioid therapy [35]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

Pain Assessment and Documentation Tool (PADT)

Guidelines by the CDC, the Federation of State Medical Boards (FSMB), and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation with patients with chronic pain receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [44]. The PADT is a clinician-

PATIENT RISK LEVEL AND FREQUENCY OF MONITORING			
Monitoring Tool	**Patient Risk Level**		
	Low	**Medium**	**High**
Urine drug test	Every 1 to 2 years	Every 6 to 12 months	Every 3 to 6 months
State prescription drug monitoring program	Twice per year	Three times per year	Four times per year

Source: [46] *Table 2*

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

The Brief Intervention Tool

The Brief Intervention Tool is a 26-item, "yes-no," patient-administered questionnaire used to identify early signs of opioid abuse or addiction. The items assess the extent of problems related to drug use in several areas, including drug use-related functional impairment [45].

Urine Drug Tests

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 2***) [46]. The CDC 2016 guideline recommends clinicians should use UDT before starting opioid therapy and consider UDT at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs [3]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate, and it is not included in the 2022 updated guideline [18].

Initially, testing involves the use of class-specific immunoassay drug panels [1]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions except with liquid chromatography coupled to tandem mass spectrometry confirmation.

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

CONCURRENT USE OF BENZODIAZEPINES

In 2021, nearly 14% of persons who died of an opioid overdose also tested positive for benzodiazepines, a class of sedative medication commonly prescribed for anxiety, insomnia, panic attack, and muscle spasm [47]. Benzodiazepines work by raising the level of the neurotransmitter gamma-aminobutyric acid (GABA) in the brain. Common formulations include diazepam, alprazolam, and clonazepam. Combining benzodiazepines with opioids is unsafe because both classes of drug cause central nervous system depression and sedation and can decrease respiratory drive—the usual cause of overdose fatality. Both classes have the potential for drug dependence and addiction.

The CDC recommends that healthcare providers use caution when prescribing benzodiazepines concurrently with opioids whenever possible [18]. If a benzodiazepine is to be discontinued, the clinician should taper the medication gradually, because abrupt withdrawal can lead to rebound anxiety and complications such as hallucinations, seizures, delirium tremens, and, in rare instances, death. The rate of tapering should be individualized [18].

CONSULTATION AND REFERRAL

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [1].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [1]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [48].

MEDICAL RECORDS

As noted, documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [1]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

PATIENT EDUCATION ON THE USE AND DISPOSAL OF OPIOIDS

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the U.S. Food and Drug Administration (FDA) has developed a patient counseling guide with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unprescribed [49; 50].

When prescribing opioids, clinicians should provide patients with the following information [49]:

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

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [51]. According to the FDA, 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 [52]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [52; 53]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [53]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so. In April 2023, the FDA issued a letter requiring all manufacturers of opioid analgesics dispensed in outpatient settings to submit a proposed modification to the Opioid Analgesic REMS. The modification requires manufacturers to make available prepaid mail-back envelopes to outpatient pharmacies and other opioid dispensers as an opioid analgesic disposal option for patients. The FDA expects to take action on this modification in 2024 [50].

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [51]:

- Consider writing prescriptions in smaller amounts.
- Educate patients about safe storing and disposal practices.
- Give drug-specific information to patients about the temperature at which they should store their medications. Generally, the bathroom is not the best storage place. It is damp and moist, potentially resulting in potency decrements, and accessible to many people, including children and teens, resulting in potential theft or safety issues.
- Ask patients not to advertise that they are taking these types of medications and to keep their medications secure.
- Refer patients to community "take back" services overseen by law enforcement that collect controlled substances, seal them in plastic bags, and store them in a secure location until they can be incinerated. Contact your state law enforcement agency or visit https://www.dea.gov to determine if a program is available in your area.

DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a physician-patient discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [1; 18].

Clinicians should provide patients physically dependent on opioids with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

As a side note, cannabis use by patients with chronic pain receiving opioid therapy has traditionally been viewed as a treatment agreement violation that is grounds for termination of opioid therapy. However, some now argue against cannabis use as a rationale for termination or substantial treatment and monitoring changes, especially considering the increasing legalization of medical use at the state level [48].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

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

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Research has more closely defined the location of prescribed opioid diversion into illicit use in the supply chain from the manufacturer to the distributor, retailer, and the end user (the pain patient). This information carries with it substantial public policy and regulatory implications. The 2021 National Survey on Drug Use and Health asked non-medical users of prescription opioids how they obtained their most recently used drugs [54]. Among persons 12 years of age or older, 33.9% obtained their prescription opioids from a friend or relative for free, 39.3% got them through a prescription from one doctor (vs. 34.7% in 2019), 7.3% bought them from a friend or relative, and 3.7% took them from a friend or relative without asking [54]. Other sources included a drug dealer or other stranger (7.9%); multiple doctors (3.2%); and theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.9% in 2019) [54].

As discussed, UDTs can give insight into patients who are misusing opioids. A random sample of UDT results from 800 patients treated for pain at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid while 19.5% were positive for an illicit drug/unreported opioid [55]. Negative UDT results for the prescribed opioid do not necessarily indicate diversion but may indicate the patient halted his/her use due to side effects, lack of efficacy, or pain remission. The concern arises over the increasingly stringent climate surrounding clinical decision-making regarding aberrant UDT results and that a negative result for the prescribed opioid or a positive UDT may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [56].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [48; 57; 58]:

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

Behaviors with a lower level of evidence for their association with opioid misuse include [48; 57; 58]:

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

INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

There are a number of actions that prescribers and dispensers can take to prevent or intervene in cases of drug diversion. These actions can be generally categorized based on the various mechanisms of drug diversion.

Prevention is the best approach to addressing drug diversion. As noted, a common source of nonmedical use of prescribed opioids is from a family member or friend, through sharing, buying, or stealing. To avoid drug sharing among patients, healthcare professionals should educate patients on the dangers of sharing opioids and stress that "doing prescription drugs" is the same as "using street drugs" [51]. In addition, patients should be aware of the many options available to treat chronic pain aside from opioids. To prevent theft, patients should be advised to keep medications in a private place and to refrain from telling others about the medications being used.

Communication among providers and pharmacies can help to avoid inappropriate attainment of prescription drugs through "doctor shopping." Prescribers should keep complete and up-to-date records for all controlled substance prescribing. When possible, electronic medical records should be integrated between pharmacies, hospitals, and managed care organizations [51]. If available, it is also best practice to periodically request a report from the state's prescription reporting program to evaluate the prescribing of opioids to your patients by other providers [51].

When dealing with patients suspected of drug seeking/diversion, first inquire about prescription, over-the-counter, and illicit drug use and perform a thorough examination [51]. Pill counting and/or UDT may be necessary to investigate possible drug misuse. Photo identification or other form of identification and social security number may be required prior to dispensing the drug, with proof of identity documented fully. If a patient is displaying suspicious behaviors, consider prescribing for limited quantities [59].

If a patient is found to be abusing prescribed opioids, this is considered a violation of the treatment agreement and the clinician must make the decision whether or not to continue the therapeutic relationship. If the relationship is terminated, it must be done ethically and legally. The most significant issue is the risk of patient abandonment, which is defined as ending a relationship with a patient without consideration of continuity of care and without providing notice to the patient. The American Medical Association Code of Ethics states that physicians have an obligation to support continuity of care for their patients. While physicians have the option of withdrawing from a case, they should notify the patient (or authorized decision maker) long enough in advance to permit the patient to secure another physician and facilitate transfer of care when appropriate [60]. Patients may also be given resources and/or recommendations to help them locate a new clinician.

Patients with chronic pain found to have an ongoing substance abuse problem or addiction should be referred to a pain specialist for continued treatment. Theft or loss of controlled substances is reported to the DEA. If drug diversion has occurred, the activity should be documented and a report to law enforcement should be made [59].

COMPLIANCE WITH STATE AND FEDERAL LAWS

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids [50]. Other elements of opioid risk mitigation include FDA partnering with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [41].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [61]:

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

CONTROLLED SUBSTANCES LAWS/RULES

The U.S. Drug Enforcement Administration (DEA) is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [62].

According to the DEA, drugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [63]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

STATE-SPECIFIC LAWS AND RULES

Most states have established laws and rules governing the prescribing and dispensing of opioid analgesics. It is each prescriber's responsibility to have knowledge of and adhere to the laws and rules of the state in which he or she prescribes.

MANAGEMENT OF OPIOID USE DISORDER

Management of opioid dependence entails different methods to achieve different goals, depending on the health situation and treatment history of the patient. These treatment approaches include [64]:

- Crisis intervention: Directed at immediate survival by reversing the potentially lethal effects of overdose with an opioid antagonist.
- Harm reduction: Intended to reduce morbidity and mortality associated with use of dirty needles and overdose.
- Detoxification/withdrawal: Aims to remove the opioid of abuse from the patient's body, either through gradual taper and substitution of a long-acting opioid or through ultra-rapid opioid detoxification.
- Maintenance treatment or opioid (agonist) replacement therapy: Aimed at reduction/elimination of illicit opioid use and lifestyle stabilization. Maintenance follows detoxification/withdrawal, whereby the patient is tapered from short-acting opioids and introduced to a long-acting opioid agonist, such as methadone or buprenorphine. Patients remain on agonist therapy short-term, long-term, or indefinitely depending on individual needs.
- Abstinence-oriented therapy: Treatment directed at cure. The patient is tapered off of short-acting opioids during the detoxification/withdrawal process and may be placed on an opioid antagonist with the goal of minimizing relapse.

All treatment approaches share the common goal of improving health outcomes and reducing drug-related criminality and public nuisance [64].

CRISIS INTERVENTION

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the criterion standard. Naloxone is effective in reversing respiratory depression and coma in patients who have overdosed. There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone. This prompted discussion of making naloxone available to the general public for administration outside the healthcare setting to treat acute opioid overdose, and in 2014, the FDA approved naloxone as an autoinjector dosage form for home use by family members or caregivers [65]. The autoinjector delivers 0.4 mg naloxone intramuscularly or subcutaneously. The autoinjector comes with visual and voice instruction, including directs to seek emergency medical care after use [65]. In 2015, the FDA approved intranasal naloxone after a fast-track designation and priority review. Intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is available in a ready-to-use 2-mg, 4-mg, or 8-mg single-dose sprayer [66; 67; 68]. In 2023, the FDA approved Narcan, the first over-the-counter naloxone nasal spray [69]. Narcan is available as a 3-, 4-, or 8-mg single dose, administered in one nostril [70].

HARM REDUCTION

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance [38; 71]. As a part of this effort, measures to prevent and minimize the frequency and severity of overdoses have been identified. Enrollment in opioid substitution therapy, with agents such as methadone and buprenorphine, substantially reduces the risk of overdose as well as the risk for infection and other sequelae of illicit opioid use [38; 71].

DETOXIFICATION AND WITHDRAWAL

The process of tapering patients with opioid dependence from agonist therapy is often referred to as detoxification, or more accurately, medically supervised withdrawal [72; 73]. Its purpose is to eliminate physical dependence on opioid medications. It can be considered the medically supported transition to a medication-free state or to antagonist therapy. A careful and thorough review of the risks and benefits of detoxification should be provided, and informed consent obtained from patients prior to choosing this option [73; 74]. Detoxification alone should not be considered a treatment and should only be promoted in the context of a well-planned relapse-prevention program [64; 73]. Studies have shown that most patients with opioid use disorder who undergo medically supervised withdrawal will start using opioids again and will not continue in recommended care [75; 76; 77; 78; 79].

Discontinuation of opioid use must be implemented slowly and cautiously to avoid a marked abstinence syndrome. Withdrawal symptoms may not begin for days after abrupt discontinuation of methadone or buprenorphine given their longer half-lives. Protracted abstinence, or post-acute withdrawal, may last for several months and is characterized by asthenia, depression, and hypotension. Post-acute withdrawal is more likely to occur with methadone than other opioids [72].

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [72]. The most frequently employed method of opioid withdrawal is a slow, supervised detoxification during which an opioid agonist, usually methadone, is substituted for the abused opioid [80]. Methadone is the most frequently used opioid agonist due to the convenience of its once-a-day dosing [72]. Methadone is highly bound to plasma proteins and accumulates more readily than heroin in all body tissues. Methadone also has a longer half-life, approximately 22 hours, which makes withdrawal more difficult than from heroin. Substitution therapy with methadone has a high initial dropout rate (30% to 90%) and an early relapse rate. Alternative pharmacologic detoxification choices include clonidine (with or without methadone), midazolam, trazodone, or buprenorphine [80]. Naltrexone is used following medically supervised withdrawal to help prevent relapse to opioid misuse [81].

Many opioid withdrawal symptoms, such as restlessness, rhinorrhea, lacrimation, diaphoresis, myosis, piloerection, and cardiovascular changes, are mediated through increased sympathetic activation, the result of increased neuron activity in the locus coeruleus. Non-opioid agents (such as clonidine), which inhibit hyperactivation of noradrenergic pathways stemming from the locus coeruleus nucleus, have been used to manage acute withdrawal [80; 82]. The first non-opioid treatment approved for the management of opioid withdrawal symptoms is lofexidine [83]. In studies, lofexidine resulted in less severe withdrawal symptoms and greater treatment retention than placebo.

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory agents may be necessary to treat these symptoms. To mitigate withdrawal symptoms and assist in detoxification, alpha2-agonists, opioid agonist-antagonists, benzodiazepines, and antidepressants have been used [80].

Following detoxification, patients may feel exhausted and weak. Other complications, such as slight variations in hemodynamic status and gastrointestinal tract symptoms, follow quickly and may take several days to resolve. Muscle cramps and low back pain can be treated with nonsteroidal anti-inflammatory drugs. However, the newer cyclooxygenase-2 (COX-2) inhibitors may be advantageous because they produce fewer gastrointestinal side effects [80]. Insomnia is a frequent aspect of acute and protracted withdrawal, as opioids disrupt the normal sleep-wake cycle and many addicts require narcotics to sleep. Although long-term disruption of the normal sleep-wake cycle cannot be corrected rapidly, melatonin (3 mg), benzodiazepines, or antihistamines can be used with beneficial effects. Hypnosis and relaxation techniques are nonpharmacologic methods that may also be used [80]. Psychosocial treatments offered in addition to pharmacologic detoxification treatments positively impact treatment retention and completion, results at follow-up, and compliance [84; 85].

Ultra-Rapid Opioid Detoxification

Ultra-rapid opioid detoxification (UROD) has been developed as a means of avoiding the physical symptoms of withdrawal from opioids through the use of general anesthesia. UROD consists of naltrexone-assisted detoxification under heavy sedation or full anesthesia. UROD is also referred to as rapid or anesthesia-assisted detoxification. Other novel names for the process include [86]:

- UROD: General anesthesia; duration <6 hours
- Rapid opioid detoxification (ROD): Deep sedation; duration 6 to 72 hours
- Compressed opioid detoxification (COD) and naltrexone-compressed opioid detoxification (NCOD): Duration three to six days; preceded by a period of abstinence from opioids under sedation prior to introduction of naltrexone

The common underlying themes in all UROD techniques are a desire to condense the detoxification process into a shorter period to blunt the awareness of physical discomfort and to shorten the time lag between a patient's last dose of opioid and transfer to naltrexone maintenance [86]. This is accomplished by precipitating withdrawal following the administration of opioid antagonists under deep sedation or anesthesia.

Detoxification and withdrawal are rarely complete following UROD, and residual withdrawal symptoms can include drug craving, sympathetic hyperactivity, muscle pain, bone pain, nausea, vomiting, diarrhea, and insomnia. UROD does little to prevent protracted abstinence syndrome, which can last 3 to 10 weeks. Naltrexone may reduce opioid craving during the post-UROD period, with 50 mg per day recommended for relapse prevention. However, patients undergoing long-term naltrexone therapy can become sensitized to opioid drugs, heightening the risk of fatal overdose if opioid use is resumed [80].

A major shortcoming of UROD is the lack of evidence that an opioid antagonist can accelerate the restoration of neurobiologic homeostasis following opioid withdrawal [86]. Although significant drawbacks and questionable long-term efficacy exist with UROD, popular demand has proven difficult to restrain, in part due to the marketing of the procedure as a painless cure for opioid dependence. Marketing and the media have also blurred the fact that the original purpose of the procedure was to induce patients as rapidly as possible onto naltrexone and not to immediately permanently terminate years of opioid dependence [87].

Serious adverse events related to the anesthetic procedure also have been reported. A randomized, controlled trial directly comparing naltrexone-assisted detoxification with and without full anesthesia clearly stated that heavy sedation or full anesthesia should not be used because it does not confer any advantages in withdrawal symptom severity or increased rates of initiation or maintenance and it increases the potential for life-threatening adverse events [64]. A trial comparing naltrexone-induced, anesthesia-assisted detoxification with buprenorphine- or clonidine-assisted detoxification found no difference in withdrawal severity and rates of completion. However, potentially life-threatening adverse events associated with the UROD anesthesia were observed [88]. The risk for adverse events, the high monetary cost, and use of scarce intensive care resources suggest that this form of treatment should not be pursued [89; 90]. Additionally, UROD has not undergone the processes of therapeutic protocols, which are recognized as essential in scientific medicine, and no animal studies have been conducted with the procedure [87].

AGONIST REPLACEMENT OR ABSTINENCE THERAPY

Two principle treatment modalities are offered for patients with opioid dependence: agonist maintenance or detoxification followed by outpatient or residential drug-free treatment. Both can be effective, with no clear indication for each, although agonist maintenance leads to greater treatment retention [91]. A reasonable approach is initial outpatient or residential treatment referral for patients relatively new to treatment, with

agonist maintenance appropriate for patients with history of treatment failures, greater disease severity, or a history of drug overdoses. Naltrexone is best reserved for patients with strong legal incentives to abstain, family involvement to monitor treatment, or concurrent enrollment and involvement in a psychosocial intervention [92].

At present, there are no direct interventions that are capable of reversing the effects of drugs of dependence on learning and motivation systems [93]. Instead, the management of opioid dependence often consists of pharmacotherapy with methadone and buprenorphine, which do not eliminate physical dependence on opioids. These medications instead reduce the use of illicit opioids and produce very strong positive health outcomes as measured by decreased mortality, improved mental and physical health, and reduced risk of disease transmission [93]. Considering the high rate of relapse after detoxification, maintenance therapy with methadone or buprenorphine is currently considered to be the first-line treatment for patients with opioid dependence [64]. Both agents are superior to withdrawal management alone and both significantly reduce illicit opioid use [94].

Any treatment for opioid dependence must take into consideration the chronic relapsing nature of opioid dependence, characterized by a variable course of relapse and remission in many patients. Treatments should emphasize patient motivation, psychoeducation, continuity of care, integration of pharmacotherapy and psychosocial support, and improved liaison between the treatment staff and the judicial system. Pharmacotherapy must be offered in a comprehensive healthcare context that also addresses the psychosocial aspects of dependence [64]. Patients who are dependent on opioids frequently suffer from physical and psychiatric disorders, and targeted interventions of psychiatric comorbidity are essential in improving treatment outcome for these patients [64]. Polysubstance abuse is the rule rather than the exception in opioid dependence, and concurrent use of other substances should be carefully monitored and treated when necessary [64]. Concurrent use of other drugs or active engagement in other addictive behaviors should lead to consideration of other treatment plan components for the patient. The presence of co-occurring substance use disorders should provoke a re-evaluation of the level of care in which the patient is treated [94]. Incarceration should never automatically result in discontinuation of an existing treatment; imprisonment offers a window of opportunity to initiate or restart treatment with a necessary continuation after release [64].

Agonist Replacement Therapy

The goal of opioid replacement therapy is to reduce illicit drug use and associated health risks, with secondary goals of reducing unsafe sexual practices, improving vocational and psychosocial functioning, and enhancing quality of life [72]. The theoretical basis of opioid replacement stems from the finding that chronic opioid use results in an endogenous opioid deficiency as a result of the down-regulation of opioid production. This creates overwhelming cravings and necessitates interventions that shift the patient's attention and drive from obsessive preoccupation with the next use of opioids to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities [72].

The neurobiologic changes resulting from prolonged opioid exposure provide a rationale for specific pharmacotherapies, such as long-acting opioid agonists, that are aimed at stabilizing these complex systems [95]. Opioid agonist maintenance treatment stabilizes brain neurochemistry by replacing short-acting opioids, which can create rapid changes in opioid levels in the serum and brain, with a long-acting opioid that has relative steady-state pharmacokinetics. Opioid agonist maintenance treatment is designed to have minimal euphoric effect, block the euphoria associated with administration of exogenous opioids (competitive antagonism), eliminate the risk of infectious disease and health consequences associated with injection drug use, and prevent opioid withdrawal [95].

Successful maintenance treatment entails stabilization of opioid dependence through opioid receptor occupation. Positron emission tomography studies have revealed that only 25% to 35% of brain opioid receptors are occupied during steady-state methadone maintenance, suggesting that unoccupied opioid receptors disrupted during cycles of opioid abuse could normalize during methadone maintenance [72]. Additionally, opioid replacement therapy blocks much of the euphoria from illicit heroin use. Long-term opioid agonist treatment also has a positive impact on public health, through significantly reducing overdose deaths, criminal activity, and the spread of infectious disease [72].

As of 2020, there were 1,754 treatment programs including opioid replacement therapy in the United States [96]. However, this represents less than 20% of all patients with opioid use disorder. Although some have criticized the practice of methadone and buprenorphine therapy on the grounds that one opioid is merely being substituted for another, the clinical benefits strongly support this treatment modality [72]. When compared to active street heroin users, these benefits include a four-times lower HIV seroprevalence rates, 70% fewer crime-days per year, and a one-year mortality rate of 1% (versus 8%) [97].

Abstinence-Oriented Therapies

The primary goal of abstinence-oriented interventions is cure, which is defined as long-term, stable abstinence from all opioids. Abstinence is achieved in two phases: detoxification and relapse prevention. Outcomes in abstinence-oriented programs are generally poor [64].

The primary goal of pharmacotherapy during detoxification is to alleviate opioid withdrawal severity and associated distress/medical complications and to enhance patient motivation to continue treatment. Withdrawal can also be reduced by psychosocial measures, such as contingency management or counseling, and as discussed, the addition of psychosocial therapy to pharmacologic treatment increases efficacy. Buprenorphine and clonidine are both used to manage withdrawal symptoms, but buprenorphine's advantages, compared with clonidine, are related to its favorable side effect profile and positive effects on well-being and psychosocial variables [64].

12-Step/Self-Help Programs

Twelve-step programs for opioid abuse and dependence include Narcotics Anonymous (NA), Heroin Anonymous (HA), and Methadone Anonymous (MA) and are modeled after Alcoholics Anonymous (AA), an abstinence-based support and self-improvement program that is based on the 12-step model of recovery. AA has helped hundreds of thousands of alcoholics achieve sobriety [98]. The 12-step model emphasizes acceptance of dependence as a chronic, progressive disease that can be arrested through abstinence but not cured. Additional elements include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and are a resource for emotional support [98]. Although research on efficacy and patient outcomes in NA and MA is very limited, many prominent researchers emphasize the important role ongoing involvement in 12-step programs plays in recovery from substance abuse [99].

The understanding of drug dependence as a chronic and relapsing disorder has helped professionals gain a better comprehension of the vital role played by 12-step programs. Every patient attempting to recover from a substance use disorder will encounter a time when he or she faces urges to use without the resources or assistance of healthcare professionals. Twelve-step programs are not considered treatment, nor are they intended as substitutes for treatment. Instead, they are organizations that provide ongoing and indefinite support in the achievement and maintenance of abstinence and in personal growth and character development [99].

Part of the effectiveness of NA, HA, and MA is related to their ability to provide a competing and alternative reinforcer to drug use. Involvement in 12-step programs can enhance the quality of social support and the social network of the member, a potentially highly reinforcing aspect the person stands to forfeit if they resume drug using. Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance of meetings [100]. Research shows that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Emphasis and facilitation of early engagement in a 12-step program involvement are key [101].

STIGMA OF ADDICTION

Many terms used in discussions of opioid use and misuse may have ambiguous meanings, and the absence of consensus in the terminology and definitions of substance use, substance use disorders, and addiction has led to considerable confusion and misconceptions. These misconceptions may be harbored by clinicians, patients, family members, and the public and can negatively impact patient interaction, assessment, treatment, and outcomes. This, coupled with pervasive stereotypes about what an opioid addict "looks" like, can negatively impact willingness to receive treatment or seek help and impair the patient's self-worth and mental health. Correction of these erroneous beliefs and attitudes is important, as is the use of nonpejorative and nonstigmatizing language when describing opioid analgesics, the patients who need them, and patients who develop aberrant behaviors or addiction involving opioids [31; 102]. It is important for all healthcare professionals to remember that addiction can affect any patients, regardless of age, sex, socioeconomic status, education, ability, or race.

PROGNOSIS OF TREATMENT FOR OPIOID USE DISORDER

The relapse rate among patients receiving treatment for opioid dependence and other substance abuse is high (25% to 97%), comparable to that of other patients with chronic relapsing conditions, including hypertension and asthma [103]. Many cases of relapse are attributable to treatment noncompliance and lack of lifestyle modification [104].

Duration of agonist replacement therapy is usually recommended as a minimum of one year, and some patients will receive agonist replacement therapy indefinitely. Longer durations of treatment are associated with higher rates of abstinence from illicit opioids [93].

Much remains unknown about patient outcomes following termination of long-term opioid replacement therapy. Some patients aim to achieve total abstinence from all opioids, but little is known about patient characteristics and strategies used among those who remain abstinent. It is likely that at least some of the patients who remain abstinent from all opioids do so with the help of a 12-step support program, such as NA [93].

CONCLUSION

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

COURSE TEST - #95152 RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

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 3 Hour activity must be completed by April 30, 2027.

1. Inappropriate opioid analgesic prescribing for pain is defined as
- A) *non-prescribing.*
- B) *inadequate prescribing.*
- C) *continued prescribing despite evidence of ineffectiveness of opioids.*
- D) *All of the above*

2. When opioids are used for acute pain, clinicians should prescribe
- A) *the highest safe dose.*
- B) *extended-release opioids.*
- C) *a quantity no greater than that needed for the expected duration of severe pain.*
- D) *All of the above*

3. A patient prescribed opioids for chronic pain who is 65 years of age and displays high levels of pain acceptance and active coping strategies is considered at what level of risk for developing problematic opioid behavioral responses?
- A) *Low*
- B) *Medium*
- C) *High*
- D) *Severe*

4. The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
- A) *consists of 5 items.*
- B) *is patient administered.*
- C) *diagnoses depression in the past month.*
- D) *assesses the likelihood of current substance abuse.*

5. Which of the following is NOT one of the 5 A's of monitoring chronic opioid response?
- A) *Analgesia*
- B) *Acceptance*
- C) *Affect (i.e., patient mood)*
- D) *Aberrant drug-related behaviors*

6. For patients considered at medium risk for misuse of prescription opioids, urine drug testing should be completed every
- A) *6 to 12 weeks.*
- B) *3 to 6 months.*
- C) *6 to 12 months.*
- D) *1 to 2 years.*

7. Which of the following statements regarding the disposal of opioids is TRUE?
- A) *Patients are almost always advised of what to do with unused or expired medications.*
- B) *There are no universal recommendations for the proper disposal of unused opioids.*
- C) *According to the FDA, most medications should be flushed down the toilet instead of thrown in the trash.*
- D) *All of the above*

8. The most common source of nonmedical use of prescribed opioids is from
- A) *a friend or relative for free.*
- B) *a prescription from one doctor.*
- C) *purchase from a drug dealer or other stranger.*
- D) *theft from a doctor's office, clinic, hospital, or pharmacy.*

9. Which of the following behaviors is the most suggestive of an emerging opioid use disorder?
- A) *Asking for specific medications*
- B) *Injecting medications meant for oral use*
- C) *Reluctance to decrease opioid dosing once stable*
- D) *Stockpiling medications during times when pain is less severe*

10. Which government agency is responsible for formulating federal standards for the handling of controlled substances?
- A) *Institutes of Medicine*
- B) *U.S. Drug Enforcement Administration*
- C) *Office of National Drug Control Policy*
- D) *U.S. Department of Health and Human Services*

Human Trafficking and Exploitation: The Texas Requirement

This course has been approved by the Texas Health and Human Services Commission (HHSC) to meet the requirement for human trafficking training.

Audience

This course is designed for Texas pharmacy professionals and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.

Course Objective

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.

Learning Objectives

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

1. Define human trafficking.
2. Identify the forms of human trafficking.
3. Identify individual, family/relationship, community/organizational, and societal/cultural factors that contribute to human trafficking.
4. Analyze the trafficking experience, including how traffickers recruit and the financial implications of trafficking.
5. Explain the psychological, health, and social consequences of human trafficking.
6. Utilize interviewing strategies to assess and identify victims and promote the ethical treatment of trafficking victims.
7. Outline the healthcare professional's responsibilities in identifying and assisting survivors of trafficking, including best practices for referral and collaboration.

Faculty

Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College, School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families.

Previously acting as a faculty member at Capella University and Northcentral University, Dr. Yick Flanagan is currently a contributing faculty member at Walden University, School of Social Work, and a dissertation chair at Grand Canyon University, College of Doctoral Studies, working with Industrial Organizational Psychology doctoral students. She also serves as a consultant/subject matter expert for the New York City Board of Education and publishing companies for online curriculum development, developing practice MCAT questions in the area of psychology and sociology. Her research focus is on the area of culture and mental health in ethnic minority communities.

Faculty Disclosure

Contributing faculty, Alice Yick Flanagan, PhD, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

Randall L. Allen, PharmD

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

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

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Special Approval

This course has been approved by the Texas Health and Human Services Commission (HHSC) to meet the requirement for human trafficking training.

About the Sponsor

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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

Human trafficking is not a new social problem; it has always existed. Trafficking has recently received increased attention as a result of awareness and outreach efforts. It has garnered attention from feminists, religious conservatives, labor activists, immigration specialists, and the mental health professions [1]. This course will provide a basic overview of human trafficking (e.g., the scope, definitions and frameworks, contributing factors, different forms). The course will attempt to provide practitioners a glimpse of the lives of human trafficking victims, including the physical, psychological, social, and sexual abuse that human trafficking victims experience and the types of control tactics that perpetrators use. Specific interventions and responses will be covered, including mental health, social services, educational, prevention, and legal efforts. Finally, for practitioners who work with human trafficking victims, the emotional toil that it takes on practitioners as well as the importance of self-care will be discussed. Practitioners will be encouraged to view films and documentaries about human trafficking, as this is one way to "enter the lives" of human trafficking victims and better understand the dynamics of the complex world of human trafficking.

BACKGROUND

Because human trafficking is a complex issue, it is difficult to determine the scope of the problem. Many scholars and researchers believe that published estimates are just educated guesses. On a global level, the International Labour Organization has estimated that there were 49.6 million people living in modern slavery in 2021, 27.6 million in forced labor, and 22 million in forced marriage [2]. The estimates for the United States are not totally clear, but there were approximately 78,000 human trafficking victims reported to the U.S. State Department in 2016; only an estimated 0.2% are rescued [3]. According to Polaris, which founded and runs the National Human Trafficking Hotline, there have been a total of 40,200 cases of human trafficking reported since 2007 [3]. According to statistics from the U.S. Department of Justice, the number of persons prosecuted for human trafficking increased from 729 in 2011 to 1,343 in 2020, an 84% increase [4].

A wide range of laws have been established to protect human trafficking victims and to prosecute perpetrators. A general knowledge of these laws is helpful when caring for victims and seeking appropriate social services. The Trafficking Victims Protection Act (TVPA) was enacted in 2000 and reauthorized in 2003, 2005, 2008, 2013, 2018, and 2022 by the Trafficking Victims Protection Reauthorization Acts [5]. It emphasizes the three Ps: prevention, protection, and prosecution [5]. The prevention component consists of training and awareness; the protection dimension gives trafficked victims the ability to receive services using federal funds like other refugees; and the prosecution component focuses on laws and policies for the prosecution of traffickers.

Because victims of trafficking are often viewed as criminals, this law states that victims of severe trafficking should not be penalized for any illegal behaviors or acts they engaged in as a result of being trafficked, including entering the United States with false documents or no documentation or working without appropriate paperwork [6]. This law also allows T Nonimmigrant Status (T visas) to be granted to victims of trafficking so they may remain in the United States with the purpose of collaborating with the federal authorities to prosecute the perpetrators. During this time, victims are offered a range of benefits and services, including access to the Witness Protection Program [6]. After three years, victims can apply for permanent resident status [7].

One of the criticisms of the Act is that it places the burden of demonstrating innocence and coercion on the victim [8]. The Act also fails to recognize the complex dynamics of human trafficking. For example, it focuses more on sex trafficking versus other forms [9]. Many victims have been abused and terrorized by the perpetrators, who they must now provide information and evidence against to stay in the country. Victims are continually fearful that they will be deported [8].

Victims who are of minor age are eligible for Unaccompanied Refugee Minors programs, the Children's Health Insurance program, and Temporary Assistance to Needy Families [10]. Furthermore, victims between 16 and 24 years of age are eligible for work permits and can apply for the Job Corps program [10]. It is important to remember that the key to this law is that the victim must have experienced a "severe form" of trafficking and must be willing to assist in the apprehension and prosecution of the perpetrator to receive services [11].

DEFINITIONS OF HUMAN TRAFFICKING

The United Nations defines human trafficking as [12]:

> The recruitment, transportation, transfer, harbouring or receipt of persons, by means of threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation. Exploitation shall include, at a minimum, the exploitation or the prostitution or other forms of sexual exploitation, forced labour or services, slavery or practices similar to slavery, servitude, or the removal of organs.

In essence, this definition involves three elements: the transport of the person, the force or coercion of the victim, and the abuse and exploitation [13]. The United Nations Office on Drugs and Crime divides the definition of human trafficking into three sections: the act, means, and purpose [14]. The act, or what is done, generally refers to activities such as recruitment, transportation, transfer, harboring, or receipt of persons. The means of trafficking consists of threats or use of force, coercion, abduction, fraud, deception, abuse of power or vulnerability, or giving payments or benefits to a person in control of the victim. Finally, these acts are carried out for the purpose of exploitation, which includes prostitution, sexual exploitation, forced labor, slavery or forced servitude, and the removal of organs [14].

The TVPA defines human trafficking to include both sex trafficking and labor trafficking [15]:

> Sex trafficking is the recruitment, harboring, transportation, provision, obtaining, patronizing, or soliciting of a person for the purposes of a commercial sex act, in which the commercial sex act is induced by force, fraud, or coercion, or in which the person induced to perform such an act has not attained 18 years of age. Labor trafficking is the recruitment, harboring, transportation, provision, or obtaining of a person for labor or services, through the use of force, fraud, or coercion for the purposes of subjection to involuntary servitude, peonage, debt bondage, or slavery. A victim need not be physically transported from one location to another for the crime to fall within this definition.

In many cases, women and children are considered the typical victims of human trafficking. Hart posits that women are more vulnerable to trafficking due to the lack of social safety nets in many developing countries [16]. Coupled with women's subordinate social status in many cultures, this leads to the "feminization of poverty." Although the social conditions may make women and children more vulnerable to human trafficking, the reality is that men are also victims of human trafficking.

Overall, the definition of human trafficking is ambiguous because of the many intersections with other issues (e.g., sexual abuse, domestic violence, forced marriage, forced labor) [17]. It occurs both domestically and internationally, but is primarily a hidden problem. This makes research efforts, the prosecution of perpetrators, and policy and community efforts to protect victims even more challenging [17]. It is vital to remember that trafficking, as defined by U.S. law, does not require crossing international or even state borders. The transport of victims from one locale to another is not a necessary component of determining whether human trafficking has occurred.

LIMITATIONS OF DATA ON HUMAN TRAFFICKING

Although the United Nations definitions are used in this course, scholars, practitioners, researchers, and policy makers have not come to a consensus definition of human trafficking. Consequently, terms such as sexual slavery, human smuggling, and modern-day slavery have all been used [18]. When the term human trafficking is utilized, it often has connotations of sexual exploitation affecting mainly women and girls, the most visible victims, but this is not accurate [18]. This perspective is partially attributable to the large number of religious and feminist organizations who have worked to eradicate non-consensual sex work [19]. This lack of consensus definition also raises questions about the study population in the

research. The involved parties (i.e., the trafficker, those who are trafficked, and the networks) are continually changing in time and space [20].

Defining these terms is essential because it will ultimately influence responses to human trafficking. As stated, all social problems are competing for attention and resources, and the response is influenced by how the social problem is defined and portrayed [21]. Ultimately, the lack of a consensus definition is one of the reasons studying human trafficking has been a challenge and that research yields unreliable prevalence estimates.

Another reason human trafficking has been a difficult topic to research is the hidden and invisible nature of its victims and perpetrators. This makes it difficult for researchers to use traditional sampling methods. Even if trafficked victims are identified, perpetrators can move them to new locations [22]. If and when researchers access this hidden population, victims are often reluctant to talk due to fear, shame, and the stigma associated with their experiences. Consequently, much of what has been studied has relied on interviews with professionals (e.g., lawyers, advocates, police/law enforcement, and other service providers), which has led to recommendations that are not based on firsthand accounts [23].

A host of ethical issues also arise for those conducting research in this area. Protecting study participants' identities is paramount, and consequently, study participants signing informed consent forms, which are often required by institutional review boards, becomes complicated. Understandably, victims and perpetrators often will not want to sign forms using their real names for fear of deportation, arrest, and/or reprisals [22].

FORMS OF TRAFFICKING

The social realities of victims of human trafficking are difficult to comprehend, and some may wonder why victims remain silent and comply with their traffickers. The Silence Compliance Model was created to explore the factors that promote victims' seeming willingness to comply with their traffickers' demands [24]. This model has three categories: coercion, collusion, and contrition. Victims are coerced, brutalized, and threatened, and basic necessities of life are withheld from them. Methods of psychological coercion include isolation, induced exhaustion, threats, degradation, and monopolizing perception [25]. This serves to silence victims and create a sense of helplessness. By isolating and controlling victims' movements and limiting their exposure to the outside world, traffickers have complete monopoly of their attention and perception of reality [25]. Victims are then forced to collude with the traffickers as a result of their relative isolation, fear, false sense of belonging, and complete dependence on the trafficker. Finally, victims feel contrite, ashamed, stigmatized, and remorseful of the things they have been made to do [24].

Another model, the Action-Means-Purpose (AMP) Model, is a device used to illustrate and articulate the federal definition of a "victim of severe forms of trafficking in persons" [26]. The Action category consists of the actions a perpetrator takes to induce, recruit, harbor, transport, provide, or obtain a victim. The Means of force, fraud, or coercion are used for the ultimate Purpose of commercial sex or labor/services trafficking [26].

It is important to remember that human trafficking is not human smuggling. Human smuggling involves an individual being brought into a country through illegal means and is voluntary. The individual has provided some remuneration to another individual or party to accomplish this goal [7].

SEX TRAFFICKING

The TVPA of 2000 is a U.S. federal statute passed by Congress to address the issue of human trafficking and offers protection for human trafficking victims [15]. This statute defines sex trafficking as, "the recruitment, harboring, transportation, provision, or obtaining of a person for the purpose of a commercial sex act" [15]. A commercial sex act is, "any sex act on account of which anything of value is given to or received by any person" [15]. In other words, it usually involves the illegal transport of humans into another country to be exploited in a sexual manner for financial gain [27]. However, it does not always involve the transport of victims from one region to another; such cases are referred to as "internal trafficking" [28]. Victims of sex trafficking could be forced into prostitution, stripping, pornography, escort services, and other sexual services [29]. Victims may be adult women or men or children, although there is a higher prevalence of women and girls. The term "domestic minor sex trafficking" has become a popular term used to connote the buying, selling, and/or trading of children younger than 18 years of age for sexual services within the country, not internationally [29; 30]. An element of force, fraud, or coercion is not necessary, as the victims are children and inherently vulnerable [30]. In the United States, the children most vulnerable to domestic minor sex trafficking are those who are homeless, abused, runaways, and/or in child protective services [29].

Although controversial, it is said that sex trafficking victims differ from consensual sex work in that sex trafficking victims are forced to involuntarily perform sexual services and are often not paid for their "work." Sex trafficking involves the use of force and coercion and can encompass other forms of criminal sexual activities, including forced erotic dancing, "mail-order brides," and pornography [28]. On the other hand, individuals involved in consensual sex work make a decision to provide sex services for a fee. The decision to enter sex work does not eliminate the possibility of being a victim of trafficking if one is held against his/her will through physical and/or psychological abuse [4]. It is also important to remember that this does not necessarily mean sex work is a choice these individuals would have made if other options were available or that they have a choice in selecting their sexual partners and/or sexual activities [31].

BONDED LABOR/FORCED LABOR

The United Nations has defined debt bondage as [32]:

> The status or condition arising from a pledge by a debtor of his personal services or of those of a person under his control as security for a debt, if the value of those services as reasonably assessed is not applied towards the liquidation of the debt or the length and nature of those services are not respectively limited and defined.

Essentially, because the individual does not have money as collateral for the debt owed, the individual pledges his/her labor or, in some cases, the labor of a child or another individual for an unspecified amount of time [33]. These individuals may be transported or trafficked into another country for the purpose of forced labor.

In many cases of bonded labor, the initial loan may be welcomed by the individual. However, the victims do not realize that with the low wages, unspoken high interest rates and other continually accruing fees, and the perpetrator's manipulation of the "accounts," laborers can never repay the loans. Some estimate that half of all persons in forced labor are bonded laborers. The majority of bonded labor cases occur in India, Bangladesh, and Pakistan [34]. Some families find themselves in a cycle of poverty as the debt cannot be paid off and is passed down from generation to generation [33]. Bonded labor can involve laborers in brick kilns, mines, stone quarries, looming factories, agricultural farms, and other manufacturing factories [33]. In the United States, individuals may be trafficked to work long hours in garment factories, restaurants, and other manufacturing sectors. Frequently, the employer/captor will take away victims' identifications, monitor their movements, socially isolate them, and/or threaten deportation if they do not comply [35]. Migrant workers are at high risk of forced labor [4].

In the United States, forced labor is predominantly found in five sectors [35]:

- Prostitution and sex industry (46%)
- Domestic servitude (27%)
- Agriculture (10%)
- Sweatshops and factories (5%)
- Restaurant and hotel work (4%)

It is speculated that most of the forced labor occurs in California, Florida, New York, and Texas, all major routes for international travel [35].

Domestic servitude refers to a category of domestic workers (usually female) who work in forced labor as servants, housekeepers, maids, and/or caregivers, often in private homes. In some cases, young women are lured with the promise of a good education and work, and when they arrive in the United States, they are exploited economically, physically, and/or sexually. Their passports or identification papers are taken away, and they are told they have to pay off the debt incurred for their travel, processing fees, and any other bogus expenses. Because they do not speak English, they find they have no other recourse but to endure exploitative working conditions [36]. Unfortunately, as in many sectors of forced labor, there are no regulations to monitor the conditions under which domestic servants operate [35].

CHILD LABOR

Child labor can be viewed as a specific form of bonded labor or forced labor. However, not all child laborers have been trafficked. Child labor is defined by International Labour Organization (ILO) as economic labor performed by a child younger than 15 years of age or hazardous labor done by a child 18 years of age or younger. Child labor is deeply rooted in poverty and the infrastructure and political stability of the country as well as market forces [37]. The ILO estimates that there were 160 million child laborers in the world in 2020 (63 million girls and 97 million boys) [38]. This accounts for nearly one in ten of all children worldwide [38]. Between 2000 and 2020 there was a nearly 35% decrease in the number of children in child labor. The reduction was greater for girls than for boys . The number of children in child labor has increased from 2008 to 2020 in sub-Saharan Africa (from 65.1 million to 86.6 million), while it has declined in other parts of the world (e.g., Asia/the Pacific, Latin America/the Caribbean) [38].

The definition of child labor is controversial because the definitions for "work" and "childhood" are ambiguous and often culturally defined [39]. On a conceptual level, work may be beneficial for the socialization and educational processes of children [39; 40]. So, it is important to differentiate between child work and child labor. Child work has been defined as activities that are supervised by an adult and that promote the development and growth of the child, while child labor does not benefit the child [37]. Many definitions of child labor create a dichotomy whereby child work is considered not harmful while child labor has negative emotional, intellectual, and social consequences [41]. Work that is exploitative for children has been defined as working long hours at a young age, work that is poorly compensated, and work that produces physical, social, and psychological stress that will hamper development, access to education, and self-esteem [42]. The ILO adds that child labor is work that "interferes with their schooling by: depriving them of the opportunity to attend school; obliging them to leave school prematurely; or requiring them to attempt to combine school attendance with excessively long and heavy work" [40].

It is important to remember that child labor occurs in the United States. Runaway and homeless youths are at greatest risk, often lured by promises of work and housing [43]. The Polaris Project found that the top three forms of child labor trafficking in the United States were begging, peddling, and traveling sales crews [43].

CHILD CONSCRIPTION

In some cases of trafficking, children are kidnapped and trafficked to serve as soldiers. Other times, children are coerced by a narrative indicating they will be serving a higher purpose and avenge the deaths of family and friends; this is known as comradeship [44; 45]. Some children are actively recruited and may be promised a small salary to "voluntarily" join.

It is estimated that at any one time up to 300,000 children younger than 18 years of age are serving as child soldiers [46; 47]. Traffickers prefer to recruit children to serve as soldiers because they are inexpensive and more easily molded and shaped to comply and obey without question [48]. It can be difficult to comprehend the atrocities that these children witness and experience [49; 50].

FACTORS THAT CONTRIBUTE TO VULNERABILITY TO HUMAN TRAFFICKING

INDIVIDUAL

A variety of individual level factors may predispose an individual to human trafficking victimization. A history of physical, sexual, or emotional abuse and/or of witnessing violence in the home has been identified at increased rates among trafficking victims. Other possible risk factors include adherence to rigid gender roles, acceptance of norms supporting sexual exploitation of women and children, overestimation of problem behavior in peers/others, lack of trafficking awareness, and substance abuse [51].

Adverse Childhood Experiences

In more recent years, research has focused on the impact of adverse childhood experiences (ACEs) in general. ACEs are defined as potentially traumatic experiences that affect an individual during childhood (before 18 years of age) and increase the risk for future health and mental health problems (including increased engagement in risky behaviors) as adults [52]. Abuse and neglect during childhood are clear ACEs, but other examples include witnessing family or community violence; experiencing a family member attempting or completing suicide; parental divorce; parental or guardian substance abuse; and parental incarceration [52].

One study found that youths with human trafficking reports were significantly more likely to have experienced ACEs [53]. Specifically, sexual abuse was the strongest predictor of human trafficking. Girls with a history of sexual abuse were 2.52 times more likely to experience human trafficking, and boys who had been victims of sexual abuse were 8.21 times more likely to be trafficked.

Poverty and Economic Disenfranchisement

Poverty and incessant economic stressors caused by civil wars, natural disasters, and collapses of government systems all contribute to human trafficking [16; 30; 54]. In one study, the odds of being trafficked were nine times greater for those who felt extremely hopeless about upward mobility compared with those with lower levels of hopelessness [54].

RELATIONSHIP/FAMILY

Families marked by instability (e.g., domestic violence, child abuse, continual unemployment) are also at higher risk of having a member trafficked [30]. In addition, families entrenched in deep poverty may feel they have no other recourse but to sell a child or may be more easily lured with promises of money and a better future [54; 55; 56].

COMMUNITY/INSTITUTIONAL

Community factors (such as high social disorganization characterized by violence, unemployment, and high crime) contribute to higher risk of trafficking [30].

The rampant use of digital technology, such as the Internet, greatly facilitates sex trafficking. The relative anonymity of online contact can empower traffickers to recruit or sell victims. Graphic images of women and children engaged in sexual acts can be easily disseminated over the Internet [57]. Traffickers may employ the Internet for advertising, marketing to those interested in making pornography [57]. In addition, social media sites such as Facebook, Craigslist, and Instagram have been used as a means of facilitating trafficking (e.g., by connecting and grooming potential victims) [58; 59; 60]. Newsgroups offer opportunities for those interested in locating women and children for sexual exploitation.

In a 2013 qualitative study, smartphones were found to be integral in the business of trafficking [58]. Researchers indicated the phones were used "to maintain contact with each other, in order to facilitate the business 'transactions' and stay in touch with transnational 'partners' and other traffickers who remained in the country of origin" [58; 59].

SOCIETAL/CULTURAL

Globalization

Human trafficking has been called one of the "darkest sides of globalization" [61]. Globalization is the term used to describe the interconnectedness of countries and nations, which facilitates easy communication, exchange of ideas, and flow of goods, capital, and services [61]. Crimes such as human trafficking are affected by globalization just as legitimate businesses are [62]. Furthermore, the ideals of Western capitalism may reinforce human trafficking as a business or industry, with its emphasis on the free market and the flow of goods and services across international borders [62].

Globalization has also created the need for cheaper labor [34; 63]. A study involving 160 countries examined the effects of globalization and human trafficking trends [64]. Researchers found a positive relationship between globalization and trafficking for forced labor, sex work, and debt bondage.

Corruption

Human trafficking cannot occur without the existence of corruption within existing infrastructures. Public officials, police officers, and local leaders in many developing countries have been known to take bribes to provide protection to parties involved in various aspects of human trafficking [61; 64; 65].

Racialized Sexual Stereotypes

Race and ethnicity have been inextricably linked to sexual violence and victimization. Myths regarding sexuality in certain cultures or racial fetishization may affect trafficking patterns. For example, there is an over-representation of Asian women on American Internet pornography sites in part due to popular myths sexualizing, eroticizing, and exoticizing Asian women. This has translated into trafficking, as traffickers respond to the demand for young Asian women and girls in part fueled by these stereotypes of exotic, docile, submissive, and eager-to-please Asian women [36]. These stereotypes devalue and dehumanize people, which is the underlying core of human trafficking. This contributes to the acceptability of the exploitation of individuals, particularly members of marginalized groups [66].

These racial stereotypes go beyond simply framing the victims in a particular manner [67]. They raise implicit questions regarding how the powers of state are depicted. In other words, the patriarchal attitudes of certain countries lead to "bad" or "backward" cultural practices or ways of being that then cause trafficking—setting up a dichotomy of the "West" and "others" [67].

Culture

Although many are careful in linking cultural factors to the etiology of human trafficking for fear of imposing judgment on a particular culture, many maintain that cultural ideologies that tolerate sexual trafficking, bonded labor, and child labor may be a stronger factor than poverty in predicting trafficking rates [36; 42]. For example, some cultures emphasize collectivism and prioritizing the needs of the family and group first before the needs of the individual. Some children may feel they have to sacrifice themselves for their family when traffickers promise money [36]. Traffickers also know that they can threaten to hurt victims' families to keep them from escaping [36].

Furthermore, in many cultures, boys are more highly valued than girls, and as a result, girls are considered more dispensable [36]. Sons are considered the family's social security, staying with the family while daughters marry into other families. Therefore, girls may be more likely to be sold into slavery than boys.

Child labor is also inextricably tied to cultural factors. In India, for example, child labor is common because it is believed that children in the lower levels of the caste system (i.e., the "untouchables") should be socialized early to understand their position in society [42]. It has been observed that when traditional cultural and societal norms about women's roles were relaxed in some European countries and more women entered the labor force, child labor decreased [42]. Ultimately, it is difficult to unravel the effects of poverty and culture because the pressures of poverty can lead families to use tradition as a justification to sacrifice young men, women, and children [42].

Ultimately, the conversation about human trafficking is complex, and to attempt to isolate the causes is beyond challenging. Multiple factors have been suggested as possibly predicting human trafficking, including macroeconomic factors (e.g., gross domestic product per capita), unemployment rates, female inequality, cultural oppression, and lack of protection of women's rights [68; 69]. In one study, ease of land access to the destination country appeared to be a powerful predictor in terms of the number of individuals trafficked [68].

TRAFFICKERS: AN OVERVIEW

Much attention has been focused on the victims of trafficking; however, it is important to also understand the perpetrators.

It has been suggested human traffickers employ five general strategies to recruit and traffic victims [6; 70; 71; 72]:

- Kidnapping: Traffickers may kidnap their victims. They may lure them with food or treats or take them by force. Victims with few if any social ties are highly vulnerable, as no one will miss them or report their disappearance.
- Targeting poor families: Traffickers may convince families to sell their children (often daughters). Because many families in developing countries live in abject poverty, traffickers will stress to victims' families how the money will help them to survive. Other traffickers may tell families that selling their daughter will provide her with more promising opportunities.
- Developing a false romantic relationship with victim: A tactic often used with young girls, perpetrators pose as boyfriends by romancing victims, buying gifts, and proclaiming their love. Victims have a difficult time believing that their boyfriends would hurt or deceive them, making them easy targets for trafficking.
- Fake storefronts: Some employment, modeling, or marriage agencies are fronts for illegal trafficking operations. A potential victim might be lured with the promise of employment, a lucrative modeling contract, or an arranged marriage in the United States. After victims have been lured in, traffickers come to assess their "product." Perpetrators may be family members or friends.
- Legal storefronts: Some legal businesses in the tourism, entertainment, and leisure industries integrate trafficking activities into their business structure.

- Recruiting local sex workers: Traffickers might purchase sex workers working in local night clubs from brothel owners or simply lure sex workers by promising them a more affluent future. These trafficked sex workers may later recruit younger victims.

IMPACT ON VICTIMS/SURVIVORS

HEALTH CONSEQUENCES

In studies of trafficked women, headaches, fatigue, dizziness, back pain, pelvic pain, stomach pain, sexually transmitted infections (STIs), unwanted pregnancies, and gynecologic infections were common, generally the result of continual physical, psychological, and sexual abuse [30; 73]. Victims of labor trafficking also experience health issues related to the type of work, workplace conditions, malnutrition, and violence [74]. It is important to remember that some of these somatic complaints, such as headaches, fatigue, and gastrointestinal problems, may be underlying symptoms of anxiety, depression, and stress [73]. Some cultural groups might not use the terms "depression," "sad," or "anxious," but may use metaphors and somatic symptoms to describe their pain, all of which are embedded within cultural ideologies. The most common culture-based idioms of distress are somatic symptoms. Some groups tend not to psychologize emotional problems; instead, they experience psychological conflicts as bodily sensations (e.g., headaches, bodily aches, gastrointestinal problems, and dizziness).

Using an in-depth, direct interview survey designed to explore each stage of the trafficking experience, a multi-country European study identified a range of aversive health, sexual, and reproductive consequences common among women and adolescent victims of human trafficking [75]:

- Pre-departure stage: All victims reported having had limited knowledge of the health implications of having sex with strangers, and only 1 in 25 felt well-informed regarding the risks of acquiring HIV or other STIs.
- Travel and transit stage: Half of those interviewed reported having been confined, beaten, and/or raped during the journey.
- Destination stage: A large majority reported having been "intentionally hurt" (as evidenced by contusions, lacerations, loss of consciousness, and signs of head trauma); subjected to solitary confinement and deprived of human contact and adequate food and nutrition; subject to a variety of physical ailments, including headache, fever, undiagnosed pelvic pain, urinary tract infection, STIs, rash/scabies, and oral/dental health issues. All had experienced repeated sexual abuse or coercion, and 1 in 4 reported at least one unintended pregnancy (often involving negative outcomes of abortions performed in unsafe and unhealthy conditions).

Child and Adolescent Victims

Among child victims of human trafficking, healthy growth and development is especially problematic. Malnourishment and poor hygiene often lead to delayed bone growth, poorly formed teeth, and early dental caries [76]. The intense nature of child labor also has severe negative physical and health consequences.

Under normal circumstances, young children are still developing physically; however, such adverse conditions can halt their development. The lungs of adolescent boys typically experience the most rapid growth around 13 to 17 years of age; working in conditions characterized by excessive toxic dust or unclean air makes them more vulnerable to developing silicosis and fibrosis [77]. In the United States, young children participating in agricultural work are at risk of the major traumas associated with farm work, such as injuries caused by tractors or falling from heights, in addition to those injuries associated with repetitive stress and exposure to toxins. Children have thinner layers of epidermis, which make them more vulnerable to the toxicity of pesticides, and this can ultimately increase their risks for certain cancers [77]. Children working in gold mines do intensive digging, lifting, and transporting and mix mercury with the crushed ore, often with their bare hands. Mercury toxicity can lead to neurologic symptoms such as loss of vision, tremors, and memory loss [78].

DENTAL CONSEQUENCES

Victims may present with dental trauma and loss of teeth from violent acts. Injuries to the face and mouth area are common in abuse cases, and the potential for tooth involvement is high. Other dental problems arise as well, including infectious complications due to HIV, and even oral cancers or gingival disease due to substance use or poor access to dental care [79].

SEXUAL/REPRODUCTIVE HEALTH CONSEQUENCES

In the context of forced sex work among trafficked victims, safeguards against infection (e.g., regular condom use), early diagnosis, and adequate antimicrobial treatment are inconsistently employed or absent entirely [75]. Consequently, in addition to unwanted pregnancy, the risk for pelvic inflammatory disease and subsequent infertility is relatively high. Moreover, the relationship between forced sex work and HIV infection is stronger when sexual violence is involved. Women who are forced into sex work are 11 times more likely to become HIV-infected than women who engage in consensual sex work [80]. Sexual violence may increase the transmission risk as a result of open abrasions and injuries to the vagina. Furthermore, sexual violence can negatively impact self-esteem, which could then deter victims from advocating more strongly for condom use [80].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The British Association for Sexual Health and HIV has identified trafficked women/commercial sex workers as a group vulnerable to sexual violence. Inquiries about such vulnerabilities will help to identify those in need of additional support and help to facilitate appropriate referrals to mental health services, general practitioners, and support agencies. Access to interpreter and advocacy services may be helpful.

(https://www.bashhguidelines.org/media/1079/4450.pdf. Last accessed January 25, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

PSYCHOLOGICAL AND MENTAL HEALTH CONSEQUENCES

Victims of trafficking experience a host of psychological, mental health, and emotional distress. Depression, suicidal ideation, substance use, and anxiety are typically cited mental health problems [30]. Post-traumatic stress disorder (PTSD) is also common given the trauma many victims experience, including physical and/or sexual violence and abuse; victims forced into sex work experience continual, daily sexual assault [81]. In a study of 192 European women who were trafficked but who managed to escape, the overwhelming majority (95%) disclosed that they experienced physical and sexual violence during the time of their trafficked experience [73]. More than 90% reported sexual abuse, and 76% reported physical abuse.

Trafficked victims experience fear from the start of their capture through the transit phase and after they arrive at their destination. During the transit stage, many victims experience dangerous border crossings, risky types of transports, injury, beatings, and sexual assault [75]. Upon arrival to their destination, many trafficking victims have been socially isolated, held in confinement, and deprived of food [82]. All sense of security is stripped from them—their personal possessions, identity papers, passports, visas, and other documents are taken [75; 82]. The continual fear for their personal safety and their families' safety and the perpetual threats of deportation ultimately breed a sense of loss of control and learned helplessness. It is not surprising that depression, anxiety, and PTSD are common symptoms experienced by trafficked victims.

In a study of 164 survivors of human trafficking who returned to Nepal, the authors examined the extent to which they experienced PTSD, depression, and anxiety [83]. All of the survivors experienced some level of these disorders, but the survivors who were trafficked for sex experienced higher levels of depression and PTSD compared to those who were not trafficked for sex. In a study with Moldovan survivors of human trafficking, researchers found that six months after their return, 54% had a diagnosable mental health issue. Specifically, 35.8% met the diagnostic criteria for PTSD, 12.5% met the criteria for major depression, and 5.8% were diagnosed with an anxiety disorder [84].

There is also some evidence that trafficked victims may experience complex PTSD, a type of PTSD that involves an acute change of the victims' sense of self, their relationship with others, and their relationship with God or a higher being [85]. These persons direct anger inwardly (toward themselves) as well as toward their perpetrators, which results in a loss of faith in themselves and the world [82; 85; 86]. Perhaps due to self-directed anger and shame, some will engage in risky sexual behaviors, self-harm, and substance abuse. Some victims also have difficulty managing and expressing how they are feeling, while others experience dissociation [82].

Substance abuse is also common among victims. In interviews, trafficked women discussed how traffickers forced them to use substances like drugs and/or alcohol so they could work longer hours, take on more clients, and/or perform sexual acts that they could not normally perform [75]. Other victims used substances as a means to cope with their situations. Trafficked individuals who are gender and/or sexual minorities report shame, confusion, and sexual identity issues if forced into heterosexual relationships [86].

Children forced into labor experience grueling hours and are frequently beaten by their captors. Underage victims of domestic sex trafficking fluctuate through a range of emotions, including despair, shame, guilt, hopelessness, anxiety, and fear [87]. Depending upon the level of trauma, some engage in self-destructive behaviors like self-mutilation or suicide attempts. For some, their ambivalence toward the perpetrators may be confusing. On the one hand, they want to escape the abuse, yet simultaneously, they may have a sort of traumatic bond with the perpetrators [87].

Children forced into conscription will also experience a host of psychological symptoms. In a study comparing former Nepalese child soldiers and children who were never conscripted, former child soldiers experienced higher levels of depression, anxiety, PTSD, psychological difficulties, and functional impairments [88]. In another study of former child soldiers from the Congo and Uganda, one-third met the criteria for PTSD [49]. The researchers found there was a relationship between greater levels of PTSD symptoms and higher levels of feelings of revenge and lower levels of openness to reconciliation [49]. In-depth narrative interviews of former child soldiers from northern Uganda found that the children spoke of the violence and atrocities they witnessed without any emotion, as if they had removed themselves from their experiences [89]. This speaks to how the victims have to numb themselves psychologically in order to cope. The researchers also found that the children who lost their mothers were more traumatized by this experience than by the violence they witnessed as soldiers.

Some have argued that the diagnostic criteria of PTSD may not be easily applied to those from different cultures. As a result, it is important to assess for other psychiatric disorders, such as depression. Japan, for example, never used the PTSD diagnosis prior to 1995, despite the fact that they have a large and intricate mental health system [90]. Ultimately, PTSD cannot be universally applied to every culture and for every humanitarian crisis; therefore, if a human trafficking victim does not necessarily fall within the *Diagnostic and Statistical Manual of Mental Disorders* criteria for PTSD, one cannot necessarily conclude that they have not experienced trauma or are not traumatized [90].

SOCIAL CONSEQUENCES AND QUALITY OF LIFE

When rescued and attempting to reintegrate into their communities, victims of human trafficking often experience stigma, ostracism, and marginalization [88; 91]. For example, in Nepal, community members perceived returning child soldiers who had performed acts such as carrying dead bodies or coed sleeping as in violation of Hindu cultural norms [88]. One documentary following former child soldiers living in a refugee camp in northern Uganda found that preconceived notions and myths about children soldiers often led to ridicule and ostracism after they were liberated from the army and returned home.

However, girls who were recruited as soldiers, who were forced to have sex, or who return with children appear to be the most marginalized group [92]. In a qualitative study of former girl soldiers in Sierra Leone, researchers found that, compared to returning boy soldiers, girls were perceived to have violated gender norms and values about sexuality. Although psychologically and developmentally they were still children, the community perceived and treated them as "damaged" or "unclean" women. Their communities were not able to re-integrate them, despite the victimization they experienced. These girls lacked voice and experienced shame, marginalization, poverty, and powerlessness upon their return [92]. In a study of former child soldiers in Uganda, the children reported having difficulty finding jobs or getting married when they returned home. Girls who had been raped were stigmatized and made to feel unwelcome in their communities. Others stated that their community perceived them as murderers [50].

IDENTIFICATION AND ASSESSMENT

INTERACTION WITH VICTIMS

Healthcare providers are often the most likely to encounter a victim of human trafficking under circumstances that provide an opportunity to intervene, and victims may be encountered in most mental health and healthcare venues. One study estimated that 30% to 87.8% of victims accessed medical services at some point during their trafficking [93]. Survivors may seek care in hospital emergency rooms, at local mental health authorities, urgent care facilities, family planning clinics, or outpatient medical settings for a variety of issues, including sexually transmitted infections, pregnancy, depression (including suicidality), injuries resulting from assault, substance abuse-related issues, and PTSD [94]. Because medical and dental appointments may allow for more privacy than a victim's other encounters, they may represent a unique opportunity for healthcare providers to intervene.

Yet, many providers lack the training and confidence to identify and assist victims. In a survey of 110 emergency department physicians, nurses, and physician assistants, the majority (76%) reported having a knowledge of human trafficking, but only 13% felt equipped to identify a trafficking victim and only 22% were confident in their ability to provide satisfactory care for such patients [95]. Less than 3% had ever received any training on this topic. In a separate survey of healthcare and social service providers, only 37% had ever received training on identification of trafficking victims [96]. This lack of healthcare provider knowledge is the root of some victim's reluctance to disclose.

Because human trafficking and exploitation are, by nature, covert processes, the identification and rescue of the victim can be difficult. As stated, traffickers often move victims from one area to another to reduce the risk of identification, and one of the main problems with the assessment of such individuals is that practitioners may only have a one-time encounter with the victim [97]. Other provider challenges include language barriers, the hidden nature of the crime, lack of self-identification as a victim, confusing or contradictory laws/regulations, lack of organizational protocols, and stereotypes/misconceptions [98].

Several barriers exist that prevent survivors from self-disclosing their experiences, including [98]:

- Unable to self-identify
- Lack of knowledge of services
- Fear of retaliation
- Fear of law enforcement/arrest/deportation
- Lack of trust
- Shame/stigma
- Learned helplessness/PTSD
- Cultural/language barriers
- Lack of transportation

TRAUMA-INFORMED CARE

All interactions with patients, regardless of whether or not they are potential victims of trafficking, should be centered on the patient's experiences, needs, and preferences. Providing patient-centered care means that care will be respectful of and responsive to individual patient preferences, needs, and values and will reflect the patient's values. This should be considered at all stages of assessment, intervention, and continued care/follow-up.

It is important to use a trauma-informed approach when assessing and caring for potential victims, which requires that practitioners understand the impact of trauma on all areas of an individual's life [99]. Physical, emotional, and psychological safety is at the heart of trauma-informed care. This approach allows for trust-building and continued communication, two factors that are vital to ensuring that patients receive the care and support they require.

Being trauma-informed is a strengths-based approach that is responsive to the impact of trauma on a person's life. It requires recognizing symptoms of trauma and designing all interactions with victims of human trafficking in such a way that minimizes the potential for re-traumatization. This involves creating a safe physical space in which to interact with survivors as well as assessing all levels of service and policy to create as many opportunities as possible for survivors to rebuild a sense of control. Most importantly, it promotes survivor empowerment and self-sufficiency. Survivors should also have access to services that promote autonomy and are comprehensive, victim-centered, and culturally appropriate. Additionally, trafficking survivors share that one of the most important steps to being trauma-informed is to be survivor-informed [100].

POTENTIAL RED FLAGS

Bruises, scars, and other signs of physical abuse may be missed on examination, as victims are often beaten in areas hidden by clothing (e.g., the lower back) so as not to affect the victim's outer appearance. Physical trauma symptoms may be present, commonly on the torso, breast, and/or genital areas [101]. Burns, broken bones, pelvic pain, and/or STIs (particularly in children) may also be red flags [102]. However, more common physical injuries are also typical with other circumstances, making physical exam of limited value. The entire clinical picture should be considered.

It may also be helpful to assess for tattoos and/or other modifications (e.g., branding, piercings). Some perpetrators use tattoos to identify victims or to signify "ownership" [60].

With regard to episodic clinical encounters, recommendations for providing safe assessments in a culturally sensitive manner are lacking. The Department of Health and Human Services Administration for Children and Families maintains a useful website that addresses practical issues of human trafficking for allied professional groups, known as the Look Beneath the Surface Campaign [76]. Included are diagnostic and interviewing tips to help healthcare providers recognize and refer trafficking victims to appropriate services [76]. Emergency and primary care providers should be cognizant of clues that a patient may be the victim of trafficking and prepared to engage in a greater depth of inquiry with special attention to the following indicators [76; 102; 103; 104]:

- Does someone, other than family, who behaves in a controlling manner, accompany the patient? Traffickers attempt to guard and control most every aspect of the victim's life, while maintaining isolation from family, friends, and other common forms of human interaction.
- Are there inconsistencies in answers to basic questions (e.g., name, age, address)?
- Does the patient speak English? If not, has he or she recently been brought to this country, and from where? Many victims of human trafficking have recently been trafficked from other countries. As discussed, common sending countries/regions include Eastern Europe, Asia, Latin America, Africa, India, and Russia.
- If the patient is accompanied by someone other than a family member, who does the talking, and why? Attempt to interview and examine the patient separately and alone, using an interpreter if necessary. Probe in a sensitive manner for detailed information on the situation and relationship.
- Does the patient show signs of psychosocial stress (e.g., appears withdrawn, submissive, fearful, anxious, depressed)? Can the individual account for this?
- Are there visible signs of physical abuse (e.g., bruises, lacerations, scars)? How does the individual explain these?
- Does the patient lack a passport or other immigration and identification documentation (e.g., driver's license, social security number, visa)? If so, what explanation is given? To control victims' movements, traffickers often take away passports and any legal identification documents.
- What is the patient's home and work situation? Basic questions about what they eat, where they live and sleep, who else lives with them, and what work they do can be revealing. For example, "Can you leave your work or job situation if you wish?" or "When you are not working, can you come and go as you please?"
- Is the explanation given for the clinical visit consistent with the patient's presentation and clinical findings?
- Does the victim appear fearful when asked questions about citizenship, country of origin, immigration status, or residence? This may indicate a fear of deportation.
- If the victim is a minor, is s/he in school? Living with parents or relatives? If not, what reasons are given for these circumstances?

If answers to these questions indicate that an individual may be a victim of human trafficking, one should contact the National Human Trafficking Hotline at 1-888-373-7888. Under the child abuse laws, practitioners who are mandated reporters and who are suspicious that a minor is being abused

should immediately report the abuse. For more information regarding specific states' reporting requirements, please visit https://www.childwelfare.gov/resources/states-territories-tribes/state-statutes.

SCREENING QUESTIONS

Examples of questions to screen for human trafficking include [105; 106; 107]:

- Can you tell me about your living situation?
- Has anyone ever threatened you with violence if you attempted to leave?
- Does anyone force/require you to have sexual intercourse for your work?
- Has anyone ever threatened your family if you attempted to leave?
- Does anyone make you feel scared at work?
- Are you free to come and go as you wish?
- Does your home have bars on windows, blocked windows/doors, or security cameras?
- How many hours do you work?
- Have you ever worked without receiving payment you thought you would get?
- Do you owe your employer money?
- Do you have to ask permission to eat, sleep, use the bathroom, or go to the doctor?

The Polaris Project has developed a flow chart for the assessment of potential trafficking victims, available at https://www.traffickingresourcecenter.org/sites/default/files/Assessment%20Tool%20-%20Medical%20Professionals.pdf. Again, if a person is thought to be a victim, healthcare providers should follow workplace protocols and/or contact the National Human Trafficking Hotline at 1-888-373-7888 for next steps.

INTERVIEWING TRAFFICKED VICTIMS: BEST PRACTICE GUIDELINES

Service providers should repeatedly weigh the risks and benefits of various actions when interviewing human trafficking victims [70; 108; 109]. Survivor safety is of utmost importance, and a private conversation should be sought, if at all possible. It may be necessary to be discrete or nonchalant when requesting to speak with the victim alone, as angering the trafficker may result in negative consequences for the victim. If the agency has a policy to always speak to patients alone, this may be easier to explain. Other strategies to separate a possible victim from a companion include stating the need for a private exam or testing (e.g., radiology, urine test). A companion's assistance with paperwork may also be requested in an outside office or lobby. If the potential victim does not want to be alone or is reluctant to go to a private location, it is vital to respect her/his wishes.

In addition, the following interviewing recommendations were published by the World Health Organization to encourage service providers to continually and ethically promote human trafficking victims' safety during every phase of the interviewing process [102; 110]:

- Each victim and trafficking situation should be treated as unique; there are no standard templates of experiences. Listen carefully to the victim's story. Each story told is unique, and each patient will voice distinctive concerns. Believe each story, no matter how incredible it may seem. As rapport and trust build (perhaps very slowly), accounts may become more extensive.
- Always be safe and assume the victim is at risk of physical, psychological, social, and legal harm.
- Evaluate the risks and benefits of interviewing before starting the interviewing process. The interviewing process should not invoke more distress. In other words, the interviewing process should not end up re-traumatizing the victim.
- Provide referrals for services where necessary; however, it is necessary to be realistic and not make promises that cannot be kept. Trust is vital because it has been severed on so many levels for trafficking victims.
- Victims' readiness to change will not be based on what society defines as "ready" or on social expectations. Some victims will eagerly grasp new opportunities, while others may be fearful of potential traffickers' threats and be less receptive to help.
- Determine the need for interpreters and if other service providers should be present during the interviewing phase. Ensure that everyone involved is adequately prepared in their knowledge about human trafficking, how perpetrators control their victims, and how to ask questions in a culturally sensitive manner. Keep in mind that often times, traffickers will offer to help with the interpreting. Using interpreters from the same community of the victim should be avoided to prevent breaches in confidentiality.
- All involved should be prepared with an emergency plan. For example, is there a set plan for a victim who indicates he/she is suicidal or in danger of being hurt?
- Always be sure to obtain informed consent. Remember that the informed consent process is going to be unfamiliar to many victims. In addition, self-determination and autonomy have been compromised by continual threats and being forced to commit dehumanizing acts. Avoid using legal and technical jargon.

Providers should assume that human trafficking victims are describing their reality to the best of their ability, given the trauma they have experienced. Responses and behaviors (e.g., being guarded, defensive, belligerent) may be coping mechanisms [99].

SAFETY MEASURES

While it may be necessary to modify the approach depending on the situation, the Advocates for Human Rights recommends that safety plans for trafficking survivors [111]:

- Are personalized, realistic, involve friends and family that the victim trusts, and cover every aspect of the victim's life
- Focus on improving safety in the victims' environment
- Assess the current risk and identify current and potential safety concerns
- Create strategies for avoiding or reducing the threat of harm
- Outline concrete options for responding when safety is threatened or compromised, including:
  - Determining who victims will call in an emergency and memorizing those phone numbers or preparing a small card listing the numbers
  - Identifying where victims will go if there is an emergency
  - Identifying what victims will do if the trafficker contacts them after they leave the trafficking situation (e.g., retain messages, contact the police or a victim advocate)
  - Assessing how to handle safety issues when victims have family or friends, including those in another country, who are at risk of harm from the trafficker
- Are re-evaluated at various stages of the trafficking situation
- Reflect changing circumstances in the victim's life and changes in support or services (e.g., victims may have felt safe with a particular situation at the time of preparing the safety plan, but they may not feel safe in that same situation in the future)
- Address what victims will do in response to flashbacks or triggers, including those in any new workplace
- Strategize how to address and replace tech-nology, such as cell phones, that the trafficker provided or had access to (e.g., leaving phones in places victims are allowed to be or providing phones just for calling 911)

In addition, non-U.S. citizens should have access to an emergency contact in the United States (potentially a legal services provider) and plans for young children (i.e., a decision-making proxy). Youth victims may require housing assistance [111].

DOCUMENTATION

Ideally, the victim of human trafficking should be offered a formal forensic evaluation; this requires written documentation of informed consent. Injuries should be documented in photographs, diagrams, or sketches. A growing number of hospitals now employ dedicated forensic nurses as part of a multispecialty sexual assault team [112]. Often, however, these trained specialists are not the first professionals to interact with the patient. Consequently, all healthcare professionals, particularly those in an emergency care setting, should have an understanding of the principles that govern proper collection and preservation of evidence during the examination of an assault victim.

The initial clinical assessment includes a careful history and physical examination, followed by selected laboratory testing and radiographic studies as indicated by clinical findings. Examination of the forensic patient is conducted in a thorough head-to-toe or toe-to-head manner, with the intent of documenting every indication of injury related to the incident (no matter how insignificant and involving every part of the body) using a body-map or wound chart. The entire body surface should be palpated to identify areas of bruising that may not yet be visible. Documentation and collection of evidence typically occurs at the same time as the physical exam—as evidence is detected it should be collected.

Forensic documentation includes a written component, a diagrammatic component, and a photographic component. Each should accurately inform the other. The written component must be detailed, accurate, and objective; the diagrammatic component must be thorough and legible; and the photographic component must include a measurement scale, be representative of the evidence, and remain objective.

RESPONSE AND FOLLOW-UP

HEALTHCARE PROVIDERS' ROLE

Care and services provided to victims can be organized into three distinct categories: immediate and concrete services at the time of rescue; services related to recovery; and long-term services pertaining to reintegration [113]. When trafficking victims are rescued, a great deal of counseling services and practical, day-to-day assistance will be required. Housing, transportation, food, clothing, medical care, dental care, financial assistance, educational training, reunification (for those who wish to return to their homeland), and legal aid are some of the concrete services needed [24]. Practitioners should connect, coordinate, and case manage these services as much as possible. During this stage, it is also important to understand victims' needs, their strengths, and their risks and vulnerabilities [82].

Safety planning is also crucial in the immediate rescue stage. Traffickers may be continuing to try to locate some victims; placing victims in safe houses may be necessary [86]. The National Human Trafficking Hotline encourages that safety planning be based on the unique needs and circumstances of the individual. One should also take steps to ensure that one's own safety is also protected.

During the recovery and reintegration stages, as discussed, human trafficking victims experience an array of mental health and psychological issues. Mental health counseling is vital, but it is important to remember that the concept of counseling or talk therapy may be foreign to victims from non-Western cultures [70]. The expression of emotions may be in opposition to cultural values of emotional restraint, which can be intensified by feelings of shame and guilt resulting from experiences with sexual and physical assault. Beyond the paramount importance of the practitioner gaining the patient's trust, practitioners may educate patients about the counseling process and explore their patients' expectations about counseling, healing, and recovery [114]. As noted, victims' symptoms may not only be a manifestation of the trauma but also coping mechanisms to cope with self-blame, shame, and trauma [60].

Given differing cultural beliefs about healing, it is crucial that practitioners be open to alternative treatment and explore with patients the use of traditional healing methods [70]. There are many indigenous healing interventions victims may be using, including cultural rituals, faith healing, therapeutic touch, herbal remedies, and spiritual practices [115]. These interventions are multi-layered, taking into account the physical, psychological, communal, and spiritual [115]. These healing methods are historically rooted in specific cultures, and therefore, practitioners should become familiar with traditional healing methods and how they can be integrated with Western counseling techniques [114]. For example, given many cultural groups' beliefs that unmarried girls are defiled if raped, a cultural cleansing ritual may be needed as a first step to help a community accept a returning victim who was sexually assaulted during her trafficking experience [36]. After this ritual is performed, it is possible that both the patient and her family may be more open to counseling and other services.

Other trauma interventions that might be beneficial include cognitive-behavioral therapies, eye movement and desensitization reprocessing therapies, mindfulness techniques, and expressive therapies [60; 86].

Physicians, social workers, nurses, therapists, and counselors must be familiar with legal, case management, educational, job and life skills training, and housing services in the community. Human trafficking victims are not only unfamiliar with navigating the social service system, but many are also not proficient in English. Therefore, practitioners will serve as coordinators and advocates, linking necessary services. In one study, the majority of agencies had to rely on collaboration in order to refer clients [116]. Social workers and practitioners relied on word-of-mouth and community meetings to learn about services in order to better meet the needs of human trafficking victims. Furthermore, because many community organizations and agencies are not familiar with human trafficking, practitioners must take a primary role in educating colleagues about the complex dynamics of human trafficking.

It is important to remember that the evidence supporting interventions and therapies for victims of human trafficking is in its infancy [113]. Most efficacy studies of therapies and interventions do not involve experimental designs, which makes it difficult to draw definitive conclusions regarding efficacy. Future work is needed to develop and evaluate interventions that address the multilayered and complex needs of human trafficking survivors.

REFERRAL

The needs of human trafficking survivors are diverse, and healthcare professionals should be prepared to refer these individuals to a wide variety of services. In the initial period, acute injuries, mental health crises, and stabilization (e.g., housing, safety) are the greatest concerns. However, many victims experience chronic health and mental health issues related to their traumatization and will also require referral to services that will allow healing throughout their lifetimes.

As such, organizations and healthcare providers should work to build a trusted local network of resources, including substance abuse treatment centers, educational and career advancement services, financial support, PTSD/complex trauma assessment and treatment, and potentially law enforcement representatives with experience providing services to victims of human trafficking. In the state of Texas, statewide and local organizations and government offices are available to assist in building this network. A listing of these resources is available at the end of this course.

The National Human Trafficking Hotline (administered by Polaris) also maintains a National Referral Directory that is searchable by gender, nationality, age, type of trafficking, type of service(s), opportunities/training, and geographic location. The directory is available at https://humantraffickinghotline.org/en/find-local-services.

REPORTING

In addition to addressing crises and stabilization upon identification of a potential trafficking victim, healthcare providers should contact the National Human Trafficking Hotline. This hotline also provides warm transfers of mandatory reporters' intakes to the Texas Department of Family and Protective Services (DFPS), helps build intelligence on human trafficking in Texas, and continuously improves its referral directory of Texas resources for victims seeking assistance for themselves. There are more than 90 Texas service providers listed on the National Referral Directory, with more than 60 of those being listed publicly.

According to Texas Family Code 261.101, any person having cause to believe that a child's physical or mental health or welfare has been adversely affected by abuse or neglect (including human trafficking victimization) by any person is required to immediately make a report to law enforcement or DFPS [117]. Professionals who are licensed or certified by the state or who are employees of a facility licensed, certified, or operated by the state and who, in the normal course of official duties or duties for which a license or certification is required, has direct contact with children are required to make reports within 48 hours; this includes physicians, nurses, social workers, counselors, and pharmacists. Reporting cannot be delegated.

ROLES AND LIMITATIONS OF LAW ENFORCEMENT INVOLVEMENT

Victims of human trafficking should be empowered with choice whenever possible, including the ability to determine whether to participate in the criminal justice process [100]. Cases involving abuse or neglect at the hands of a traditional caregiver may be investigated by the DFPS, but all other cases must be handled by a law enforcement agency [118]. For victims who choose to participate in the criminal justice process, safety and protection considerations apply.

There are limitations to law enforcement involvement, particularly with victims who may be reluctant to trust these figures. It is important that the law enforcement contact be trained and experienced in the intricacies of human trafficking and complex trauma. While building a criminal case and prosecuting perpetrators is important, measures should be taken to avoid re-traumatizing the victim.

ORGANIZATIONAL PROTOCOLS

Whenever possible, facilities should create trauma-informed organizational protocols to ensure that human trafficking survivors receive the best possible care. These protocols should include guidelines for appropriate assessment, documentation, reporting, intervention, and referral and may be incorporated into existing protocols for interacting with potential victims of child abuse, violence, and/or sexual assault.

CONCLUSION

Human trafficking is a severe human rights violation. Because the roots of human trafficking are multifaceted, no one solution exists to eliminate this problem. Unfortunately, as the problem grows, practitioners will be confronted with the issue in their patient populations. Practitioners should be committed to the collaboration amongst disciplines to address poverty, racism, discrimination, and oppression in order to reduce the vulnerable positions of human trafficking victims and their families. Because of the social justice component in the codes of ethics of professionals such as physicians, nurses, social workers, psychologists, and counselors, all practitioners can play a key role in the individual, community, and systemic levels to help address this gross abuse of power. One way to begin is to educate oneself and one's respective disciplines about the global nature of human trafficking and the complex dynamics of the problem.

COURSE TEST - #97471 HUMAN TRAFFICKING AND EXPLOITATION: THE TEXAS REQUIREMENT

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 Hour activity must be completed by January 31, 2027.

1. Which of the following is an element of the United Nations definition of human trafficking?
- A) *Transport of the person*
- B) *Force or coercion of the victim*
- C) *Abuse and exploitation*
- D) *All of the above*

2. How is human smuggling different from human trafficking?
- A) *In smuggling, the individual has been forced or coerced into a country.*
- B) *In smuggling, the individual willingly volunteered to enter the new country.*
- C) *Specific gender differences exist, as those who get smuggled into the new country are typically men.*
- D) *The perpetrators who bring the individual into the new country often utilize legal means to get them in.*

3. What is domestic minor sex trafficking?
- A) *The selling of runaways for sexual services across international borders.*
- B) *The selling of minors to those in other countries for sex purposes and for financial gain.*
- C) *The selling, buying, and/or trading of children for sexual services within the United States.*
- D) *The selling and buying of minors for primarily domestic work, such as housekeeping, but that eventually turns sexually abusive.*

4. What is the main factor that differentiates sex workers and sex trafficking victims?
- A) *Sex trafficking victims tend to be younger than sex workers.*
- B) *Victims of sex trafficking often do not get paid for their sexual work, while sex workers do.*
- C) *Sex workers have more options in regards to sexual activity, partners, and the hours they prefer to work.*
- D) *Sex trafficking victims experience higher levels of physical and psychological abuse than their sex workers counterparts.*

5. Domestic servitude is a
- A) *form of forced labor.*
- B) *form of sexual trafficking.*
- C) *form of child work in many developing countries.*
- D) *term that refers to trafficking confined to the United States.*

6. Why do some traffickers prefer to recruit children to serve as soldiers?
- A) *They are inherently more violent.*
- B) *Studies show children have no moral conscience.*
- C) *Demographically, they make up a large percentage of the population.*
- D) *They tend to be more easily molded and submit to orders without question.*

7. How does digital technology play a role in human trafficking?
- A) *It helps to perpetuate the cycle of poverty.*
- B) *It makes identifying potential victims more difficult.*
- C) *The Internet can create a greater supply of slaves, which then brings down the cost.*
- D) *Young women may be purchased to perform sexual acts, with graphic images then sent via the Internet for purchase.*

8. Which of the following is NOT an example of how culture can contribute to human trafficking?
- A) *Beliefs that girls are less valued than boys makes them more dispensable.*
- B) *Values that emphasize collectivism may encourage victims to sacrifice themselves for their family.*
- C) *Myths that certain races or ethnicities are more erotic and exotic do not affect sex trafficking patterns.*
- D) *In some cultures, it is believed that children in lower socioeconomic/cultural groups should be taught early on to understand their positions in life.*

Test questions continue on next page ➞

9. Which of the following is a method of recruitment used by human traffickers?
- A) *Promises of employment*
- B) *Convincing poor families to sell their children*
- C) *Collaborating with storefronts who pretend they are employment agencies*
- D) *All of the above*

10. All of the following are common findings in trafficked women, EXCEPT:
- A) *Headaches*
- B) *Back and pelvic pain*
- C) *Unexplained euphoria*
- D) *Sexually transmitted infections (STIs)*

11. Which of the following is a common culture-based idiom of distress?
- A) *Depression*
- B) *Stigmatization*
- C) *Somatic symptoms*
- D) *Gynecologic problems that result from rape*

12. Child laborers who work in agricultural fields might be more susceptible to certain cancers due to
- A) *lack of sleep.*
- B) *poor nutrition.*
- C) *their rapid growth.*
- D) *their thinner epidermal layers.*

13. Which of the following statements about the psychological consequences of human trafficking is FALSE?
- A) *For some human trafficking victims, the feelings of shame lead to self-destructive behaviors.*
- B) *Post-traumatic stress disorder is a universal diagnostic category and should be used for all human trafficking victims.*
- C) *There seems to be an association between those who had greater levels of revenge and higher levels of PTSD among former child soldiers.*
- D) *Some victims may have substance abuse problems because traffickers may force sex trafficking victims to take drugs in order to perform sexual acts.*

14. One study estimated that what percentage of victims accessed medical services at some point during their trafficking?
- A) *3% to 8.8%*
- B) *23% to 40.7%*
- C) *30% to 87.8%*
- D) *87% to 100%*

15. Which of the following is a barrier that prevents trafficking survivors from self-disclosing their experiences?
- A) *Lack of transportation*
- B) *Cultural/language barriers*
- C) *Fear of law enforcement/arrest/deportation*
- D) *All of the above*

16. Which of the following statements regarding trauma-informed care is FALSE?
- A) *Trauma-informed care promotes survivor empowerment and self-sufficiency.*
- B) *Trauma-informed care involves interacting with survivors in all spaces, regardless of physical safety.*
- C) *Being trauma-informed is a strengths-based approach that is responsive to the impact of trauma on a person's life.*
- D) *Trauma-informed care requires recognizing symptoms of trauma and designing all interactions with victims of human trafficking in such a way that minimizes the potential for re-traumatization.*

17. If a practitioner suspects an individual is a victim of human trafficking, who should he/she contact?
- A) *The suspected perpetrator*
- B) *A local social service agency*
- C) *Executive director of the agency*
- D) *The National Human Trafficking Resource Center*

18. What should a practitioner consider when interviewing a victim of human trafficking?
- A) *Be spontaneous and act in accordance with what the victim says.*
- B) *Assess the level of secondary traumatization experienced by the victim.*
- C) *Bypass informed consent because it may be threatening to the victim.*
- D) *Assess if an interpreter is needed and ensure the interpreter is knowledgeable about the dynamics of human trafficking.*

19. Care and services provided to trafficking victims include
- A) *services related to recovery.*
- B) *long-term services pertaining to reintegration.*
- C) *immediate and concrete services at the time of rescue.*
- D) *All of the above*

20. In the initial period, referral of trafficking victims should focus on all of the following, EXCEPT:
- A) *Reintegration*
- B) *Acute injuries*
- C) *Mental health crises*
- D) *Stabilization (e.g., housing, safety)*

Child, Adolescent, and Adult Immunization Schedules

This course meets the Texas requirement for 3 hours of immunizations education.
This course meets the Louisiana requirement for 1 hour related to vaccine administration.

Audience
This course is designed for healthcare professionals working in all practice settings who may encourage patients to receive appropriate vaccinations and improve the overall vaccination rates.

Course Objective
There have been significant changes to the immunization schedules for children, adolescents, and adults, and the approval of multiple new vaccines has increased the opportunities for preventive care for both children and adults. However, coverage with some vaccines remains far below national goals, and outbreaks of vaccine-preventable diseases continue to occur. The purpose of this course is to provide healthcare professionals with the information necessary to identify patients who should be vaccinated and methods to increase vaccination coverage in outpatient practice.

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

1. Discuss the regulation of vaccines and identify the child, adolescent, and adult immunization schedules.
2. Explain the rationale behind the addition of new vaccines and changes to existing recommendations, and differences between current vaccines and newer options in development.
3. State contraindications to the administration of specific vaccines.
4. Explain recent safety data regarding vaccines.
5. Identify barriers to timely vaccination.
6. Describe methods for maximizing vaccination coverage.

Faculty
John J. Whyte, MD, MPH, is currently the Chief Medical Officer at WebMD. In this role, he leads efforts to develop and expand strategic partnerships that create meaningful change around important and timely public health issues. Previously, Dr. Whyte was the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research and the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. (A complete biography can be found at NetCE.com.)

Faculty Disclosure
Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

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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

Since the mid-1990s, a childhood vaccination schedule approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians has been published annually by the Centers for Disease Control and Prevention (CDC). A standardized adult immunization schedule has been published each year since 2002.

Over the years, there have been significant changes to the immunization schedules for children, adolescents, and adults. The approval of multiple new vaccines has increased the opportunities for preventive care for both children and adults. Yet, coverage with some vaccines remains far below national goals, and outbreaks of vaccine-preventable diseases continue to occur. The introduction of new vaccines, plus additional changes to the immunization schedules, makes it increasingly difficult for healthcare professionals to ensure that patients receive the recommended preventive care.

Changes in disease incidence illustrate the successes of widespread vaccination. Between 2000 and 2015, the incidence of acute hepatitis B declined in all age groups. Between 2015 and 2022, the rate has remained low and steady in most age groups. In 2022, the rate was highest (though still decreased from 2015) among persons 40 to 49 years of age and lowest among adolescents and children 19 years of age and younger [1]. Five years after the introduction of the heptavalent pneumococcal conjugate vaccine (PCV), the incidence of invasive pneumococcal disease (IPD) decreased by 82% among children 1 year of age and by 77% in children younger than 5 years of age [2]. The introduction of this vaccine in children appears to have reduced the incidence of IPD caused by covered strains in older adults as well [3].

However, for vaccines against communicable diseases to have the greatest impact, large proportions of the population must be covered. On a national scale, more than 90% of children have received age-appropriate doses of inactivated polio vaccine (IPV), measles/mumps/rubella (MMR), *Haemophilus influenzae* type b (Hib), hepatitis B (HepB), and varicella (VAR) vaccines by 24 months of age [4]. The Healthy People 2030 goal is to maintain a high level of coverage for these vaccines [114].

Certain vaccines remain significantly underutilized. For children birth to 24 months of age, completion of four doses of the heptavalent PCV (added to the immunization schedule in 2001) has been increasing but had reached only 82.3% in 2018, with no significant improvements since 2010 [4]. In 2018, full coverage with the hepatitis A vaccine (HepA) for all young children (by 35 months of age) was approximately 77.7%. Coverage with vaccines against rotavirus (by 8 months of age) was approximately 75.6% [4]. The influenza vaccination rate among children younger than 24 years of age remains low (60.6%), although this is higher than the overall rate for the U.S. population (49.2%). In 2018, 48% of adolescents were up to date on the human papillomavirus (HPV) vaccine [114]. This vaccine was considered too new to expect coverage to have met the national goal of 90% by 2020, particularly for teenage boys, for whom the recommendation was added in 2012. The Healthy People 2030 goal is for at least 80% coverage among all adolescents.

Undervaccination remains a concern among children even when national data show broad coverage. Coverage varies geographically and among different socioeconomic groups. Not all children receive their vaccinations on time, leaving them unnecessarily vulnerable [5]. Some parents opt out of vaccination entirely because of concerns about adverse effects or because they assume that the vaccine-preventable diseases are no longer a threat. There is also considerable misinformation about vaccine safety. However, recent measles outbreaks confirm that vaccination is still an important public health measure [4; 6].

In the adult population, vaccines are significantly underutilized (***Table 1***). For many years, the 23-valent pneumococcal polysaccharide vaccine (PPSV) has been recommended as a routine vaccination for adults 65 years of age and older, and

U.S. ADULT IMMUNIZATION RATES, 2018		
Vaccine	**Subgroup**	**Percent Vaccinated**
Influenza	50 to 64 years of age	46.9%
	65 years of age and older	68.8%
Pneumococcal disease	19 to 64 years of age, high risk	23.3%
	65 years of age and older	69.0%
Human papillomavirus	Women 19 to 26 years of age	52.8%
	Men 19 to 26 years of age	26.3%
Herpes zoster (shingles)	50–64 years of age	11.5%
	65 years of age and older	39.5%
Td or Tdap	19 years of age and older	62.9%
Hepatitis A	19 years of age and older	11.9%
Hepatitis B	19 years of age and older	30.0%
Td = diphtheria and tetanus toxoids, Tdap = diphtheria and tetanus toxoids and pertussis.		
Source: [7]		*Table 1*

multiple studies confirm that it can reduce the risk of IPD in this population. Yet according to estimates from the 2018 National Health Interview Survey, only 69.0% of adults in this age group have been vaccinated with PPSV [7]. Similarly, only about 47% of adults 50 to 64 years of age and about 69% of adults 65 years of age and older recalled receiving an influenza vaccination within the previous 12 months [7]. Even more than in the pediatric population, special effort may be needed to ensure that adults are aware of and have access to newer vaccines. In the first year after the herpes zoster vaccine was approved, only 2% of adults 60 years of age and older were vaccinated [8]. Attention to disparities is also needed. For example, Hispanics and non-Hispanic blacks are substantially less likely than whites to receive the influenza vaccine.

The following course will focus on the immunization schedules for children, adolescents, and adults, with an emphasis on vaccinations that are routine for most healthy persons. It will address the recommendations as of 2024, the rationale for the addition of new vaccines and for several potential new changes, contraindications and precautions as identified by the CDC and the ACIP, and methods to increase vaccination coverage in outpatient practice. The full schedules, including recommendations for patients with specific risk factors and catch-up schedules for patients who have missed doses, are available from the CDC.

Of note, the decision to vaccinate any individual patient should be based on a careful review of the patient's history and of current recommendations regarding each specific vaccine. The recommendation to vaccinate "all" children or adults with a given vaccine should not be interpreted to include those with contraindications or those for whom risks would outweigh benefits.

AN OVERVIEW OF IMMUNIZATION SCHEDULES

It is helpful to understand how vaccines are approved and then recommended as part of a schedule. The U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) is responsible for regulating vaccines in the United States. Vaccine clinical development follows the same general pathway as drugs and other biologics. A sponsor who wishes to begin clinical trials with a vaccine must submit an investigational new drug application (IND) to the FDA. The IND describes the vaccine, its method of manufacture, and the types of quality control testing done prior to administering the vaccine to humans. Also included is information about the vaccine's safety and ability to elicit an immune response in animal testing. In addition, the IND contains the proposed clinical protocol.

If the clinical trials are considered successful, a manufacturer will then submit a biologics license application. To be considered, the license application must provide the multidisciplinary FDA reviewer team with the efficacy and safety information necessary to make a risk/benefit assessment and to recommend or oppose the approval of a vaccine. In some cases, the FDA may present their findings to the Vaccines and Related Biological Products Advisory Committee. This non-FDA expert committee (consisting of scientists, physicians, biostatisticians, and a consumer representative) provides advice to the FDA regarding the safety and efficacy of the vaccine for the proposed indication. The FDA makes the final decision for/against approval but relies heavily upon the recommendation of its advisory committees.

It is also important to note that vaccine approval requires the provision of adequate product labeling to allow healthcare providers to understand the vaccine's proper use, including its potential benefits and risks. This information allows healthcare providers to communicate with patients and parents and to safely deliver the vaccine to the public.

FDA approval, however, does not guarantee that a vaccine will be considered routine. Rather, the CDC plays a critical role in determining the schedule. The ACIP consists of 15 experts in fields associated with immunization who have been selected by the Secretary of the U.S. Department of Health and Human Services to provide advice and guidance on the control of vaccine-preventable diseases. The Committee develops written recommendations for the routine administration of vaccines to children and adults in the civilian population; recommendations include age for vaccine administration, number of doses and dosing interval, and precautions and contraindications. The ACIP is the only entity in the federal government that makes such recommendations. These recommendations create the immunization schedules.

THE CHILD AND ADOLESCENT IMMUNIZATION SCHEDULE

In 1995, the first year that a harmonized childhood immunization schedule was published, there were only five items on the childhood immunization schedule, incorporating protection against nine diseases. Even then, a comment in the journal *Pediatrics* noted that the schedule's complexity could be confusing for both physician and patient [10]. The recommended shots were [11]:

- HepB
- Diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), or tetanus and diphtheria toxoids vaccine (Td), depending on age
- Hib
- Oral polio vaccine (OPV)
- MMR

To achieve full coverage, children required a total of 15 shots and four oral doses spread out over at least six visits. DTaP has since replaced DTP and IPV replaced OPV without any changes in the necessary visits.

However, with the many new changes that have occurred, parents may be taken by surprise by the number of doses and visits their youngest children need. In 2013, the child and adolescent schedules were combined for the first time, resulting in one schedule for persons 0 to 18 years of age, a format that continues today (***Table 2***). This combined schedule contains vaccines against up to 16 infectious agents. Expansion of flu vaccine recommendations means annual visits. Other vaccines require multiple visits in the first year of life and at 11 or 12 years of age. Depending on the specific options used, full coverage can involve more than three dozen shots. A "catch-up" schedule for children and adolescents who fall behind on immunizations has also been established (***Table 3***).

Major changes to the annually published childhood schedule in the last decade have included [9; 11]:

- 2003: Influenza vaccination was to be "encouraged" for all children 6 to 23 months of age.
- 2004: Influenza vaccination was recommended for all children 6 to 23 months of age and close contacts of children 0 to 23 months of age.
- 2006: Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine replaced Td for adolescents, meningococcal conjugate vaccine (MCV) was recommended for certain age groups, and HepA was expanded to include all children, not just those in selected areas.
- 2007: Rotavirus and HPV vaccines were added. Influenza vaccination was expanded to all children 6 to 59 months of age. A second VAR dose was recommended for all children.
- 2008: The recommendation for MCV was expanded to include immunization of all children 11 years of age and older at the earliest opportunity.
- 2009: The recommendation for influenza vaccination was expanded to include children 6 months to 18 years of age (beginning with the 2008–2009 season).
- 2012: HPV vaccination recommendation extended to include boys 11 or 12 years of age.
- 2016: Meningococcal B vaccine added for high-risk children and adolescents 10 years of age and older.
- 2022: Dengue vaccine added for children and adolescents 9 to 16 years of age living in endemic areas who have had a laboratory-confirmed dengue infection.

Other changes to the childhood schedule have added to the potential for confusion. For example, there are two different rotavirus vaccines, with different numbers of doses. Understanding the differences is essential to these vaccines' safe and effective use.

Until 2009, a shortage of Hib had led to many children missing their 12 to 15 month booster dose; however, a new vaccine to cover that dose was approved during 2009 and has led to a recommendation that children 12 months to 4 years of age receive a catch-up dose at the earliest opportunity [13]. In mid-2009, the ACIP also made some changes and clarifications to the recommendations for IPV, including extending the minimum interval between doses 3 and 4 from four weeks to six months and noting that the final dose in the IPV series should be given when the patient is 4 years of age or older, regardless of the number of previous doses [14]. This updated recommendation also includes clarifications regarding the use of combination vaccines.

RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS 0 THROUGH 18 YEARS OF AGE, 2024

Vaccine	Birth	1 mo.	2 mos.	4 mos.	6 mos.	9 mos.	12 mos.	15 mos.	18 mos.
Respiratory syncytial virus (RSV-mAb [Nirsevimab])	1 dose depending on maternal RSV vaccination status[h]				RSV-mAb (1 dose)				
Hepatitis B	HepB	HepB			Hep B				
Rotavirus			RV	RV	RV[a]				
Diptheria, tetanus, acellular pertussis			DTap	DTap	DTap			DTap	
Haemophilius influenzae type b			Hib	Hib	Hib[b]		Hib[b]		
Pneumococcal conjugate (PCV15, PCV20)			PCV15, PCV20	PCV15, PCV20	PCV15, PCV20		PCV15, PCV20		
Inactivated poliovirus			IPV	IPV	IPV				
COVID-19					1 or more doses of updated (2023–2024) vaccine				
Influenza					IIV4 (yearly, 1 or 2 doses)				
Measles, mumps, rubella					MMR		MMR		
Varicella							VAR		
Hepatitis A					HepA[f]		HepA (2 doses)[c]		
Meningococcal ACWY			MenACWY-CRM (≥2 mos), MenACWY-TT (≥2 years)[d]						

RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS 0 THROUGH 18 YEARS OF AGE, 2024

Vaccine	19–23 mos.	2–3 yrs.	4–6 yrs.	7–8 yrs.	9–10 yrs.	11–12 yrs.	13–15 yrs.	16–18 yrs.
Diptheria, tetanus, pertussis			DTap			Tdap		
Haemophilius influenzae type b			Hib					
Pneumococcal conjugate			PCV15, PCV20					
Inactivated poliovirus			IPV					
Influenza	IIV4 (yearly, 1 or 2 doses)	IIV4 or LAIV (yearly, 1 or 2 doses)			IIV4 or LAIV (yearly, 1 dose)			
Measles, mumps, rubella			MMR					
Varicella			VAR					
Hepatitis A	HepA[c]	HepA						
Human papillomavirus					HPV[e]	HPV[e]		
Meningococcal ACWY	MenACWY-CRM, MenACWY-TT[d]					MenACWY		MenACWY
Meningococcal B						MenB-4C, MenB-FHbp		
Respiratory syncytial virus						Seasonal administration during pregnancy		
Dengue					DEN4CYD[g]			
Mpox								Mpox[i]

[a] If RV-1 is used, administer a 2-dose series at 2 and 4 months of age. If RV-5 is used, administer a 3-dose series at ages 2, 4, and 6 months.
[b] Administer a 3- or 4-dose Hib vaccine primary series and a booster dose to all infants. The primary series doses should be administered at 2, 4, and 6 months of age; however, if PRP-OMP is administered at 2 and 4 months of age, a dose at age 6 months is not indicated. One booster dose should be administered at age 12 through 15 months.
[c] Initiate the 2-dose HepA vaccine series for children aged 12 through 23 months; separate the 2 doses by 6 to 18 months.
[d] Minimum age: 2 months for Menveo (MenACWY-CRM) and 2 years for MenQuadfi (MenACWY-TT).
[e] Administer 2-dose series of HPV vaccine on a schedule of 0 and 6–12 months to all adolescents 11 to 12 years of age (minimum age: 9 years). A 3-dose series (0, 1–2, and 6 months) is recommended for persons who initiate at 15 years of age or later.
[f] For infants traveling to countries with high or intermediate endemic hepatitis A, 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between 12 and 23 months of age.
[g] A 3-dose series (0, 6, and 12 months) only for those living in dengue-endemic areas AND with laboratory confirmation of previous dengue infection.
[h] For infants born in October through March whose mother did not receive RSV vaccine, who received the vaccine less than 14 days prior to delivery, or whose RSV vaccination status is unknown should receive 1 dose nirsevimab within one week of birth. For infants born between April and September whose mothers fit these criteria, 1 dose nirsevimab should be administered shortly before start of RSV season. All infants born to mothers who received RSV vaccine at least 14 days prior to delivery generally do not require vaccination.
[i] A 2-dose series administered 28 days apart recommended only for those 18 years of age and older who are at risk for Mpox infection.
□ = Range of recommended ages. ▭ = Certain high-risk groups only.

Source: [12] *Table 2*

CATCH-UP IMMUNIZATION SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 18 YEARS WHO START LATE OR WHO ARE MORE THAN 1 MONTH BEHIND, 2024					
Vaccine	**Minimum Age for Dose 1**	**Minimum Interval Between Doses**			
		Dose 1 to 2	**Dose 2 to 3**	**Dose 3 to 4**	**Dose 4 to 5**
Children 4 months through 6 years of age					
Hepatitis B	Birth	4 weeks	8 weeks and at least 16 weeks after first dose. Minimum age for final dose: 24 weeks.	--	--
Rotavirus	6 weeks Maximum age for first dose: 14 weeks, 6 days	4 weeks	4 weeks Maximum age for final dose: 8 months, 0 days	--	--
Diphtheria, tetanus, pertussis	6 weeks	4 weeks	4 weeks	6 mos.	6 mos. (if necessary)
Haemophilius influenzae type b	6 weeks	4 weeks (if dose before 1st birthday). 8 weeks (as final dose) if first dose at 12 to 14 mos. If first dose at ≥15 mos., no further doses needed.	4 weeks (if current age <12 mos. and first dose administered at <7 mos. and at least one previous dose was PRP-T, DTaP-IPV-Hib-HepB, or unknown). 8 weeks and age 12 mos. through 59 mos. (as final dose) if current age is <12 mos. and first dose administered between 7 and 11 mos.; OR if current age is 12 through 59 mos. and first dose administered before 1st birthday and second dose administered at <15 months; OR if both doses were PRP-OMP and were administered before 1st birthday If previous dose at ≥15 mos., no further doses needed.	8 weeks (as final dose), only for children age 12 through 59 mos. who received 3 doses before 1st birthday.	--
Pneumococcal	6 weeks	4 weeks (if first dose before 1st birthday). 8 weeks (as final dose for healthy children) if first dose at ≥12 mos. No further doses needed for healthy children if first dose at ≥24 mos.	4 weeks (if current age <12 mos. and previous dose given at <7 mos.) 8 weeks (as final dose for healthy children) if current age ≥12 mos. and previous dose given at 7 to 11 mos. No further doses needed for healthy children if previous dose at ≥24 mos.	8 weeks (as final dose), only for children 12 through 59 mos. who received 3 doses before 12 mos. or for children at high risk who received 3 doses at any age.	--

Table 3 continues on next page

CATCH-UP IMMUNIZATION SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 18 YEARS WHO START LATE OR WHO ARE MORE THAN 1 MONTH BEHIND, 2024 *(Continued)*

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to 2	Dose 2 to 3	Dose 3 to 4	Dose 4 to 5
Inactivated poliovirus	6 weeks	4 weeks	4 weeks if current age <4 yrs. 6 mos. (as final dose) if current age >4 yrs.	6 mos. (Minimum age for final dose: 4 years)	--
Meningococcal ACWY	2 months for MenACWY-CRM, 2 years for MenACWY-TT	8 weeks[a]	[a]	[a]	--
Measles, mumps, rubella	12 mos.	4 weeks	--	--	--
Varicella	12 mos.	3 mos.	--	--	--
Hepatitis A	12 mos.	6 mos.	--	--	--
Persons 7 through 18 years of age					
Tetanus, diphtheria; tetanus, diphtheria, acellular pertussis	7 years	4 weeks	4 weeks if first dose DTaP/DT before 1st birthday. 6 mos. (as final dose) if first dose of DTaP/DT or Tdap/Td at ≥12 mos.	6 mos. if first dose DTaP/DT before 1st birthday	--
Human papillomavirus	9 years	Routine dosing intervals are recommended.			
Hepatitis A	--	6 mos.	--	--	--
Hepatitis B	--	4 weeks	8 weeks and at least 16 weeks after first dose		
Inactivated poliovirus	--	4 weeks	6 mos. A fourth dose is not necessary if the third dose was administered at ≥4 years and at least 6 months after the previous dose.	A fourth dose indicated only if all previous doses administered <4 yrs. OR if third dose administered <6 mos. after second dose	--
Meningococcal ACWY	--	8 weeks	--	--	--
Measles, mumps, rubella	--	4 weeks	--	--	--
Varicella	--	3 mos. if age <13 years OR 4 weeks if age ≥13 years	--	--	--
Dengue	9 years	6 mos.	6 mos.		

[a] Administer MenACWY vaccine at age 13 through 18 years if not previously vaccinated. If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses. If the first dose is administered at age 16 years or older, a booster dose is not needed.

Source: [12] *Table 3*

RECOMMENDED ADULT IMMUNIZATION SCHEDULE BY VACCINE AND AGE GROUP, 2024					
Vaccine	**19–23 years**	**24–26 years**	**27–49 years**	**50–64 years**	**65 years and older**
COVID-19	1 or more doses of updated vaccine				
Influenza (IIV4, RIV4, or LAIV4)	1 dose (IIV4, RIV4, or LAIV4) annually[a]			1 dose (IIV4 or RIV4) annually[a]	
Respiratory syncytial virus	Seasonal RSV during pregnancy only				RSV[c] RSV[a]
Tetanus, diphtheria, pertussis (Td or Tdap)	One dose of Tdap, then boost with Tdap or Td every 10 years				
	One dose Tdap during each pregnancy; one dose Td for wound prophylaxis[a]				
Varicella	2 doses (if born in 1980 or later)[a]			2 doses[b]	
Human papillomavirus	2 or 3 doses[a]		2 or 3 doses[c]	—	—
Zoster (RZV)	2 doses (if immunocompromised)[b]			2 doses	
Measles, mumps, rubella	1 or 2 doses (if born 1957 or later)[a]				—
Pneumococcal 13-valent conjugate (PCV15, PCV20, PPSV23)	1 dose PCV20 OR 1 dose PCV15 followed by PPSV23[b]				1 dose PCV20 OR 1 dose PCV15 followed by PPSV23[a]
Hepatitis A	2,3, or 4 doses[b]				
Hepatitis B	2, 3, or 4 doses				2, 3 or 4 doses[b]
Meningococcal ACWY	1 or 2 doses, then booster[b] every 5 years				
Meningococcal B (MenB)	2 or 3 doses[c]	2 or 3 doses[b]			
Haemophilus influenzae type b (Hib)	1 or 3 doses[b]				
Mpox	2 doses[b]				

[a]For all patients in this category who lack evidence of immunity.
[b]Recommended if other risk factor is present.
[c]Recommended based on clinical decision-making.

Source: [19] *Table 4*

THE ADULT IMMUNIZATION SCHEDULE

As noted, the adult immunization schedule was created in 2002 to bring together the recommendations for routine vaccination of adults and to help healthcare professionals recall the specific needs of patients in certain chronic disease groups. The intention was to provide an up-to-date tool for providers to use in assessing patients' vaccination needs, creating standing orders and reminder systems, and otherwise reducing missed opportunities for vaccination [15].

The original adult schedule had a relatively short list of routine vaccinations for healthy persons, including [11]:

- Td every 10 years
- Annual influenza vaccine for adults 50 years of age and older
- PPSV for adults 65 years of age and older, with 1 booster for certain patients
- MMR (up to age 49 years) and varicella for those who are susceptible

Since that time, several changes have been made (***Table 4*** and ***Table 5***). The recommendation for routine vaccination against influenza was temporarily changed to age 65 years and older due to a vaccine shortage, but it has now returned to include all patients 6 months of age and older. Tdap is now recommended in lieu of one Td dose for adults up to 64 years of age. HPV vaccine is recommended for women and men up to 26 years of age, and the herpes zoster vaccine is routine for adults 60 years of age and older.

Since 2009, annual influenza vaccination has been recommended for all persons 6 months of age and older. The 2023–2024 influenza vaccine contained an H1N1-like antigen as well as H3N2 and two B antigens [20].

VACCINES AND RECOMMENDATIONS

Given the large number of vaccines now recommended, both parents and adult patients often have concerns about whether all the doses are needed. The following review of the rationale behind the changes to the child, adolescent, and adult immunization schedules is intended to help clinicians improve their own understanding and explain the rationale to patients.

VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS, UNITED STATES, 2024					
Vaccine	**Pregnancy**	**Immuno-compromised (excluding HIV)**	**HIV infection**		**Men who have sex with men (MSM)**
			CD4+ <200 cells/mcL	**CD4+ ≥200 cells/mcL**	
COVID-19	1 or more doses of updated vaccine[a]				
Tetanus, diphtheria, pertussis (Td or Tdap)	1 dose Tdap each pregnancy	1 dose Tdap, then boost with Td every 10 years[a]			
Human papillomavirus (HPV)	Delay	2 or 3 doses through 26 years of age[a]			
Varicella	Contraindicated			2 doses[a]	
Zoster (RZV)	–	2 doses at 19 years of age		–	2 doses[a]
Measles, mumps, rubella	Contraindicated			1 or 2 doses[a]	
Influenza	1 dose annually[a] (LAIV contraindicated)				1 dose annually[a]
Respiratory syncytial virus (RSV)	Seasonal administration[a]	Seasonal administration[c]			
Pneumococcal (PCV15, PCV20, PPSV23)	–	1 dose PCV15 followed by PPSV23 or 1 dose PCV20[a]			Vaccinate if other risk factors[b]
Hepatitis A	2 or 3 doses[b]	–	2 or 3 doses[a]		
Hepatitis B	3 doses[b]		3 doses[a]		
Meningococcal ACWY	–		1 or 2 doses, then booster every 5 years[a]		–
Meningococcal B (MenB)	Exercise precaution	–			
Haemophilus influenzae type b (Hib)	–	3 doses post-stem cell transplant recipients only[a]	–		
Mpox	2 doses[b]				

VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS, UNITED STATES, 2024 *(Continued)*					
Vaccine	**Heart disease, lung disease, chronic alcoholism**	**Asplenia, complement deficiencies**	**Chronic liver disease**	**Diabetes, end-stage renal disease, hemodialysis**	**Healthcare personnel**
COVID-19	1 or more doses of updated vaccine[a]				
Tetanus, diphtheria, pertussis (Td/Tdap)	1 dose Tdap, then boost with Td or Tdap every 10 years[a]				
Human papillomavirus (HPV)	2 or 3 doses through 26 years of age[a]				
Varicella	2 doses[a]				
Zoster (RZV)	2 doses ≥50 years[a]				
Measles, mumps, rubella	1 or 2 doses[a]				
Influenza	1 dose annually (exercise precaution with LAIV)[a]	1 dose annually (LAIV contraindicated)[a]	1 dose annually (exercise precaution with LAIV)[a]		1 dose annually[a]
Respiratory syncytial virus (RSV)	Seasonal administration[c]				
Pneumococcal polysaccharide (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 or 1 dose PCV20[a]				1 dose PCV15 followed by PPSV23 or 1 dose PCV20[b]
Hepatitis A	2 or 3 doses[b]		2 or 3 doses[a]	2 or 3 doses[b]	
Hepatitis B	2, 3, or 4 doses depending on vaccine or condition[a]				
Meningococcal ACWY	–	1 or 2 doses, then booster every 5 years[a]	–		
Meningococcal B (MenB)	–	2 or 3 doses[a]	–		
Haemophilus influenzae type b (Hib)	–	1 dose for asplenia only	–		
Mpox	2 doses[b]				

[a] For all patients in this category who lack evidence of immunity.
[b] Recommended if other risk factor is present.
[c] Recommended based on shared clinical decision-making.

Source: [19] *Table 5*

SEASONAL INFLUENZA

Recommendation for Children: Influenza vaccine is recommended annually for children 6 months through 18 years of age. Two doses, separated by at least four weeks, should be given to children if they are receiving influenza vaccine for the first time. Also give two doses if the child was vaccinated for the first time the prior season but received only one dose. For the 2023–2024 season, use of live attenuated influenza vaccine (LAIV) may be considered for children 2 years of age and older.

Recommendation for Adults: Vaccination is recommended annually for all adults without a contraindication with inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live attenuated influenza vaccine (LAIV). Other options include high-dose or adjuvanted IIV for adults 65 years of age or older. Women who are or may become pregnant should not receive LAIV.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Advisory Committee on Immunization Practices (ACIP), routine annual influenza vaccination is recommended for all children 6 months through 18 years of age.

(https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf. Last accessed May 24, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

The expansion of the recommended ages for the vaccination of children and adults against influenza is one of the most significant changes to the schedule in recent years. It requires an annual visit to a healthcare provider, including among older children and young adults who typically have low rates of physician visits.

The ACIP considered multiple factors in making this recommendation. First, according to accumulated evidence, the influenza vaccine appears to be both safe and effective, with the benefits of vaccination outweighing the small risk of adverse effects [21]. Widespread vaccination is also intended to lower the social and economic impact of influenza. The number of missed days of school for children and missed days of work for parents is substantial. Physician visits for the flu may lead to a prescription for antibiotics—treatment that is unnecessary and potentially dangerous.

The recommendation is also intended to simplify the decision to advise vaccination for children [21]. In previous years, vaccination was recommended for a number of groups with specific risk factors. These included older children with certain medical conditions and children who were close contacts of people who should be immunized. Making vaccination routine for all children is expected to lead to a 50% increase in coverage for those children who have a specific risk-based or contact-based indication.

Another change, for both children and adults, was the development of LAIV, a nasal-spray vaccine that can be easier for some patients to accept than an injection [22]. Data from the 2015–2016 flu season found an only 3% efficacy rate with LAIV (compared with 63% with IIV), and LAIV was not recommended between the 2015 and 2018 seasons [19; 20]. However, the 2018–2019 influenza guideline reintroduced LAIV as an option for persons 2 to 49 years of age for whom it is appropriate, and it remains an option in the 2023–2024 guideline [20]. This excludes women who are pregnant and those with HIV, immunocompromise, asplenia, and/or complement deficiencies.

In the past, egg allergy (beyond urticaria) was considered a contraindication or cause for additional safety measures when influenza vaccination was considered. However, it is now recommended that all persons 6 months of age or older with egg allergy should receive any influenza vaccine (egg-based or non-egg-based) that is otherwise appropriate for the recipient's age and health status [20]. It is no longer recommended that persons who have had an allergic reaction to egg involving symptoms other than urticaria should be vaccinated in an inpatient or outpatient medical setting supervised by a healthcare provider who is able to recognize and manage severe allergic reactions if an egg-based vaccine is used.

TETANUS/DIPHTHERIA/PERTUSSIS

Recommendation for Children: DTaP is recommended at 2, 4, 6, and 15 to 18 months of age (or as early as 12 months, if 6 months have passed since the last dose) and at 4 to 6 years of age. Tdap is recommended at 11 to 12 years for children who have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose and for older children who have not received a dose. If a child has already received Td, a five-year interval before Tdap is encouraged unless pertussis protection is specifically needed.

Recommendation for Adults: Td or Tdap booster every 10 years. Tdap replaces one Td dose for adults who have not already received Tdap. (See immunization schedule for special situations, including adults who have not received primary childhood vaccination and pregnant women.)

The inclusion of Tdap on the adult immunization schedules may create confusion because it replaces a dose of Td that was previously routine and patients may be uncertain about which vaccine they received. However, Tdap also has the potential to make an important impact on the public's health [23]. In the past, vaccination against pertussis was given only during young childhood. However, immunity against pertussis declines within about 5 to 10 years [23; 116]. Reported cases of pertussis increased steadily from the 1980s to a peak in 2014. In 2021, 2,116 cases were reported—a decrease of more than 88% since 2019—but many more go undiagnosed and unreported [24]. Infants younger than 1 year of age are at highest risk and continue to have the highest reported rate of pertussis; nearly half require hospitalization. Adolescents 11 to 19 years of age and adults 20 years of age and older accounted for approximately 66.2% of reported cases in 2021; cases among

children 7 to 10 years of age accounted for approximately 3.5% of reported cases [24]. Adults may also have complications including pneumonia, rib fracture, and loss of consciousness ("cough syncope") [25]. The true risks are somewhat unclear, however, because cases without a classic presentation are less likely to be diagnosed and reported.

The primary objective of the ACIP in recommending Tdap for adolescents is to protect individual adolescents against pertussis while continuing the standard protection against tetanus and diphtheria [23]. An important secondary goal is to reduce the reservoir of pertussis within the population as a whole. This may be particularly important for infants. The recommendation for adults was put in place primarily to protect individual adults against pertussis and also to reduce the reservoir of pertussis [25]. Widespread immunization of adults may also reduce the impact of pertussis on healthcare facilities and other institutional settings.

The recommended timing of Tdap vaccination takes into account recommendations for the administration of other tetanus and/or diphtheria toxoid-containing vaccines, including MenACWY, because of an association between frequent doses of such vaccines and a risk of increased local and systemic reactogenicity [23].

HUMAN PAPILLOMAVIRUS

Recommendation for Adolescents: HPV vaccine is recommended for girls and boys 11 to 12 years of age and for older adolescents who have not yet been vaccinated. Children 9 to 10 years of age may also be vaccinated.

Recommendation for Adults: HPV vaccine is recommended for adults up to 26 years of age who have not completed the vaccine series. HPV vaccine is also recommended for those 27 to 45 years of age if desired or if a risk factor is present.

When it was first added, there was significant public controversy over the inclusion of the HPV vaccine on the adolescent immunization schedule. Some parents remain concerned about the vaccine's safety or about the possibility of promoting sexual activity among young teens. Meanwhile, in some places this vaccine is now required for school attendance, although exemptions are generally allowed [27].

Statistics regarding HPV infection and cancer illustrate the rationale behind the vaccine itself. About 13,820 cases of cervical cancer will be diagnosed in the United States in 2024, and more than 4,360 will die from the disease [28]. The CDC estimates that 46,700 cancers attributable to HPV occur each year, including (in order of frequency) cancer of the oropharynx, cervix, anus, vulva, penis, and vagina [16].

There is one HPV vaccine available in the United States: Gardasil 9, which is approved for use in individuals 9 to 45 years of age [12; 19; 113]. Cervarix was a bivalent vaccine covering HPV types 16 and 18; however, this vaccine is no longer available in the United States [12; 30]. Quadrivalent Gardasil (no longer available in the United States) was a quadrivalent vaccine covering types 6, 11, 16, and 18 [31]. In 2014, a 9-valent HPV recombinant vaccine (Gardasil 9) was approved for use in individuals 9 to 26 years of age and added protection to HPV types 31, 33, 45, 52, and 58 in addition to those types covered by the original Gardasil [108; 113]. In 2018, the FDA approved expanded use of Gardasil 9 to include women and men up to 45 years of age [113]. Three-fourths of cervical cancers are squamous cell tumors, and HPV 16 and 18 account for about 68% of these [32]. The rest are adenocarcinomas, and HPV types 16 and 18 account for about 83% of these tumors [32]. The increased coverage of the 9-valent vaccine has the potential to prevent up to 90% of oropharyngeal, cervical, anal, vulvar, penile, and vaginal cancers [108].

Epidemiologic data on HPV incidence and age of sexual debut suggest that the pre-teen years are an appropriate time to begin HPV protection [32]. Genital HPV is the most common sexually transmitted infection in the United States, with 13 million new infections among people ≥15 years of age each year [95]. Teens and young adults are particularly at risk; about half of those infections occur in individuals 15 to 24 years of age [32]. One multisite, clinic-based study of sexually active females found the highest prevalence of HPV in girls 14 to 19 years of age. In another study, using a representative, population-based sample, HPV prevalence was 26.9% among sexually active women 18 to 25 years of age [33]. The prevalence of types 16 or 18 was 7.8%. Another study, also intended to be representative of the general population, found that the prevalence of HPV was 26.8% for women 14 to 59 years of age and nearly 45% among women 20 to 24 years of age [34]. In the overall study population, the prevalence of type 16 was 1.5%, and type 18 was 0.8%.

An important consideration in protecting adolescents who are not yet sexually active is that HPV infection is common within the first few years after sexual debut [32]. In addition, studies have shown high antibody titers with vaccination at age 11 to 12 years. 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 [17]. Considering the modest uptake of this vaccine, the potential impact is significant.

The recommendation to vaccinate young adults takes into account the fact that many will already be sexually active and may have been exposed to one or more types of HPV. Young adults who are not yet sexually active can receive the full benefit of vaccination. In addition, it is likely that many individuals who are infected have not yet encountered each of the vaccine-covered types, so they can receive at least partial benefit [35; 36]. The recommendation to vaccinate adults to the age of 26 years reflects the safety and efficacy testing on which the

initial vaccines' approvals were based [30; 31; 37]. Use in older individuals is also effective, and many patients will benefit from vaccination at 27 to 45 years of age. Medical professionals can inform patients of the option to receive the vaccine series or to complete the series, help assess the benefits and individual risk factors, and facilitate decision-making. As noted, the HPV vaccine remains significantly underutilized as of 2024.

ROTAVIRUS

Recommendation for Children: Rotavirus vaccine is recommended for infants 6 weeks to 14 weeks of age (maximum age for first dose: 14 weeks, 6 days). The last dose should be given by age 8 months, 0 days.

A rotavirus vaccine was first added to the immunization schedule in 1999 but was quickly taken off the market due to concerns about intussusception. The two available vaccines have each been tested in hundreds of thousands of infants [38; 39]. A large-scale study completed in 2014 found a slight increase in risk with RV5 (1.5 excess cases of intussusception per 100,000 recipients of the first dose) and some evidence of an elevated risk with RV1 [38]. However, these data should be considered in light of the benefits of vaccination. In an effort to maximize safety, these vaccines have a narrow age range for administration, reflecting the ages of the children in the large safety studies.

In adding rotavirus vaccination to the routine immunization schedule, the ACIP observed that rates of illness are similar in industrialized and less developed countries, suggesting that public health measures such as clean water supplies and good hygiene are not enough to control rotavirus disease [40]. Further, there is a high level of morbidity due to rotavirus in the United States in spite of available medical care. In the years before vaccination was available, rotavirus was responsible for approximately 20 to 60 deaths each year, 55,000 to 70,000 hospitalizations, more than 200,000 emergency department visits, 400,000 physician visits, and direct and indirect costs of approximately $1 billion [40; 41].

The vaccines are designed to mimic the effect of a first bout of rotavirus, which is usually the most serious [40]. Subsequent bouts of symptomatic infection can occur after a first natural infection, but they tend to be milder. As such, vaccination is not expected to prevent disease entirely but to reduce the severity of symptoms, the need for medical care, and the risk of serious sequelae, including hospitalization and death.

In 2009, the age parameters for vaccine administration were adjusted to harmonize the schedules of the two approved rotavirus vaccines [40]. One is a pentavalent reassortant vaccine based on a bovine rotavirus, often abbreviated as RV5. The other is a live, attenuated human rotavirus vaccine, often abbreviated as RV1. RV5 has a three-dose schedule, while RV1 requires two doses [41]. The maximum ages for these vaccines are somewhat different, according to their prescribing information, but an ACIP workgroup has concluded that safety and efficacy are unlikely to be affected if the same age limits are used for both [40].

MENINGOCOCCAL DISEASE

Recommendation for Children: MenACWY is recommended routinely for children 11 to 18 years of age, for older children who have not yet been vaccinated, and for children 6 weeks to 10 years of age in certain risk groups. MenB vaccination is recommended for children 10 to 18 years of age in certain risk groups. In addition, young adults 16 to 23 years of age (preferred age range: 16 to 18 years) may be vaccinated to provide short-term protection against most strains of serogroup B meningococcal disease.

Recommendation for Adults: MenACWY vaccine is recommended for adults 19 years of age and older with increased risk for meningococcal disease, including military recruits, freshmen college students living in dormitories, persons without a spleen or with a damaged spleen, those with terminal complement deficiency, and persons traveling to or residing in countries in which the disease is common. Revaccination with MenACWY every five years is recommended for adults previously vaccinated who remain at increased risk of infection. MenB vaccine is recommended for adults with certain risk factors, including all adults with anatomical or functional asplenia or persistent complement component deficiencies.

Historically, before widespread vaccination, there were about 1,400 to 2,800 cases of meningococcal disease in the United States each year [42]. Although not a common illness, meningococcal disease has a rapid course and a high degree of mortality, with a case-fatality ratio of about 10% to 14%. Among survivors, 11% to 19% will experience serious sequelae, such as neurologic deficit, deafness, or loss of a limb [43]. The degree of severity means that, in addition to putting the patient's life at risk, each case requires a substantial public health effort to identify additional cases quickly and prevent the disease from spreading [44].

There are two main types of serogroup A, C, W, and Y meningococcal vaccine: MenACWY and MPSV. However, MPSV is no longer available in the United States. The two available vaccines are MenACWY-TT (≥2 years) and MenACWY-CRM (≥2 months) [19; 45]. MenACWY vaccines cover serogroups C, Y, A, and W-135 [44]. In the United States, serogroups C, Y, and B have each been responsible for about one-third of cases overall.

Incidence of meningococcal disease also increases during adolescence, and this group is the main focus of the recommendations for vaccination with MenACWY. Among people 11 years of age and older, 75% of cases are caused by group C, Y, or W-135, which are all covered by the vaccine [42]. The original recommendation for the use of MenACWY focused on certain age groups: children 11 to 12 years of age, children entering high school, and college freshmen who would be living in dorms. These specifications were created because of concerns about there being a short supply of vaccine during the first few years of production [47]. Now that supply is expected to be adequate, the recommendation is to vaccinate all children 11 years of age and older who have not previously received vaccination against meningococcus, with a booster at 16 years of age. This broader recommendation is intended to simplify decisions about vaccinating and improve overall

coverage. The child and adolescent immunization schedules provide details about revaccinating children who have received MPSV in the past.

Creating a vaccine against serogroup B was particularly challenging because of its immunochemical structure. However, the first vaccine to protect against invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B was approved by the FDA in 2014 [46]. There are now two MenB vaccines available: MenB-FHbp and MenB-4C [18]. The MenB vaccines are approved for use in persons 10 to 25 years of age; however, because there is no theoretical difference in safety for persons older than 25 years of age compared to those in the approved age-group, MenB vaccine is recommended for use in persons older than 10 years of age who are at increased risk for serogroup B meningococcal disease, including situations and settings in which MCV would be appropriate [19]. MenB vaccine should either be administered as a three-dose series of MenB-FHbp or a two-dose series of MenB-4C. The two vaccines are not interchangeable; the same vaccine product must be used for all doses [18]. MenB vaccine may be administered concomitantly with an MCV vaccine but at a different anatomic site, if feasible [19].

In 2023, a pentavalent vaccine combining MenACWY and MenB coverage (termed MenABCWY) became available [120]. The MenABCWY vaccine consists of substance from MenB-fHbp and MenACWY-TT and is recommended as an option for people 10 years of age or older who are getting MenACWY and MenB vaccines at the same visit [120]. It is administered in two doses at least six months apart. If a patient receives MenABCWY vaccine, MenB-fHbp should be used for additional MenB dose(s) when MenACWY is not indicated; any MenACWY vaccine may be used for booster when given alone. The MenABCWY vaccine can be used only when both MenACWY and MenB vaccines are indicated at the same visit. Otherwise, MenACWY and MenB vaccines should be given separately as appropriate [120].

HEPATITIS A

Recommendation for Children: HepA is recommended for all children 12 to 23 months of age and for unvaccinated children 24 months and older (as catch-up vaccination).

Recommendation for Adults: HepA or combination HepA-HepB is recommended for certain risk groups, for those travelling to countries with endemic hepatitis A, and for those who desire protection (with no risk factor required for vaccination).

Hepatitis A can be a serious disease. According to U.S. surveillance data, an estimated 11% to 22% of people who contract hepatitis A are hospitalized [48]. Adults who are hospitalized lose an estimated 33 days of work, and those who do not require hospitalization lose about 15 days [48]. In the pre-vaccine era, infection was especially common among children. Although young children often had asymptomatic or unrecognized infection, they were an important source of disease transmission.

The ACIP has been pursuing an incremental strategy to increase immunization, with the goal of potentially eliminating indigenous hepatitis A virus transmission entirely [48]. At first, routine vaccination for healthy children was recommended only for areas with high rates of disease. Implementation of vaccination in such regions led to a decline in local disease rates to the lowest levels ever recorded. This left the highest rates in places where routine vaccination was not yet recommended. The next step was the current recommendation to vaccinate all children at 1 year of age [12]. (Some local programs also incorporate vaccination of older children.)

The range to begin routine vaccination, 12 to 23 months of age, was chosen in part because well-child visits are more frequent before 2 years of age. Vaccination is also recommended for older children and adults in certain high-risk groups. Younger children (6 to 12 months of age) may be vaccinated if they will be travelling internationally [12].

HERPES ZOSTER

Recommendation for Adults: RZV is recommended for individuals 50 years of age and older with no vaccination history and for individuals who previously received the ZVL vaccine. RZV is also recommended for individuals 19 years of age or older who are immunocompromised or who will be immunodeficient/immunosuppressed due to disease or therapy.

There are an estimated 1 million cases of herpes zoster each year, and incidence increases with age [49]. Without vaccination, about one-third of Americans will experience shingles at some point in their lives [49]. In addition to discomfort and inconvenience for the patient, there is also a risk of viral transmission leading to primary varicella in at-risk contacts. Postherpetic neuralgia (PHN) is an unfortunate but fairly common complication. A community-based study in Minnesota looked at the incidence of PHN as defined by various durations of pain [50]. Eighteen percent of patients experienced PHN-type pain for at least 30 days, 13% for at least 60 days, and 10% for at least 90 days [50]. The ACIP added the zoster vaccine to the adult immunization schedule to take advantage of the opportunity to decrease both the burden of disease and the risk of complications. In 2018, the recombinant zoster vaccine (RZV) was added as the preferred vaccine, and in 2020, the ZVL vaccine was discontinued [19]. RZV has better proven efficacy in preventing herpes zoster compared with ZVL, and breakthrough cases are associated with less severe herpes zoster-related pain and less interference on activities of daily living [56].

Although treatment for herpes zoster is available, it does not always fully alleviate symptoms [63]. In addition, the potential effectiveness of treatment initiated more than 72 hours after rash onset has not been established. When PHN occurs, treatments often have limited effectiveness, and tolerance in older patients may be poor. In a large clinical trial comparing RZV to placebo, the incidence of herpes zoster was reduced by 97.2% in vaccinated patients, and pain associated with shingles was substantially reduced [51]. The overall efficacy of

RZV against the incidence of of PHN (defined as persistent pain for 90 days) was 91.2%.

Of note, the zoster vaccine is recommended whether or not the patient has had a prior episode of shingles [19; 63]. Patients who previously received the ZVL vaccine should be revaccinated with RZV [19; 117]. Unlike the ZVL vaccine, RZV can be used in patients who have received the varicella vaccine and in those who are immunocompromised [117].

PNEUMOCOCCAL VACCINES

Recommendation for Children: PCV13 is recommended at 2, 4, 6, and 12 to 15 months of age. (PPSV23 is also recommended for certain risk groups at 2 years of age or older, with a single revaccination after 2 years.)

Recommendation for Adults: Pneumococcal vaccination (1 dose of PCV20 or 1 dose PCV15 followed by 1 dose PPSV23 at least one year later) is recommended for individuals 65 years of age and older and for younger adults in certain risk groups.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The ACIP recommends immunizing all adults 65 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown. One dose of PCV15 or PCV20 is given initially. If PCV15 is used, this should be followed by a dose of PPSV23 given at least one year after the PCV15 dose.

(https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Last accessed May 24, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

The pneumococcal conjugate vaccine recommended for routine use in healthy children, PCV13, covers 13 serotypes of *Streptococcus pneumoniae*. The use of this vaccine has led to a significant decline in IPD, from 98.7 cases per 100,000 children younger than 5 years of age in 1997–1999, to less than one case per 100,000 by 2007 and continuing to 2015 [2; 52]. Rates of all-cause pneumonia in children younger than 2 years of age have also declined, by about 35% between 1997 and 2006 with use of a vaccine covering seven serotypes [53]. Most of this decline occurred shortly after the vaccine became available.

However, the rates of non-PCV type IPD had been rising, and overall rates of IPD plateaued between 2002 and 2005 [52]. This prompted the development of the 13-valent pneumococcal conjugate vaccine, licensed in 2010. PCV13 includes coverage for six additional serotypes, which are responsible for a large proportion of remaining IPD [54]. Invasive pneumococcal disease caused by the 13 serotypes covered by PCV13 decreased from 91 cases per 100,000 people in 1998 to 0.56 cases per 100,000 people in 2021 [26].

Of note, PPSV, the 23-valent vaccine included on the adult immunization schedule, protects against 12 of the 13 serotypes in PCV13. PPSV23 can also be used in children and is recommended for certain risk groups, but it is not immunogenic in infants and very young children and is indicated for use only in people 2 years of age and older.

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINATION

Recommendation for Infants: Within one week of birth, RSV immunization (one dose nirsevimab) should be administered to infants born in October through March whose mothers did not receive RSV vaccine, who received the vaccine less than 14 days prior to delivery, or whose RSV vaccination status is unknown. For infants born between April and September whose mothers fit these criteria, one dose nirsevimab should be administered shortly before the start of RSV season.

Recommendation for Adults: One dose RSV vaccine is recommended for all pregnant patients at 32 to 36 weeks' gestation from September through January in most of the continental United States, regardless of previous RSV infection. Based on shared clinical decision-making, one dose RSV vaccine may be administered to patients 60 to 74 years of age. One dose RSV vaccine is recommended for all patients 75 years of age and older with no evidence of immunity.

Starting in 2024, the immunization schedule includes recommendations for use of the RSV vaccines. Two RSV vaccines are available in the United States: Arexvy and Abrysvo. The strongest recommendation is for the use of RSV vaccination during pregnancy to prevent RSV lower respiratory tract infection in infants. Abrysvo is the only RSV recommended for use during pregnancy. All infants born to mothers who received RSV vaccine at least 14 days prior to delivery generally do not require immunization. However, infants born to mothers who did not receive the vaccine or whose vaccine status is unknown should receive nirsevimab immunization. In addition, infants with prolonged birth hospitalization discharged October through March should be immunized shortly before or promptly after discharge [121].

Vaccination with a single RSV vaccine dose has demonstrated moderate-to-high efficacy in preventing symptomatic RSV-associated lower respiratory tract disease among adults 60 years of age or older. In 2024, the ACIP added a recommendation for RSV vaccination for older adults based on shared clinical decision-making and generally for all patients 75 years of age and older [123]. Persons 60 years of age and older who are most likely to benefit from vaccination include those with chronic medical conditions (e.g., lung diseases, cardiovascular diseases, neurologic or neuromuscular conditions, kidney disorders, liver disorders, hematologic disorders, diabetes, and moderate or severe immune compromise); those who are considered to be frail; those of advanced age; those who reside in nursing homes or other long-term care facilities; and those with other underlying medical conditions or factors that a healthcare provider determines might increase the risk of severe respiratory disease [122].

HYPERSENSITIVIES AND VACCINE RECOMMENDATIONS		
Hypersensitivity	**Vaccine**	**CDC Recommendation**
Yeast	HPV HepB PCV13	Do not use
Latex	Rotavirus (RV1), MenB	Check packaging to see if latex is used and for guidance
Gelatin	MMR Varicella	Use extreme caution if administering
Neomycin	IPV MMR Varicella HepA Some influenza vaccines	Do not use
Streptomycin	IPV	Do not use
Polymyxin B	IPV Some influenza vaccines	Do not use
Thimerosal	Some brands/formulations, including certain DTaP, influenza (IIV), Td, DT	Check package insert
Source: [20; 29]		*Table 6*

In general, the timing of RSV vaccination is based on the seasonal patterns of RSV disease transmission. Providers in jurisdictions with RSV seasonality that differs from most of the continental United States (e.g., Alaska, tropical climates) should follow guidance from public health authorities or regional medical centers on timing of administration based on local RSV seasonality [12; 19].

VACCINE CONTRAINDICATIONS

GENERAL INFORMATION

Confusion about contraindications can lead to undervaccination or, occasionally, to serious adverse events if contraindicated vaccines are given. There are a few general safety considerations that apply to all vaccines. There are also several situations in which healthcare professionals may hesitate to administer vaccines, when in fact most could be given with a high degree of safety.

As a general rule, a serious allergic reaction to a prior dose or a severe allergy to any vaccine component is a contraindication to the use of any vaccine; however, mild or moderate allergy to a vaccine component is not considered to be a contraindication [55]. In most cases, vaccination should be deferred in the setting of moderate or severe acute illness.

On the other hand, vaccination is generally not contraindicated in the following situations [55]:

- Mild acute illness, with or without low-grade fever, or recovering from illness
- Lack of previous physical examination in well-appearing person
- Current use of antimicrobial therapy (except certain antivirals with VAR and zoster)
- Premature birth (except HepB in certain circumstances)
- Recent exposure to infectious disease
- History of non-vaccine allergy
- Current use of allergen extract immunotherapy
- History of Guillain-Barré syndrome (GBS)

The prescribing information for VAR does note a small possibility of transmission of vaccine virus to healthy susceptible contacts (including pregnant women if they are susceptible to varicella) and recommends weighing this small risk against the risk of acquiring and transmitting natural varicella virus [57].

The following details about specific contraindications and cautions are based primarily on recommendations from the CDC. The CDC reports and current prescribing information should always be consulted.

ALLERGY/HYPERSENSITIVITY

The ingredients, contraindications, and precautions for any vaccine should be reviewed before administering it to a patient with known allergies or a history of a severe reaction to a previous dose or to any vaccine ingredient. However, clinicians can be well served by recalling many of the potential hypersensitivities. ***Table 6*** is based on a list of contraindications and cautions as recommended by the CDC, which provides recommendations when anaphylactic allergy is present [55]. (A fully definitive list is beyond the scope of this course. For a comprehensive list, visit https://www.vaccinesafety.edu/components.)

IMMUNODEFICIENCY

Immunodeficiency creates a potentially confusing situation regarding vaccination, because there are different degrees and causes of immune suppression. In general, the CDC recommends that MMR, varicella, and LAIV, which contain live virus, should not be used [55]. The prescribing information for LAIV notes that administration to immunocompromised patients requires careful weighing of benefits and risks [22]. If the patient is healthy but there is a close contact who is severely immunosuppressed and requires care in a protective environment, IIV4 is preferred over LAIV [55].

VAR also contains live virus. According to the CDC, it is contraindicated in patients with cellular immunodeficiencies but may be used in patients with impaired humoral immunity [55]. The prescribing information, however, includes hypogammaglobulinemic and dysgammaglobulinemic states as contraindications [57]. If a first-degree relative has congenital or hereditary immunodeficiency, VAR should not be given unless the patient's own immune competence has been verified [57; 59]. For such patients, the prescribing information for MMR notes that it, too, should also be deferred until immune competence is confirmed [60]. According to the prescribing information for VAR, because there may be rare transmission of the vaccine virus between recipients and susceptible contacts, recipients should try to avoid contact with susceptible, high-risk contacts for up to six weeks [57]. This includes immunocompromised persons and pregnant women if they are susceptible to chickenpox. (If contact is unavoidable, vaccination risk should be weighed against the risk of acquiring and transmitting natural varicella virus.)

Unlike the ZVL vaccine, which was contraindicated in most immunodeficient individuals, RZV is considered safe and is recommended for patients with immunodeficiency. According to the ACIP, RZV should be administered to adults 19 years of age or older who are or will be at increased risk for herpes zoster due to immunodeficiency or immunosuppression caused by known disease or therapy [58; 117].

The safety and efficacy of the rotavirus vaccines have not been established in patients who are immunosuppressed. In such patients, the ACIP recommendation is to consult with an infectious disease specialist or immunologist before giving the vaccine [40]. In phase 3 studies of RV5, viral shedding was observed as long as 15 days after a dose, raising concerns about use in patients with immunosuppressed contacts [61]. However, the actual risk of transmission is unknown. RV1 can also be shed after a dose, with shedding tending to peak at about seven days [62]. Again, the risk of transmission is not known.

Many vaccines may be less immunogenic in patients who are immunosuppressed. Potential effectiveness, as well as timing in patients taking immunosuppressive therapy, should be considered.

PREGNANCY

A few of the routine vaccines for healthy persons are contraindicated in pregnancy. MMR and VAR should not be used, and the CDC recommends against the use of LAIV [55]. The zoster vaccine should also be delayed, although the ACIP makes no recommendation for use during pregnancy [58]. For many other vaccines, safety during pregnancy is unknown. For example, there is little safety data on MCV and HPV vaccines when used in pregnant women, although caution is indicated with HPV [32; 42; 48; 55]. If Td or Tdap is to be given, administration during the second or third trimester is preferred. For many vaccines without good pregnancy data, providers are encouraged to report any exposure to the vaccine in a pregnant woman to the manufacturer's pregnancy registry; details are provided in the prescribing information.

In general, prescribing information should be consulted for recommendations regarding individual vaccines and pregnancy, and risks and benefits reviewed with the patient as necessary.

TUBERCULOSIS

While a positive purified protein derivative (PPD) test on its own is not generally a contraindication to vaccination, some vaccines should not be used in the presence of active, untreated tuberculosis. In such cases, MMR should not be given, due to a theoretical risk of exacerbating the disease [55].

HISTORY OF GUILLAIN-BARRÉ SYNDROME

Some vaccines have been associated with Guillain-Barré syndrome (GBS), although it is often unclear whether the vaccines actually cause this syndrome [55]. This section will summarize contraindications of routine vaccines for healthy children and adults with a history of GBS; more information about certain vaccines and GBS is included in the section on vaccine safety.

DTaP, Tdap, and Td all require caution if GBS occurred in a patient within six weeks after a previous dose of a vaccine containing tetanus toxoid [21; 23; 64; 65]. Similarly, IIV/RIV requires caution if GBS occurred within six weeks of a prior influenza vaccination, and the CDC suggests considering not vaccinating such patients if they are not at high risk of influenza complications [21; 64]. The prescribing information for LAIV recommends caution in any patient with a history of GBS, and the ACIP has identified history of GBS after an influenza vaccination as a contraindication [21; 22]. The actual risks with these or other vaccines are not known, and providers should weigh the potential risk of vaccinating against the patient's risk of serious illness.

OTHER ISSUES

There are several other concerns or cautions with specific vaccines. Although it is not possible to list every issue here, a few of the specific contraindications will be discussed.

Rotavirus Vaccine and Gastrointestinal Disease

Some studies have suggested a small increase in the risk of intussusception following rotavirus vaccination [38; 66]. In patients with a history of intussusception, benefits and risks should be weighed on an individual basis.

DTaP, Tdap, and Neurologic Events

Both DTaP and Tdap are contraindicated if encephalopathy occurred within seven days of a prior dose of a vaccine with pertussis components [23; 25; 55]. This is based on a possible link between DTP and encephalopathy and evidence suggesting an association between acellular pertussis vaccines and encephalopathy in Japan (about one attributable case per 10 million doses). Canadian surveillance data from 1993 to 2002, on the other hand, did not find a link between whole-cell or acellular pertussis vaccines and acute encephalopathy cases. Contraindications and precautions listed in the prescribing information for vaccines with pertussis components also include the presence of unstable or evolving neurologic disorders, and package inserts and the ACIP recommendations should be reviewed for details [67; 68; 69; 70; 71; 72]. The CDC recommends that decisions about DTaP in children with proven or suspected neurologic conditions be decided on an individual basis [55].

With DTaP, caution should also be observed if reactions after a prior dose included events such as high fever, collapse or shock-like state, or persistent/inconsolable crying lasting three hours or more within two days of prior dose, or seizure within three days [23; 25; 55]. However, according to the ACIP recommendations, such reactions following DTP or DTaP should not be considered contraindications to use of Tdap or Td in adolescents and adults.

Of note, the prescribing information for some, but not all, tetanus toxoid-containing vaccines does caution against use in patients who have had neurologic reactions following a previous dose of Td or of tetanus toxoid.

DTaP, Tdap, Td, and Arthus Reactions

History of an Arthus reaction is another consideration with tetanus toxoid-containing or diphtheria toxoid-containing vaccines [23; 25; 55]. An Arthus reaction is a local vasculitis that is associated with an immune reaction. Although it is an uncommonly reported event after vaccination, it can occur with vaccines containing tetanus or diphtheria toxoid. Signs include swelling, induration, edema, and hemorrhage, and there may be local necrosis. Pain is severe. The CDC recommends that, in a patient who experienced an Arthus reaction after a prior dose of tetanus toxoid- or diphtheria toxoid-containing vaccine, providers should consider deferring doses of DTaP, Tdap, or Td for at least 10 years [55]. If the reaction was to a vaccine with diphtheria toxoid but not tetanus toxoid, and more than 10 years have elapsed since tetanus vaccination, the patient can be evaluated for serum antitetanus level to determine if tetanus protection is needed before vaccination is considered.

Vaccines Containing Diphtheria or Tetanus Components

Certain vaccines contain diphtheria or tetanus components, although they are indicated for prevention of other diseases. For example, MCV and PCV contain a diphtheria component (but no tetanus toxoid) and therefore should be avoided in patients with hypersensitivity to diphtheria toxoid [73; 74]. In MCV, *Neisseria meningitides* capsular proteins are conjugated to diphtheria toxoid protein. In PCV, capsular antigens of *Streptococcus pneumoniae* are conjugated to diphtheria CRM197 protein. Certain Hib vaccines contain a *Haemophilus influenzae* capsular polysaccharide bound to a tetanus toxoid [75]. As always, vaccine components should be reviewed in patients who have known hypersensitivities or have had serious reactions to prior vaccinations.

Influenza (LAIV) and Acute or Chronic Illness

The ACIP recommends that LAIV not be used in patients with asthma or other conditions predisposing to flu complications [12; 21]. In most cases, IIV or another type can be used instead. LAIV should also be avoided in children and adolescents who are receiving aspirin or salicylate therapy. Acute respiratory illness with nasal congestion, which could interfere with delivery of the vaccine, is a reason to consider delaying the use of this vaccine until the congestion has decreased. Children younger than 5 years of age who have recent or recurrent wheezing should not receive LAIV [12; 21].

PPSV Considerations

According to the prescribing information, PPSV should be deferred in patients with febrile respiratory illness or other active infection, unless the benefit of vaccinating at that time outweighs the risk [76]. Some providers revaccinate with PPSV every five years. However, revaccination is not recommended in most healthy patients [77]. Most adults will need one lifetime dose. A second dose should be given to patients who are 65 years of age and older if they were previously vaccinated with PPSV prior to 65 years of age and if more than five years have passed [19]. Children and adults at very high risk of serious pneumococcal disease or who are likely to have a rapid decline in antibody levels (such as those with anatomic or functional asplenia or who are immunocompromised) should also receive a second dose at least five years after the first [19].

VACCINE SAFETY

Vaccine safety is initially established through clinical trials, and benefits must be shown to outweigh any risks before a new vaccine can be approved. However, the trial populations are not necessarily large enough to ensure that all possible adverse events are observed. Postmarketing surveillance provides additional safety information.

In the United States, vaccine safety is monitored through three major systems. The Vaccine Adverse Event Reporting System (VAERS) invites voluntary reporting [80]. VAERS receives approximately 30,000 reports annually, with most reports coming from vaccine manufacturers and healthcare providers. Approximately 20% of reports relate to storage and handling of vaccines, and about 85% to 90% of the reports relating to vaccine reactions describe mild side effects such as fever, arm soreness, and crying or mild irritability. Reporting forms are available at the VAERS website, https://vaers.hhs.gov. This type of surveillance is a useful way to collect information about possible adverse events, particularly uncommon events.

However, with no control group, it is often difficult to be certain whether reported events are truly related to vaccination. Researchers often compare reported events to background rates of disease, but because reporting is voluntary (referred to as passive reporting), it is not possible to know the true number of events. VAERS therefore serves primarily as an "early warning system," alerting the CDC to potential problems that require further investigation.

The Vaccine Safety Datalink (VSD) is a collaborative project, partnering the CDC with nine large managed-care organizations [81]. Each managed-care organization tracks and reports data about vaccinations given, medical outcomes, and patient demographics. The VSD project is designed to allow planned safety studies and rapid investigations of concerns raised by patterns in VAERS data or other sources.

The Clinical Immunization Safety Assessment (CISA) Project is a network of vaccine safety experts from the CDC's Immunization Safety Office, seven medical research centers, and other partners [82]. Researchers at these centers evaluate and investigate questions about health risks that may be associated with immunization.

Safety information about several specific vaccines is discussed below, with an emphasis on issues that have been in the news and may thus be on patients' or parents' minds.

MMR AND AUTISM

Although measles was considered effectively eliminated in the United States in 2000, resurgence in the disease and regional outbreaks have resulted from suboptimal vaccination rates. In 2014, there were 667 cases of measles in the United States, more than 10 times the number of cases in 2000; another even larger spike occurred in 2019 (1,282 cases in 31 states) [6]. A large outbreak in 2014–2015 was linked to unvaccinated children visiting Disneyland, the source patient probably being infected overseas (likely the Philippines) [6]. The decrease in vaccine coverage is in part attributed to the false belief that the MMR vaccine may cause autism. Based on multiple studies, experts generally agree that there is no evidence for a link between the MMR vaccine and autism, and it is important that clinicians address these misconceptions with patients. In 2004, the Institute of Medicine (IOM) reported that "the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism" [83]. The American Academy of Pediatrics has also concluded that the evidence does not support such a connection. In addition, autism is not thought to be immune-mediated, and there is no clear mechanism by which MMR would cause this disorder [84].

Research on the topic includes a Canadian study involving 27,749 children born between 1987 and 1998 [85]. This study found no association between rates of pervasive developmental disorder and either one or two doses of the MMR vaccine. In a 2015 retrospective cohort study of 95,727 children, MMR vaccine receipt was not found to predict autism diagnosis, even among children with older siblings with an autism spectrum disorder [78]. A study of 657,461 children born in Denmark between 1999 and 2010 found no increased risk of autism in those who received the MMR vaccine, including in special subgroups (e.g., autism risk factors, other childhood vaccinations) [115].

Some of the concern about MMR and autism is based on a study in the late 1990s that found measles virus ribonucleic acid (RNA) in the gastrointestinal tissue of children with gastrointestinal problems and autism. However, a case-control study designed to explore this issue further found no association between autism and persistent measles virus RNA in the gastrointestinal tract, or between autism and MMR exposure [86].

Another study used polymerase chain reaction to detect measles virus nucleic acids in the peripheral blood mononuclear cells of children with autism spectrum disorder [87]. This study found no evidence of measles virus persistence in affected children.

THIMEROSAL AND AUTISM

Some of the concerns about autism involve the use of thimerosal, a mercury-containing preservative. The IOM has concluded that, as with concerns about MMR, the evidence favors rejecting the idea of a causal relationship between thimerosal-containing vaccines and autism [83]. In addition, the same study that looked at MMR and autism in a large cohort of Canadian children also looked for any relationship between ethylmercury exposure and autism and failed to find a connection [85]. Exposure levels were comparable to levels in the United States during the 1990s. Another study, which examined the incidence of autism in California children before and after thimerosal was removed from childhood vaccines, found no decrease in autism following the change [88].

Most vaccines for children 6 years of age or younger that had contained thimerosal either no longer contain this preservative or contain only trace amounts—small enough that the FDA considers them "preservative free" [89]. IIV vaccines are now largely in this category, as "preservative-free" preparations of IIV are widely available. For the 2023–2024 season, 91% of IIV vaccines are thimerosal-free or thimerosal-reduced formulations [118].

MULTIPLE VACCINES AND THE IMMUNE SYSTEM

Some parents worry that receiving multiple vaccines at a single visit is hard on a child's immune system or that it will weaken the child's immune defenses. However, there is no evidence that giving multiple vaccinations at a single visit weakens the immune system [84]. In addition, although more childhood vaccines are given than in the past, the immunologic load has actually decreased due to advances in vaccine technology [84].

ROTAVIRUS VACCINES AND INTUSSUSCEPTION

Parents and physicians who remember the withdrawal of the original rotavirus vaccine may worry about a risk of intussusception. Each of the current rotavirus vaccines has been tested in large safety studies.

Safety testing for RV5 included the Rotavirus Efficacy and Safety Trial, involving more than 68,000 infants [90]. However, postlicensure data from the Mini-Sentinel program for 2004–2011 indicate a slightly increased risk of intussusception after the first dose (but not after subsequent doses) [38]. Prelicensure clinical trials did raise the possibility of Kawasaki disease as an uncommon adverse event, with five cases seen in infants who received the vaccine and one case in a child who received placebo (a non-significant difference) [40]. There have been a few cases reported since licensure, but these are not thought to exceed the background rate [91].

Original studies with RV1 involved more than 63,000 infants [39]. Again, no association with intussusception was observed. Since then, a major study in the United States did note a possibly increased risk of intussusception [38]. According to the CDC, there is a 1 in 20,000 to 1 in 100,000 risk of intussusception from either rotavirus vaccine [92]. Composite safety data have shown numerically higher cases of Kawasaki disease with the vaccine than with placebo, but again this was not a statistically significant difference [62].

INFLUENZA VACCINE AND GUILLAIN-BARRÉ SYNDROME

GBS was associated with a swine flu vaccine in 1976, with an estimated 1 case per 100,000 people vaccinated [21]. Some observational studies since then have found a small increase in GBS cases associated with influenza vaccination, while others have found no link. Whether there is an association between current influenza vaccines and GBS is not known. According to the CDC, based on studies in prior seasons, if an association does exist the risk would likely be low (i.e., one case per 1 million people vaccinated). The IOM conducted a thorough scientific review of this issue in 2003 and concluded that people who received the 1976 swine influenza vaccine had an increased risk for developing GBS. Scientists have multiple theories regarding why this increased risk may have occurred, but the exact reason for this association remains unknown [93].

MCV AND GUILLAIN-BARRÉ SYNDROME

As of early 2008, there had been 26 confirmed case reports of GBS within six weeks of vaccination with MenACWY-D [94]. This is likely similar to the background rate, and causality has not been established. However, the CDC and the FDA have noted that the timing in relation to vaccination was reason to pursue the question further and to gather more information. Two large studies were conducted to determine if MenACWY-D was the cause of GBS in pre-teens and teenagers, but no link was found among 21 million vaccinated individuals [94; 119]. The other MenACWY vaccines are also not associated with GBS.

Providers are asked to report any cases of GBS that coincide with vaccination to VAERS. Providers are also asked to report all GBS cases to their state health departments, in accordance with local guidelines. More complete data collection will help to clarify whether GBS is a concern with these vaccines.

HPV VACCINE AND ADVERSE EVENTS

Clinical trials and the post-licensure monitoring data of three HPV vaccines (two discontinued and one in current use) show that they are safe [107]. Since the licensure of the HPV vaccines, both the CDC and the FDA have monitored HPV vaccine safety through VAERS, VSD, and CISA systems. It should be noted that most of the available data is from the quadrivalent Gardasil formulation, which is no longer available in the United States. A 2009 CDC/FDA report found that the most common adverse events reported to VAERS following vaccination with Gardasil were fainting, swelling at the injection site, headache, and nausea. Seven percent were considered serious. However, no common pattern for serious events has emerged, making it difficult to form theories about causality. GBS was reported but did not appear to occur at a rate above background levels. Blood clots were reported in a small number of patients, most of whom had pre-existing risk factors (e.g., smoking, obesity, use of oral contraceptives). Over the first three years of its use, more than 28 million doses of Gardasil 9 were administered, and 7,244 adverse events were reported to VAERS, of which 3% (217 events) were classified as serious [107].

VSD surveillance examined adverse events associated with administration of Gardasil (e.g., GBS, stroke, venous thromboembolism) and found no statistically significant increased risk for any of these adverse events [79]. Ongoing safety studies for HPV include review of serious individual reports to VAERS; VAERS data reviews by the FDA; review of two years of safety data on Gardasil used in boys and men; research on venous thromboembolism following HPV vaccination; and continued consultation with CISA [107].

Because of postmarketing reports, the prescribing information for the HPV vaccines includes a warning that syncope, sometimes associated with seizure-like activity, has been reported following vaccination [107]. Patients should be observed for 15 minutes following injection.

OVERCOMING BARRIERS FOR CHILDREN AND ADOLESCENTS

Barriers to on-time vaccination among children and adolescents can be traced to many different issues, including parental concerns, the need for multiple visits, cultural differences, and financial constraints. Some parents are uncomfortable with the idea of multiple shots given at a single visit, and some have safety concerns that lead them to forgo certain vaccinations for their children or refuse immunization entirely. In some cases, parents are simply unaware of their children's preventive care needs.

EDUCATING PARENTS ABOUT VACCINES AND VACCINE SAFETY

In the last decade, news reports and social media misinformation have increased parents' concerns about vaccine safety and

have led some parents to reconsider the value of immunization. Although certain vaccinations are required for school attendance, parents can usually opt out for religious reasons. Some states allow "philosophical" objections as well, creating room for parents who feel uneasy about childhood vaccinations to avoid them. In places where requirements are stricter, some parents are choosing to home school their children rather than accept vaccination [96].

Healthcare providers can have an influence when parents are concerned or confused about vaccines. For example, in one survey, 28% of parents had some level of uncertainly about vaccines [97]. For those who ultimately decided to allow timely vaccination, assurances or information provided by a healthcare provider were important reasons for the decision.

When explaining vaccine recommendations or vaccine safety, the provider should take into account the parents' level of health literacy, any language or reading literacy barriers, and social and cultural expectations. For example, for some parents, written material may not be sufficient due either to a low level of literacy or to a desire to discuss the information with the physician directly.

Because patient education is such a vital aspect of vaccine promotion, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/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.

REDUCING THE NUMBER OF INJECTIONS

Many parents are upset by the idea of multiple shots on a single visit, feeling that their children will be too frightened or upset. Some parents request that certain shots be delayed, and some providers have devised alternative immunization schedules that spread injections out over time. However, there is evidence that delaying vaccinations to reduce the number of injections can lead to undervaccination. When doses are deferred, immunization coverage at both 1 and 2 years of age declines [98]. Future visits may be missed or delayed, and children may be left vulnerable to vaccine-preventable illnesses.

One way to help reduce the number of injections is to make use of combination formulations, which allow for multiple vaccines in one shot [99]. In addition to the familiar MMR and DTaP, Tdap, and Td vaccines, available combination products include [12; 19]:

- HepA and HepB (adults only)
- DTaP and IPV
- DTaP, IPV, and HepB
- DTaP, IPV, and Hib
- DTaP, IPV, Hib, and HepB
- MMR and varicella
- MenACWY and MenB

Some of these products include premixed components, while others involve components that must be combined by the healthcare provider according to instructions. Except for products that are designed to be used in this manner, individual vaccines should not be combined in a single syringe.

In their 2024 General Recommendations on Immunization, the ACIP recommended the use of combination vaccines whenever possible to reduce the number of injections and improve coverage [100]. The 2024 immunization schedule includes these formulations as an option when any component of the combination is indicated, other components are not contraindicated, and the combination vaccine is FDA approved for that dose of the series [12].

ADDRESSING CONCERNS ABOUT VACCINE COSTS

The Vaccines for Children (VFC) program is designed to help overcome cost as a barrier to childhood vaccination. All of the ACIP-recommended vaccines are available for children enrolled in Medicaid, with VFC covering children through 18 years of age [101]. Children who have no health insurance coverage, children who are underinsured, and children who are American Indian or Alaska Native are also eligible for vaccines through VFC.

"Underinsured" children are those who have private health insurance coverage that does not include vaccines, that covers only certain vaccines, or that has a cap on the amount to be paid for vaccinations [101]. In each case, VFC will cover vaccines that the insurance does not. These children must visit a Federally Qualified Health Center (FQHC) or Rural Health Clinic (RHC) to receive the covered vaccines. An FHQC is a center with a special government designation to provide care to an underserved population. A typical FQHC would be a community health center in an underserved area. An RHC is a specially certified clinic in an underserved area or one where there is a recognized shortage of healthcare professionals [101]. All other children may receive vaccines from any enrolled VFC Program provider; most physicians, clinics, hospitals, public health clinics, community health clinics, and some schools are VFC Program providers.

Although the vaccines are free and patients cannot be charged for them, providers participating in VFC may charge an administrative fee to cover other costs [101]. These fees are established by the states. Healthcare providers can learn more about VFC, including how to become a VFC provider, at the Vaccines for Children Program website, https://www.cdc.gov/vaccines/programs/vfc/index.html.

INSTITUTING REMINDER SYSTEMS

Reminding parents to bring their children in for vaccinations is a proven way to increase coverage and is recommended in standards developed by the National Vaccine Advisory Committee and supported by other organizations [102; 103]. Reminders need not take up extensive staff time. Mailed reminders have been shown to increase child vaccination rates and so have telephone calls, which may be computer-generated to save work by the office staff [104; 105; 106]. Outreach should be more intensive for families at high risk of missing appointments [102].

Setting up a system of reminders for the physician who is responsible for prescribing the vaccinations can also be helpful. Charts can be flagged, or a computerized database can be used. The National Vaccine Advisory Committee also recommends conducting chart audits to review how well the practice is meeting immunization needs and to look for areas for improvement [102].

OVERCOMING BARRIERS FOR ADULTS

Barriers to adult vaccination are similar to those impacting children and adolescents. These include: cultural differences, lack of information about what vaccinations are needed and when, lack of physician recommendation, unawareness that the protection they received as children for some diseases decreases over time, unawareness of vaccines received in childhood, lack of insurance, and mismanagement of time/priorities during office visits.

Lack of awareness is a primary reason that adults miss recommended vaccinations. It is common for adults to report that no healthcare provider had recommended a given vaccination, and so they did not know it was needed. There may also be cultural differences in how adults approach vaccination or in how services are provided. According to 2021 surveillance data, racial/ethnic disparities exist for all seven vaccines the CDC is tracking [7]. The gap is most marked for black adults, whose vaccination rate averaged 18% lower than their white counterparts with respect to seasonal influenza, tetanus (with pertussis), pneumococcal, herpes zoster, and hepatitis B [7].

"Missed opportunities," visits during which a patient was eligible for a vaccination but did not receive it, are common for adults. Reasons include constraints on time during office visits, a focus on acute care needs instead of prevention, and a lack of standing orders or an office reminder system that could prompt staff to offer the recommended vaccines [109; 110].

REDUCING "MISSED OPPORTUNITIES" FOR ADULTS

There is evidence that when physicians recommend preventive services, patients are interested in receiving them. For example, 95.1% of patients in a national survey stated that they would accept the herpes zoster vaccination if their doctor recommended it [111]. Standards provided by the National Vaccine Advisory Committee, in cooperation with more than 60 organizations, offer evidence-based methods to help reduce missed opportunities for adults [110]. Providers should assess the vaccination status of all new patients and review vaccination status annually. Pneumococcal vaccination status should be reviewed when patients present for influenza vaccination.

Standing orders for vaccination should be used, based on evidence that they improve adult vaccination coverage in many different settings [110]. Reminder systems for staff can also improve vaccination rates. In one review of studies, use of physician reminder systems, such as chart notations, stickers, and patient lists, improved coverage by a median of 22% [112]. Assessing a practice's success at vaccinating patients who are eligible and reporting the results to staff can also help to improve coverage [110].

REMINDER SYSTEMS FOR ADULT PATIENTS

Telephone calls, mailed reminders, and texts/electronic reminders can help raise vaccination coverage among adults as well as among children [110]. Reminders can specify that patients are due or overdue for vaccinations, or they can invite patients to contact the provider's office to see which vaccinations they need. As with children, adults who are likely to miss appointments or fail to comply with recommendations may need particularly intensive follow-up.

CONCLUSION

Staying up-to-date, working with patients to maximize vaccination coverage, and monitoring and improving day-to-day practice can all help to improve vaccination rates. However, keeping up with changes to the child, adolescent, and adult immunization schedules can be challenging. Annual schedules often change from year to year and include both major changes and subtle ones. Mid-year announcements from the CDC and the ACIP require clinicians to be alert to new information and to make adjustments to practice. To help clinicians check for updates, verify information about vaccines, and locate answers to common clinical questions, the CDC provides a Vaccines and Immunizations website, as does the Immunization Action Coalition. Healthcare professionals should consider every healthcare visit as an opportunity to assess vaccination status and administer vaccines when needed. This will improve rates across the life spectrum, from infancy to elderly.

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COURSE TEST - #91743 CHILD, ADOLESCENT, AND ADULT IMMUNIZATION SCHEDULES

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 Hour activity must be completed by February 28, 2026.

1. In the United States, what group is responsible for regulating vaccines?
- A) *Centers for Disease Control and Prevention*
- B) *Advisory Committee on Immunization Practices*
- C) *FDA Center for Biologics Evaluation and Research*
- D) *FDA Vaccines and Related Biological Products Advisory Committee*

2. According to the 2024 immunization schedule, what are the recommended vaccine doses for a healthy, 2-month-old infant born in June with no special risks or contraindications who is up-to-date on vaccinations so far?
- A) *DTaP, Hib, IPV, and HepB if needed*
- B) *DTaP, Hib, PCV, IPV, and HepB if needed*
- C) *Rotavirus, DTaP, Hib, IPV, and HepB if needed*
- D) *Rotavirus, DTaP, Hib, PCV13, IPV, and HepB if needed*

3. Assuming no special risk groups or contra-indications and assuming that the ACIP recommendations are followed, what vaccines would a male patient, 50 years of age, be likely to receive?
- A) *Tdap or Td only*
- B) *Tdap or Td, IIV, and zoster*
- C) *Tdap or Td, IIV, and PPSV23*
- D) *Tdap or Td, IIV, zoster, and PPSV23*

4. The ACIP rationale for expanding the recommendation for influenza vaccination to include all children from 6 months to 18 years of age includes
- A) *adolescents typically have high rates of physician visits.*
- B) *universal childhood vaccination is expected to help increase coverage for at-risk groups.*
- C) *missed school days due to influenza have been low but proven to adversely affect children's grades.*
- D) *a large new clinical trial reinforced confidence in the safety and efficacy of influenza vaccination in school-age children.*

5. According to the ACIP recommendations, and considering healthy patients without special risk factors or contraindications, who should receive the HPV vaccine?
- A) *Girls 11 to 12 years of age, plus adult women at high risk of contracting HPV*
- B) *Girls 15 years of age or older, plus adult women at high risk of contracting HPV*
- C) *Girls younger than 18 years of age who are sexually active, plus adult women through age 26 who have not been vaccinated*
- D) *All individuals 11 to 26 years of age who have not been vaccinated*

6. The ACIP rationale for recommending HPV vaccination to preteens includes all of the following, EXCEPT:
- A) *HPV infection is particularly common in teenagers and young adults.*
- B) *Vaccination before the age of sexual debut is likely to offer the most benefit.*
- C) *Infection with HPV often occurs within the first few years after sexual debut.*
- D) *After an individual has been infected with any type of HPV, the vaccine is no longer of benefit.*

7. What change was made to the recommendations regarding vaccination against rotavirus in 2009?
- A) *Three rotavirus vaccines are now available.*
- B) *Ages for dosing were harmonized for the two available vaccines.*
- C) *The number of doses was standardized, with both vaccines now requiring 2 doses.*
- D) *The age to initiate rotavirus vaccination was expanded to include infants up to 1 year of age.*

8. Why is MCV included as a routine vaccination for healthy children?

A) *Unlike MPSV, MCV covers all of the most common meningococcal serotypes.*
B) *The high number of cases, about 45,000 in the United States each year, makes vaccination essential.*
C) *Vaccinating children protects them against meningococcal disease in middle age, when incidence becomes highest.*
D) *In addition to the high case-fatality rate, each case of meningococcal disease requires substantial resources to identify additional cases and prevent disease spread.*

9. The zoster vaccine is included on the adult immunization schedule. The recommendation for this vaccine includes

A) *adults 50 years of age and older.*
B) *adults 65 years of age and older.*
C) *only adults with certain medical risk factors.*
D) *only adults who have never had chickenpox.*

10. Before vaccination was available, what proportion of the population experienced herpes zoster at some point in their lives?

A) *About one-tenth*
B) *About one-third*
C) *About one-half*
D) *About two-thirds*

11. If a patient has a severe (anaphylactic) latex allergy, how would this affect the vaccinations he or she could receive?

A) *No vaccinations should be given.*
B) *Some vaccines would be contraindicated.*
C) *All vaccines can be used, but 15 minutes of observation is recommended.*
D) *There would be no change, because latex is not used in manufacturing vaccines.*

12. A father brings his 5-year-old son, Patient S, in for a checkup one morning in November. He states that Patient S has had "the sniffles" for the past two days and that he has been " running a bit of a fever." On exam, Patient S appears well except for nasal congestion. His temperature is 99.0°F. Patient S's medical history is unremarkable, he has no known allergies, and he tolerated his previous vaccinations well. He was up-to-date on all recommended vaccinations through 2 years of age, but has not received any vaccinations since then. At today's visit, which of the following vaccines should probably be deferred?

A) *IPV*
B) *DTaP*
C) *MMR*
D) *LAIV*

13. A mother brings her young daughter to a new pediatrician for the first time. She is changing doctors because her previous pediatrician refuses to see patients whose parents decline to have them vaccinated. She explains, "I know that MMR vaccine can cause autism, and I don't want that to happen to my child." What can you tell her?

A) *Large observational studies have failed to find a link between MMR and autism.*
B) *Experts do not believe that MMR causes autism, but this issue has not been studied.*
C) *An older type of MMR was a cause of autism, but this specific vaccine is no longer used.*
D) *Good evidence links MMR and autism, but the benefits of vaccination are considered to outweigh the risks.*

14. Some parents have concerns about the presence of thimerosal in childhood vaccines. Which of the following is correct?

A) *Experts believe that thimerosal does not cause autism, but this has not been studied.*
B) *Thimerosal remains a component of most childhood vaccines, but observational studies have not found a connection with autism.*
C) *Vaccines recommended for children 6 years of age and younger now either contain no thimerosal or contain only trace amounts, because thimerosal was shown to cause autism.*
D) *Vaccines recommended for children 6 years of age and younger now either contain no thimerosal or contain only trace amounts, although observational studies have not found a connection between thimerosal and autism.*

Test questions continue on next page ➞

15. A woman, 70 years of age, who is in generally good health, comes in to discuss some knee pain she has been having. While she is in your office, you take advantage of the opportunity to offer vaccination against seasonal influenza. She tells you that one of her friends is recovering from Guillain-Barré syndrome (GBS), and she recalls hearing something about the flu shot and GBS. What can you tell her?

A) There is a proven risk with some of the current influenza vaccines, but not all.
B) The rumor that incidence of GBS increased with the 1976 swine flu vaccine is untrue.
C) There is a proven risk with the current influenza vaccines, but it is small, about 1 case per 1 million people.
D) There is a theoretical risk with the current influenza vaccines, but even if there is a risk it would probably be small, about 1 case per 1 million people.

16. As of 2024, what is known about HPV and problems following vaccination?

A) The majority of events reported to VAERS have been considered non-serious.
B) Postmarketing reports rule out any connection between vaccination and syncope.
C) The only events reported to VAERS have been non-serious, such as fainting, swelling at the injection site, headache, nausea, or fever.
D) All of the above

17. Research regarding parents' concerns about vaccination suggests that

A) it is unusual for parents to have questions or concerns about vaccines.
B) the majority of parents have some level of uncertainty about vaccinating their children.
C) information from healthcare providers is unlikely to influence decisions about vaccination.
D) information from healthcare providers can have an important impact on parents' decisions to vaccinate.

18. In addition to children who are enrolled in Medicaid, children who are eligible for free vaccines under the Vaccines for Children program include children who

A) are underinsured.
B) have no health insurance coverage.
C) are American Indian or Alaska Native.
D) All of the above

19. You have found that there is room for improvement in pediatric vaccination rates. One of the nurses suggests sending letters to remind both adult patients and the parents of pediatric patients when vaccinations are needed. However, your office manager reminds you that the budget is tight this year. Sending letters would be an extra expense. Based on evidence and current recommendations, what should you do?

A) Either send the letters or institute a system of reminder phone calls.
B) Send letters only for pediatric patients, because reminders work for children but not adults.
C) Do not use letters or phone calls, because reminder systems for patients do not work.
D) Institute a system of reminder phone calls instead of letters, because calls have been proven to have greater effect.

20. Your group practice recently conducted a chart audit and discovered many "missed opportunities" for adult vaccination. You would like to institute a reminder system for yourself and your colleagues, but the others ask if there is any evidence it will work. Based on the evidence, what can you tell them?

A) A review of studies was inconclusive, but a reminder system will do no harm and might help.
B) The office should only use an electronic medical records system, because placing reminders in paper charts has been proven not to work.
C) A review of studies found that physician reminder systems, such as chart notations, stickers, and patient lists, can improve vaccination coverage.
D) Reminder systems for patients work, so even though reminder systems for physicians have not been studied, they can also be expected to increase vaccination rates.

Anxiety Disorders

This course meets the Texas requirement for drug therapy management education.

Audience
This course is designed for pharmacists involved in the care of patients with anxiety disorder.

Course Objective
The purpose of this course is to provide pharmacists with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.

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

1. Review basic concepts related to anxiety disorders, including safety behaviors/signals and primary features.
2. Outline the epidemiology of anxiety disorders in the United States.
3. Describe general risk factors for and comorbidities of anxiety disorders.
4. Describe risk factors for and the clinical course of specific anxiety disorders.
5. Discuss the pathogenesis of anxiety disorders in relation to contributing genetic, physiologic, and psychologic factors.
6. Review the pathophysiology of specific anxiety disorders, including social anxiety disorder, agoraphobia, and specific phobia.
7. Evaluate the clinical and diagnostic criteria for anxiety disorders presented in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).
8. Analyze key components of screening for anxiety disorders.
9. List conditions to consider in the differential diagnosis of anxiety disorders.
10. Describe general treatment considerations for anxiety disorders, including predictors of response or nonresponse to therapy.
11. Discuss the role of various psychotherapy approaches in the treatment of anxiety disorders.
12. Outline pharmacotherapy options for the treatment of anxiety disorders.
13. Recognize clinical issues related to the treatment of anxiety disorders.
14. Compare and contrast the treatment recommendations for specific anxiety disorders.
15. Analyze the evidence base supporting the efficacy of novel, emerging, and alternative/complementary approaches to the treatment of anxiety disorders.

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

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

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INTRODUCTION

Anxiety disorders are characterized by states of chronic, excessive dread or fear of everyday situations. The fear and avoidance can be life-impairing and disabling. Anxiety disorders result from the interaction of biopsychosocial factors, whereby genetic vulnerability interacts with situations, stress, or trauma to produce clinically significant syndromes. The influence of hereditary factors and adverse psychosocial experiences on pathogenesis and pathophysiology is complex, but neuroscience advances have greatly improved the understanding of the underlying factors in the development and maintenance of anxiety disorders.

BACKGROUND

SAFETY BEHAVIORS AND SIGNALS

Safety behaviors are coping tactics by persons with anxiety disorders, especially panic disorder, agoraphobia, and social anxiety disorder, to temporarily diminish feelings of threat and reduce one's anxiety level. Safety behaviors can emerge in response to an external (e.g., situations, persons, activities) or internal (e.g., thoughts, emotions, memories) focus of perceived threat and are anticipatory (avoidant) or consequential (escape) [1].

Safety signals are the people or objects used by patients with anxiety disorders to diminish distress in situations that elicit anxiety. Safety signals maintain anxiety over time by preventing direct confrontation of feared stimuli in the absence of "safe" objects/people and by maintaining perceptions of risk/harm and coping inability. Patient use of safety signals can interfere with therapy progress, especially exposure therapy, and are considered anti-therapeutic. However, safety behaviors may be helpful early in treatment by making exposure therapy more tolerable and less threatening [1].

PRIMARY FEATURES OF ANXIETY AND RELATED DISORDERS

The distinguishing features of specific anxiety disorders are summarized in the following section. Related conditions of post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are included because, although no longer classed as anxiety disorders by the 2013 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), they are often included in research that pre-dates 2013 and can co-occur with anxiety disorders [2]. Situations or objects that evoke intense anxiety in patients with agoraphobia, social anxiety disorder, or specific phobia are either avoided or endured with significant personal distress.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive and inappropriate worrying that is persistent (lasting more than a few months) and not restricted to particular

circumstances [3]. Patients with GAD have physical anxiety symptoms and key psychologic symptoms (i.e., restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and disturbed sleep). GAD is often comorbid with major depression, panic disorder, phobic anxiety disorders, health anxiety, and OCD [3].

Panic Disorder

Panic disorder is characterized by recurrent unexpected surges of severe anxiety ("panic attacks"), with varying degrees of anticipatory anxiety between attacks [3]. Panic attacks are discrete periods of intense fear and discomfort accompanied by multiple physical and/or psychologic anxiety symptoms. These attacks typically peak within 10 minutes and last around 30 to 45 minutes. Most patients also develop a fear of having further panic attacks [3].

Agoraphobia

Around two-thirds of patients with panic disorder develop agoraphobia, defined as fear of having panic attacks in places or situations from which escape might be difficult or where help might not be available [3]. These places or situations can include crowds, outside of the home, or using public transport [2].

Social Anxiety Disorder

Social anxiety disorder (SAD) is characterized by a marked, persistent, and unreasonable fear of being negatively evaluated by others [3]. It is associated with physical and psychologic anxiety symptoms.

Specific Phobia

Specific, simple, or isolated phobia is the excessive or unreasonable fear of (and restricted to) animals, objects, or specific situations (e.g., dentists, spiders, elevators, flying, seeing blood) [3].

Separation Anxiety Disorder

Adult separation anxiety disorder (SEPAD) is characterized by fear or anxiety concerning separation from those to whom an individual is attached. Common features include excessive distress when experiencing or anticipating separation from home and persistent and excessive worries about potential harms to attachment figures or untoward events that might result in separation [3].

Post-Traumatic Stress Disorder

PTSD is characterized by exposure to actual or threatened death, serious injury, or threats to the physical integrity of self or others (the trauma) with development and persistence of intrusive symptoms (e.g., recollections, flashbacks, dreams), avoidance symptoms (e.g., efforts to avoid activities or thoughts associated with the trauma), negative alterations in cognitions and mood, and hyper-arousal symptoms (e.g., disturbed sleep, hypervigilance, exaggerated startle response) [2].

Obsessive-Compulsive Disorder

OCD is characterized by recurrent obsessive ruminations, images, or impulses and/or recurrent physical or mental rituals. These obsessions are distressing and time-consuming, causing interference with social and occupational function. Common obsessions relate to contamination, accidents, and religious or sexual matters; common rituals include washing, checking, cleaning, counting, and touching [3].

Illness Anxiety Disorder

Illness anxiety disorder is a somatic-symptom related disorder characterized by excessive or disproportionate preoccupations with having or acquiring a serious illness. This includes excessive health-related behaviors and high levels of alarm about personal health status [3].

OVERALL PREVALENCE, RISK FACTORS, AND CLINICAL COURSE

Each year in the United States, anxiety disorders (DSM-5 plus PTSD and OCD) impact approximately 42 million adults, or 19% of the population [4; 5]. The pattern of sex distribution is consistent among anxiety disorders, and the overall female-to-male ratio is approximately 2:1 across all age ranges [6].

PAST YEAR AND LIFETIME PREVALENCE

Data on anxiety disorders in the United States reported 12-month prevalence, lifetime prevalence, and lifetime morbid risk (***Table 1***). The two lifetime measures differ. Lifetime prevalence measures the proportion currently or previously diagnosed with the disorder, while lifetime morbid risk measures the proportion who will develop the disorder at some point, whether or not they have a lifetime history at the time of assessment. By including future cases, lifetime morbid risk is believed to be more accurate. Lifetime prevalence and lifetime morbid risk are usually equivalent for disorders with early-life onset, but diverge for disorders with increasingly later onset. The ratio of lifetime prevalence to lifetime morbidity risk falls below 1.0 in disorders with increasingly later onset; the further the ratio values fall below 1.0, the later the median age of onset [7].

Anxiety disorders with earlier median age of onset are phobias and separation anxiety disorder (15 to 17 years of age), and those with latest age of onset are panic disorder and generalized anxiety disorder (23 to 30 years of age). Lifetime morbid risk is considerably higher than lifetime prevalence for most anxiety disorders, with magnitude of difference much higher for disorders with later than earlier age of onset. Also, the ratio of 12-month to lifetime prevalence roughly reflects persistence, but varies meaningfully in ways consistent with differential persistence of these disorders [7].

COMPARISON OF PREVALENCE, MORBID RISK, AND RATIO OF LIFETIME PREVALENCE TO MORBID RISK FOR ANXIETY DISORDERS				
Anxiety Disorder	**12-month**	**Lifetime**	**Lifetime Morbid Risk**	**Lifetime/Lifetime Morbid Risk**
Generalized anxiety disorder	2.0%	4.3%	9.0%	0.5
Panic disorder	2.4%	3.8%	6.8%	0.5
Agoraphobia	1.7%	2.5%	3.7%	0.7
Social anxiety disorder	7.4%	10.7%	13.0%	0.8
Specific phobia	12.1%	15.6%	18.4%	0.8
Separation anxiety disorder	1.2%	6.7%	8.7%	0.8
Source: [7]				*Table 1*

OVERALL RISK FACTORS

Demographic

The odds for a lifetime diagnosis of any anxiety disorder were calculated, and the same pattern was found for past 12 month diagnosis [8]. These odds are organized according to sex, socioeconomic status, education level, and age. Overall, the risk of developing an anxiety disorder is greater for women/girls than men/boys.

Persons with lower incomes also experience increased odds versus those with higher incomes (48% increased risk with $35,000 to $69,000; 52% with $20,000 to $34,000; 100% with $19,000 or less). Lower educational attainment is a risk factor. Compared with college graduates, the odds of developing an anxiety disorder are increased 44% with 13 to 15 years of education, 76% with 12 years of education, and 86% with 0 to 11 years of education. These disorders are also 40% more likely in persons 15 to 24 years of age compared with older adults (45 to 54 years of age) [8].

Temperament

Behavioral inhibition is defined as the tendency for timid and shy responses to novel situations, and it is highly associated with temperament factors of neuroticism and introversion. Anxiety disorders are associated with behavioral inhibition in childhood, and behavioral inhibition is an identifiable early childhood predictor of later anxiety disorders. Introversion and behavioral inhibition are also strongly linked to later development and severity of situational avoidance, which is a core feature and risk factor in agoraphobia and SAD [9].

CLINICAL COURSE

Anxiety disorders in aggregate show a U-shaped age of onset—higher in childhood and young adulthood and lower in adolescence. The greatest concentration occurs during transition to early adulthood. Unlike biologically driven pubertal transitions, adulthood transitions involve distinct psychosocial events (e.g., independent living, full-time employment), and this represents a key period for understanding the development of adult anxiety disorders such as panic disorder and agoraphobia [10].

Community studies of persons with sub-diagnostic anxiety symptoms over time often show episodic symptoms and prolonged periods of remission, with symptoms reappearing or worsening during adverse life events and psychosocial stressors. In contrast, studies of clinical anxiety disorder populations typically show a chronic course with fluctuating symptom severity between periods of remission and relapse, with long-term course varying by disorder [3].

Healthcare Utilization

Distressing anxiety symptoms can spur patients to initiate primary care contact. If anxiety is unrecognized, costly medical tests may be performed. Recognizing a pattern of subjective worry or anxiety with accompanying physical signs can help healthcare providers avoid costly diagnostic tests but still consider possible medical causes of anxiety. Effective treatment with pharmacotherapy or cognitive-behavioral therapy (CBT) should reduce symptoms and healthcare seeking [2; 3].

COMORBID DEPRESSION

Anxiety symptoms often co-occur with other psychologic symptoms. Depressive symptoms are highly prevalent with more severe anxiety symptoms, with anxiety and depressive symptom severity strongly correlated. Patients with anxiety disorder have high comorbidity rates of major depressive disorder (almost 50%), schizophrenia, substance use disorders, and physical illness [3; 11]. Overlapping symptoms of anxiety and depression, such as sleep disturbance, fatigue, and difficulty concentrating, make differentiation challenging. Depressive disorders are sometimes termed "anxious-misery" when high levels of sadness and anhedonia are present [2].

SPECIFIC DISORDERS

Generalized Anxiety Disorder

Epidemiology

Studies in the United States on GAD prevalence rates have found a 5.1% lifetime rate and a 2.0% to 3.1% past-year rate. The lifetime and past-year prevalences are 3.6% and 2.0% in men/boys and 6.6% and 4.3% in women/girls. The majority of persons with GAD diagnoses are female. Childhood or adolescent onset was found in more than 50% of those seeking help for anxiety, reflecting the chronicity of the disease [2].

Risk Factors

No single etiology has been identified for GAD, but it likely involves the interaction of multiple familial/genetic and environmental risk factors. A review of twin and family studies found significant associations between GAD, other anxiety disorders, and depression, suggesting a common underlying genetic basis. A significant number of patients and their first-degree relatives develop GAD (odds ratio 6:1) [12]. Civilian trauma (e.g., motor vehicle accidents, physical or sexual assault, sudden unexpected loss of a loved one, bullying or peer victimization in childhood or adolescence) is a risk factor for GAD [13]. The presence of another anxiety disorder (e.g., panic disorder, SAD, specific phobia) is another possible factor. Panic disorder is comorbid in 25% of patients with GAD [13].

Late-onset GAD (on or after 65 years of age) is very uncommon. The primary predictors include female sex, recent adverse life events, and chronic physical (e.g., respiratory and cardiac disorders, dyslipidemia, cognitive impairment) or mental health (e.g., depression, phobia, past GAD) disorders. Other risk factors include poverty, parental loss/separation or low emotional support during childhood, and history of parental mental health problems. Late-onset GAD is described as a multifactorial, stress-related affective disorder resulting from proximal and distal risk factors of which some are potentially modifiable by healthcare intervention [14].

Clinical Course

The course of GAD tends to be chronic in primary care patients, and GAD may "switch" to other diagnoses, particularly depression and somatoform disorders [15; 16]. GAD is associated with impairments in psychosocial functioning, role functioning, work productivity, and health-related quality of life comparable to major depressive disorder or panic disorder. Patients with GAD and comorbid major depression show significantly greater impairment in health-related quality of life than in either disorder alone. Primary care patients with GAD showed significantly higher annual medical costs than patients without GAD (median $2,375 versus $1,448) and higher mean annual medical costs ($2,138) than patients with other anxiety disorders. GAD is frequently under-recognized in primary care, and only 20% to 32% of patients receive adequate treatment. Suboptimal treatment adds to the health-related quality of life burden of this disorder [17].

Panic Disorder

Epidemiology

In the United States, 4% to 28% of the population experience panic attacks at some time during their life. The 2.4% annual incidence of panic disorder in the United States is one of the highest prevalence rates worldwide [7; 18].

Panic disorder prevalence in primary care is approximately 7%, and substantially higher in patients presenting with cardiac or gastrointestinal symptoms. Relative to white patients, the odds of developing panic attacks and panic disorder are higher in Native Americans, and lower in Asian, Hispanic, and black patients [18; 19].

Panic attacks are most likely to develop in patients who are in their mid-20s and slightly earlier in men than women. Panic disorder age of onset is usually between late adolescence and 35 years of age, while the age of onset for panic disorder with agoraphobia spans the early 20s to early 30s. Panic disorder is more common among women, with a 2:1 ratio and increasing to 3:1 with panic disorder with agoraphobia. Panic symptoms during adolescence elevate risks for other anxiety and mood disorders in adulthood. Depressive disorders are highly comorbid (33% to 85%), especially among those with agoraphobia [2; 20]. Panic disorder is highly comorbid with other anxiety, mood, and substance use disorders, including nicotine dependence, and cigarette smoking may increase the risk for later-onset panic disorder [21].

Risk Factors

As with GAD, the etiology of panic disorder probably results from a combination of risk factors. There is a five-fold greater risk of developing panic disorder when the disorder is present in first-degree relatives. Shared genetic factors account for 30% to 40% of panic disorder heritability [12]. In addition, major adverse life events precede the onset of panic attacks in roughly 80% of patients. Trauma history is prevalent in patients with panic disorder, especially women [22].

Behavioral inhibition may contribute to panic risk in adulthood. Learned escape and avoidance behaviors can maintain the condition and worsen functional impairment over time. Anxiety sensitivity, or the tendency to catastrophically misinterpret physical symptoms as dangerous, is a risk factor for panic disorder. Personality pathology, particularly avoidant and dependent personality traits, are predictors of panic disorder or agoraphobia development [23; 24].

Asthma severity is associated with an incremental risk for panic disorder, and respiratory variability may also increase risk for later onset panic disorder [25]. Baseline respiratory abnormalities are specific to panic disorder pathophysiology [6]. As noted, cigarette smoking and nicotine dependence is disproportionately high among patients with panic disorder and may be temporally related to elevated risk for developing panic disorder [26]. Additionally, panic attacks may be related to poorer cessation outcome during smoking treatment among patients with cancer [27]. Caffeine use is also positively correlated with increased anxiety symptoms and risk of inducing panic attacks in patients with panic disorder [28].

Clinical Course

Prospective studies of panic disorder show high rates of symptom chronicity, relapse after remission, and "switching" to other diagnoses [29; 30]. Panic disorder symptoms remain persistent for 50% to 80% of cases even after treatment, increasing disability and impaired quality of life [31].

Agoraphobia

Epidemiology

Agoraphobia usually, but not always, occurs with panic disorder. In community populations, about 25% of those with

panic disorder also have agoraphobia, but the proportion is substantially higher in clinical populations [20].

Agoraphobia was made an independent diagnostic entity in the DSM-5, and accordingly, epidemiologic and clinical data that consider agoraphobia in the absence of panic disorder are pending. In the DSM-IV-TR, panic disorder could be specified with or without agoraphobia. Lifetime and 12-month prevalence of panic disorder with agoraphobia were 1.0% and 0.5%, respectively [32].

Risk Factors

Much of the published agoraphobia research assumes panic disorder causation or comorbidity. As such, many of the known risk factors are the same. Comorbid panic disorder and agoraphobia aggregate in families, while agoraphobia without panic disorder is non-familial but may enhance familial transmission of panic disorder [33]. The risk of agoraphobia development in patients with panic disorder is elevated with female sex, more severe dizziness during panic attacks, cognitive factors, dependent personality traits, and SAD. Panic disorder with agoraphobia is associated with greater severity and worse prognosis [34].

Longitudinal studies show low remission rates (0% to 23%) over time in panic disorder or agoraphobia, and subjects with panic disorder with agoraphobia or agoraphobia with panic attacks at baseline were more likely to develop agoraphobia, panic attacks, and other anxiety disorders and experience greater severity (e.g., impairment, disability, treatment-seeking, comorbidity) than subjects with panic disorder without agoraphobia or agoraphobia without panic attacks at baseline [35].

A late-life subtype of agoraphobia (onset at or after 65 years of age) was identified through assessing elderly patients at baseline and four years later. Baseline agoraphobia prevalence was 10.4%, and 11.2% developed agoraphobia during the four-year follow-up. Agoraphobia in the elderly, unlike younger populations, was not more common in women and not associated with panic attacks. Risk factors for late-onset agoraphobia were severe depression, trait anxiety, and poor visuo-spatial memory [36]. Incident anxiety appears to be a response to subjective memory complaints independent of depressive symptoms [37].

Patients with panic disorder who experience their first panic attack driving or using public transportation had higher rates of comorbid agoraphobia. Those with first panic attack at home had higher fear-of-dying rates than with first panic attack outside of the home and felt more severe distress from their first panic attack whether or not agoraphobia developed. Treatment of patients with panic disorder whose first panic attack was at home should address fear and distress elicited by the attack [38].

Clinical Course

In persons with panic disorder with or without agoraphobia, the strongest predictors of incidence and relapse were past history of panic attacks, GAD/major depression, nicotine dependence, female sex, younger age, and major financial crises. Most predictor variables were similar between panic disorder and panic disorder with agoraphobia. Clinicians should understand the relapsing-remitting nature of panic disorder/panic disorder with agoraphobia in order to avoid prematurely reducing or eliminating effective treatments. Close attention should be paid to concurrent factors linked to relapse that can be clinically addressed, such as comorbid major depression, GAD, and nicotine dependence [39].

One study followed 711 participants with anxiety disorder diagnoses over 15 years. At baseline, those with early-onset (≤ 20 years of age) panic disorder were more likely to have comorbid major depressive disorder, GAD, and SAD. Those with early-onset panic disorder with agoraphobia were less likely to be married and more likely to have comorbid GAD and SAD. During follow-up, persons with panic disorder with agoraphobia were significantly more likely to have illness recurrence after periods of recovery, while findings for the other disorders failed to reach significance. This was thought to reflect differences in typical age of onset among anxiety disorders. The onset of panic disorder with or without agoraphobia is usually early adulthood; earlier onsets are relatively uncommon and may signal a particularly pernicious form of illness. The results further support the particularly adverse effects of early-onset psychiatric illness [40].

Social Anxiety Disorder

Epidemiology

SAD can develop at any time during a lifespan, but the average age of onset is during late childhood and adolescence. The prevalence of SAD in pre-adolescence is 3.5%, with rates increasing to about 14% during adolescence [41]. The incidence is as high as 7% in primary care settings [19]. Gender distribution is generally equal during pre-adolescence and becomes increasingly more common in girls/women through adolescence and adulthood. An estimated 70% to 80% of individuals with SAD have comorbid anxiety, mood, or substance use disorders. There are cultural variants in Asian and Eastern cultures that involve fears of offending others or making others uncomfortable [2].

Risk Factors

A combination of biologic, familial, environmental, and cultural risk factors contributes to the development of SAD. Transitions, losses, poverty, and experiences of humiliation or embarrassment may contribute to SAD risk [42]. Compared with data from the general population, first-degree relatives are up to six times more likely to be at risk of SAD. Concordance rates are 24% in monozygotic twins and 15% in dizygotic twins [43].

Behavioral inhibition, shyness, introversion, and anxiety sensitivity are all common among patients with SAD. Emerging early in life, behavioral inhibition is a heritable trait, and 15% to 20% of young children with behavior inhibition exhibit extreme signs. Relative to children without behavioral inhibition, these patients are typically shy, fearful, and cautious and show elevated physiologic arousal signs at resting, such as higher

stable heart rate, increased pupil dilation, and higher cortisol levels. Brain profiles of children with behavioral inhibition show distinct patterns, including electroencephalography asymmetry, functional differences in amygdala response to faces, and structural differences in the ventral prefrontal cortex. Roughly 40% of children with behavioral inhibition develop SAD, and childhood behavioral inhibition is a primary predictor of SAD. Other components of SAD probably appear later in development, including social-evaluative concerns and coping skills deficits that contribute to functional impairment [44; 45].

A bi-directional relationship exists between parenting style and childhood anxiety. Parenting styles of criticism, over-protection, over-control, and lack of warmth can create insecure attachment and risk for SAD. Likewise, temperamentally introverted and anxious children may shape and change parenting styles, with parents becoming over-protective or over-controlling [42]. Studies suggest that challenging parenting behavior (especially in fathers) may play a protective role in anxiety development in the most vulnerable children [46; 47].

Early childhood anxiety disorders, especially separation anxiety and other phobias, are associated with elevated SAD risk in adulthood. SAD is highly comorbid with other anxiety disorders, mood disorders, and substance use disorders; substance abuse is often used to regulate anxiety symptoms and social skills [48].

Multiple social cues can develop the capacity to elicit anxiety-related symptoms. Learned escape and avoidance behaviors maintain anxiety, interfere with skill development, and can lead to functional impairment and disability over time. Similarly, safety behaviors, such as only entering social situations with a trusted companion, averting eye contact, and staying on the periphery of social gatherings, may maintain anxiety-related impairments. Selective attention to social cues of negative evaluation and internal cues supporting danger perception may develop [49; 50].

Primary Prevention

Childhood presence of fearfulness and behavioral inhibition can lead to chronic, disabling SAD. Early recognition of childhood impairments and evidence-based treatment intervention may offset the SAD trajectory of persisting into and through adulthood. Educational-behavioral interventions involving older children/adolescents, parents, school staff, and healthcare providers have been found to reduce the development of social anxiety [51; 52; 53].

Clinical Course

SAD tends to run a chronic course in primary and secondary care settings [54; 55].

Specific Phobia

Epidemiology

Women are two to three times more likely to develop phobias than men, with the exception of blood-injection-injury phobia, which is evenly distributed by sex. Roughly 70% of specific phobics report more than one clinically relevant fear. Animals and heights are the most common stimuli, followed by flying, enclosed spaces, and blood-injection-injury. The average age of onset is 7 to 10 years, with declining probabilities of onset into later adulthood. The majority of animal phobias develop before 8 years of age [2; 41; 56]. The average age of treatment engagement is 31 years, although only 8% of persons with specific phobia are reported to seek treatment [56].

The odds of developing phobias are significantly less in Hispanic and Asian individuals and greater in white individuals. Animal fears are prevalent in Japan and Hong Kong [56; 57].

Risk Factors

For specific phobias, familial concordance rates among first-degree relatives are moderate. The greatest heritability indices are found in animal and blood-injection-injury phobias [58; 59; 60].

Intense anxiety or unexpected panic responses in the presence of specific objects or situations can mark phobia onset but are not the sole causal route. Disgust, either alone or combined with fear, may trigger the onset and maintenance of animal (particularly spiders, snakes, and worms) or blood-injection-injury phobias. Onset can occur indirectly by observing others reacting fearfully. Some stimuli are more likely to induce phobias than others (e.g., animals vs. electrical outlets) through evolutionary threat relevance.

Phobia onset can be precipitated by relationship problems, relocation, employment loss, or economic difficulties. In addition, anxiety, mood, or substance use disorders can co-occur with or predate phobia onset. Substance use disorder can maintain phobic symptoms. Phobia symptoms in adolescence predict adult symptoms but are not a risk factor for developing other anxiety, mood, or substance use disorders.

Adult Separation Anxiety Disorder

Epidemiology

The lifetime prevalence of adult SEPAD is 6.6% in the general population, 12% to 40% in psychiatric clinic settings, and more than 75% among those seeking treatment at anxiety disorder clinics [61]. In adults with lifetime SEPAD, 22.5% have childhood age of onset that persisted into adulthood, while 77.5% had adult onset. Girls/women show higher overall prevalence than boys/men and substantially higher rates of childhood-onset SEPAD persisting into adulthood [62]. SEPAD and panic disorder are highly comorbid in clinical settings. Among adult patients with panic disorder, 53.2% were diagnosed with SEPAD. Patients with panic disorder and SEPAD (versus no SEPAD) were more commonly female and younger and showed higher rates of childhood SEPAD and greater lifetime prevalence of mood disorder spectrum symptoms [63].

Risk Factors

Children of adults with anxiety disorders have higher rates of anxiety disorders. Early, traumatic separation from attachment

figures and a positive family history of anxiety or depressive disorders may also elevate risk of SEPAD, school phobia, and depressive-spectrum disorders during adolescence or adulthood. Early, traumatic separation can include prolonged severance of contact with the primary caregiver during the neonatal period; later sudden hospitalization; early loss of attachments from death or divorce; or an interactive pattern with an overprotective, needy, or depressed parent [64].

Clinical Course

In one study, children with SEPAD were 3.5 times more likely to later develop panic disorder and more than twice as likely to develop any anxiety disorder but did not significantly differ in later development of depression or substance use disorder. These findings were considered supportive of a developmental psychopathology model of anxiety disorders [65].

ETIOLOGY AND PATHOPHYSIOLOGY

ANXIETY DISORDERS IN GENERAL

Anxiety disorders are characterized by diverse neuroendocrine, neurotransmitter, and neuroanatomical disruptions, the result of interactions between multiple genetic, environmental, and social factors. Although each disorder may have unique features, this group shares some underlying pathophysiology.

Pathologic Alterations in Brain Structure and Function

Fear and anxiety are thought to involve two major brain circuits: the limbic system and the prefrontal cortex. In the limbic system, which consists of the amygdala, hippocampus, central nucleus of the amygdala, insular cortex, and cingulate cortex, emotion-processing brain structures generate primitive innate responses to simple, overtly threatening stimuli. Functions of limbic structures include processing emotionally important external stimuli and initiating behavioral responses; mediating expressions of fear, aggression, and defensive behavior; and forming and retrieving emotional and fear-related memories [66; 67]. The prefrontal cortex, comprised of the orbitofrontal cortex and the prefrontal, ventromedial, and dorsomedial prefrontal cortex, dampens emotional responses to anxiety-inducing stimuli. The prefrontal cortex functions to regulate impulses, emotions, and behavior via inhibitory "top-down" control of emotional-processing structures; this works to control impulses and regulate mood [66; 67].

Altered limbic and prefrontal cortex functioning characterize anxiety disorders, with amygdala hyper-responsivity to threatening stimuli and impaired ventromedial prefrontal contex inhibitory control over limbic-generated, anxiety-inducing signals, associated with aberrant communication and functional connectivity between the amygdala and the prefrontal cortex [67].

Narrowing brain region contribution, amygdala and insula hyperactivation contribute to anxiety disorders triggered by specific stimuli (e.g., panic disorder, specific phobia). The insula integrates sensory, emotional, and cognitive information through extensive connections between the lateral prefrontal cortex, ventromedial prefrontal cortex, orbitofrontal cortex, cingulate, amygdala, bed nucleus of the stria terminalis, and ventral striatum. Changes in the level of insula activation influence anxiety level [66].

Amygdala-medial prefrontal cortex functional connectivity shows a developmental trajectory, and early temperamental risk for anxiety is associated with disruption of these circuits. Aberrant amygdala-prefrontal cortex connectivity is found in patients with adult-onset anxiety disorders who showed childhood temperament risk factors but did not develop early-onset anxiety. This suggests aberrant connectivity is a lingering biomarker of risk [68].

Familial and Environmental Contribution

Persons with anxiety and mood disorders show a shared genetic predisposition, with specific manifestation the product of genetic and environmental interactions. A developmental dynamic pattern of genetic influence on individual differences in anxiety and depression symptoms is apparent. Genetic influence on psychopathology changes over the lifespan, with different developmental stages associated with a unique pattern of risk factors [67].

Significant early-life stress (e.g., maternal deprivation) may degrade prefrontal cortex functional connectivity with subcortical panic-generating circuits, elevating risks of anxiety disorders and other psychopathology. Many significant early-life stress events (e.g., child abuse, neglect, parental loss from death or abandonment) are receiving heightened attention as contributing factors to anxiety disorders and trauma pathology, as in PTSD. Previous childhood or adult trauma is considered a predisposing/contributing factor to panic disorder and SEPAD as well as major depressive disorder and PTSD that may be primary or comorbid with other anxiety disorders [69]. Aversive experiences can lead to complex behavioral adaptations, including increased levels of anxiety and fear generalization.

Alterations in Brain Transmitter Chemicals

Neurotransmitters allow communication between brain regions. Alterations in neurotransmitter systems implicated in anxiety disorder pathogenesis include the monoamines serotonin (5-hydroxytryptamine or 5-HT), norepinephrine, and dopamine. Aberrant limbic signaling is associated with decreased inhibitory signaling by gamma-amino-butyric acid (GABA) or increased excitatory neurotransmission by glutamate. Many other neurotransmitter systems participate in the modulation of fear and anxiety, including the neuropeptide substances P, N, and Y; corticotropin-releasing factor (CRF); and endocannabinoids. Abnormalities in these systems are associated with structural and functional alterations in specific brain areas, such as the amygdala, prefrontal cortex, locus coeruleus, and hippocampus, and represent the therapeutic targets of drug therapy [70].

Gene products that regulate monoamine signaling may be critical in facilitating antidepressant effect. Monoaminergic regulators include transmitter receptors; vesicular monoamine transporter, which packages monoamines into vesicles; oxytocin and vasopressin; transmitter-specific reuptake transporters, such as the serotonin transporter, norepinephrine transporter, and dopamine transporter; monoamine oxidase, which degrades monoamines; and catecholamine-O-methyltransferase, which degrades norepinephrine and dopamine [67]. However, the cause of anxiety disorders is not simply a deficiency of one neurotransmitter or excess of another. The networks governed by these transmitters are extensively inter-related, with multiple feedback mechanisms and complex receptor structures. This complexity contributes to unpredictable and sometimes paradoxical medication responses [70].

GENERALIZED ANXIETY DISORDER

Neuronal circuits implicated in GAD are distinct from panic disorder, likely involving much greater frontal and prefrontal lobe than amygdala involvement. GAD is characterized by abnormalities in frontal and limbic structures and in the connectivity between these regions. The most frequently implicated frontal regions are the prefrontal cortex and the anterior cingulate cortex; in the limbic region, the amygdala and possibly the hippocampus are involved. Structural abnormalities and decreased structural and functional connectivity between frontal and limbic regions have repeatedly been documented in GAD [71; 72]. Functional neuroimaging suggests that GAD is characterized by inefficient biologic mechanisms associated with emotion regulation. Worry induction increases prefrontal cortex activation and decreases amygdala activity in patients with GAD and non-anxious controls, but unlike non-anxious subjects, patients with GAD are unable to normalize this neural activity afterward. The results from studies using tasks that require conflict monitoring and emotion regulation support a model of GAD characterized by hypoactivation in the prefrontal cortex and anterior cingulate cortex indicative of deficient "top-down" emotional control [73].

PANIC DISORDER

Core Pathophysiology

Genetic, developmental, hormonal, and environmental factors interact to impair the ventromedial prefrontal cortex's ability to inhibit panic impulses generated by limbic regions. This underlies the pathogenesis of the initial onset of unexpected panic attacks. This pathology is further compounded by recurrent panic attacks with repeated activation of panic-generating subcortical sites, leading to recruitment and plasticity within extended amygdala fear-hippocampus-cortical circuits. This in turn facilitates the development of situational and anticipated panic attacks and agoraphobia. Imaging studies have demonstrated ventromedial prefrontal cortex structural abnormalities in patients with panic disorder, reflecting the loss of inhibitory control over panic-generating sites. CBT enhances medial prefrontal cortex activity in subjects with anxiety disorders, which may explain its efficacy in treating panic disorder [69].

Other Pathophysiologic Models

In addition to ventromedial prefrontal cortex inhibition, other alterations in brain function have been suggested in panic disorder. Involvement of the central nuclei of the amygdala and activation of other fear centers in the thalamus, hypothalamus, and hippocampus may dysregulate respiratory control in the brainstem [74; 75]. Additionally, it has been proposed that genetic risk variants partly drive fear network activity [76]. Exaggerated hypothalamic-pituitary-adrenal axis reactivity to environmental stimuli may be involved in panic disorder etiology [77; 78].

In patients with panic disorder, CBT significantly reduces left interior frontal gyrus region activation, and reduced activity is correlated with reduced agoraphobic symptoms [79]. This reduced activation appears to be a specific substrate of CBT effects in patients with panic disorder/agoraphobia without comorbid depressive disorders [80]. Functional magnetic resonance imaging (MRI) shows that pre-treatment activation of the bilateral insula and left dorsolateral prefrontal cortex during threat processing is associated with rapid response to CBT [81].

AGORAPHOBIA

Patients with panic disorder and agoraphobia who are anticipating agoraphobia-specific stimuli have shown stronger region-specific activations in the bilateral ventral striatum and left insula versus controls. Patients processed these stimuli more intensively based on individual salience, and this activation is stronger than found in patients with panic disorder alone. Ventral striatum and insula hyperactivation when anticipating agoraphobia-specific situations may be a key neurofunction modulator in agoraphobia [82].

In patients with panic disorder/agoraphobia, fear conditioning has shown enhanced activation of the bilateral dorsal inferior frontal gyrus. Simple conditioning, safety signal processing, and anxiety sensitivity correlate with the extent of midbrain activation. These findings suggest alterations in "top-down" and "bottom-up" processes during fear conditioning, interpreted within a neural framework of defensive reactions that mediate threat through distal (forebrain) versus proximal (midbrain) brain structures. This network may play a key role in panic disorder pathogenesis [83].

Genetic polymorphism (variation) may influence panic disorder with agoraphobia treatment response. Serotonin transporter gene promoter polymorphism (5-HTTLPR) is conclusively linked to emotion regulation and related patterns of brain connectivity. During functional MRI imaging, the patient subgroup that showed inhibitory anterior cingulate cortex-amygdala coupling during fear conditioning predominantly possessed the L/L genotype of 5-HTTLPR polymorphism. This activation of inhibitory function, the normal function in non-anxious persons, suggests an intermediate connectivity phenotype that modulates response to exposure-based CBT [84].

Expanding on these results, patients with panic disorder/agoraphobia and the low-expression allele of 5-HTTLPR showed more favorable exposure therapy response than patients with other 5-HTTLPR genotypes. This genetic contribution to exposure therapy outcome implicates the serotonergic system as a response mediator to exposure treatments [85].

Balance System Abnormalities

Patients with panic disorder/agoraphobia have shown subclinical abnormalities in balance system function that seemed to influence agoraphobia severity and contribute to dizziness and disorientation symptoms in complex sensory environments (e.g., shopping malls, traffic, crowds). These patients also display greater balance control reliance on non-vestibular, proprioceptive, visually dependent cues and greater balance system reactivity to peripheral visual stimulation. These possibly link to a more active visual alarm system involving visual, vestibular, and limbic areas. Patients with panic disorder/agoraphobia also show high sensitivity to light or brightness stimuli with photophobic behavior and abnormal retinal and pupillary reflex responses possibly linked to serotonergic and/or dopaminergic dysfunction. This overall amplified sensitivity to environmental stimuli suggests that agoraphobia involves activation of complex systems beyond panic attack fear and behavioral avoidance, including emotional responses to destabilizing/distressing environmental stimuli and operant-learning avoidance of experiences that provoke this distress [86].

SOCIAL ANXIETY DISORDER

Patients with SAD have shown hyper(re)active limbic, frontal, and parietal brain regions involved in emotional and attentional processes. Compared to healthy subjects, patients with SAD display increased cortical thickness in frontal, parietal, and other brain areas. CBT treatment success and symptom improvement have been associated with changes in prefrontal regions involved in emotion regulation [87].

Persons with SAD and GAD share core features of persistent, debilitating focus on negative or potentially threatening experience. This negative affective bias is characterized by increased threat processing at the neural, psychologic, and behavioral levels, with engagement of the dorsal medial prefrontal cortex-amygdala circuit during aversive processing. Anxiety disorder subtypes frequently co-occur, and while abnormal activation of this neural circuitry that mediates bias toward threats is diagnosis-independent, it also represents a cardinal feature of SAD and GAD [88].

SAD pathophysiology includes heightened autonomic arousal to social cues and novelty. Fear processing appears mediated by the amygdala, in which neuroimaging studies show exaggerated activations with exposure to novel facial stimuli. Amygdala activation to novelty is also found in persons with a behavioral inhibition temperament. Other pathophysiologic models suggest that exaggerated hypothalamic-pituitary-adrenal axis reactivity to environmental stimuli may be involved in SAD [89; 90; 91; 92].

SPECIFIC PHOBIA

Amygdala, anterior cingulate cortex, and insula hyperactivity is believed to be the underlying pathophysiology of specific phobia. Neuroimaging studies have shown increased amygdala activation with exposure to phobic-relevant cues, and heightened activity in thalamic, insula, and dorsal anterior cingulate cortex regions [93; 94; 95]. Meta-analyses suggest the left amygdala/globus pallidus, left insula, right thalamus, and cerebellum regions are all more active among patients with a phobia compared with controls when exposed to phobic-relevant stimuli. Acute, exaggerated parasympathetic nervous system activity with exposure to stimuli is thought to underlie the vasovagal syncope experienced by up to 80% of people with blood-injection-injury phobia [96]. Exposure-based therapy leads to deactivation in the right frontal cortex, limbic cortex, basal ganglia, and cerebellum, and increased activity in the thalamus [97].

ADULT SEPARATION ANXIETY DISORDER

SEPAD etiology is thought to arise during childhood by disrupted caregiving environments that promote greater hypothalamic/pituitary stress responsivity. Neuroimaging research has focused on brain circuitry that shows abnormal activity at single time points during anxiety from close attachments. The underlying neural circuitry that mediates separation-hypersensitive attachment includes subcortical areas (amygdala, hippocampus, striatum) and cortical limbic areas (insula, cingulate). Predisposing endophenotypes may interact with circuitry involved in attention, learning, and executive control (medial prefrontal cortex, superior temporal sulcus, and temporoparietal junction). With social interaction central to separation anxiety, neural circuitry involved in separation-sensitive social representations that predict danger when separation occurs may include the anterior temporal cortex [98]. SEPAD is associated with hypersensitivity to inhaled carbon dioxide, with a similar pattern to patients with panic disorder, suggesting SEPAD and panic disorder may share a common pathophysiologic basis [99; 100].

CLINICAL AND DIAGNOSTIC FEATURES

As with other psychiatric disorders, the treatment of anxiety disorders is guided by conceptualization of the disorder and theoretical basis for disorder/treatment relationships. The understanding of anxiety disorders has changed over time with input of new evidence. In the United States, the DSM, published by the American Psychiatric Association, is the authoritative reference in defining and diagnosing psychiatric disorders. In the modern era, revised DSM editions have been published in 1980, 1994, 2000, and most recently in 2013 with the DSM-5.

To better reflect current thinking on anxiety disorders, the DSM-5 made several important changes from the 1994 DSM-IV and its 2000 text revision [32; 101]. As noted, the chapter on anxiety disorders no longer includes OCD, PTSD, and acute

stress disorder. New sections were added for these conditions: obsessive-compulsive and related disorders and trauma- and stressor-related disorders. Duration criteria for several anxiety disorders were extended to six months or longer to minimize overdiagnosis of transient symptoms, applied to all ages.

With agoraphobia, specific phobia, and SAD, the requirement that patients recognize their anxiety as excessive or unreasonable has been eliminated. This change was based on evidence that individuals with such disorders often overestimated the danger in "phobic" situations and that older individuals often misattributed "phobic" fears to aging. Instead, the anxiety must be out of proportion to the actual situational danger or threat, with consideration of cultural contextual factors [102].

The DSM-5 (and previous DSM editions) has been criticized for emphasis on reliability at the expense of diagnostic validity and for use of symptom-based diagnosis when symptoms alone may not best inform treatment selection. In response, the National Institute of Mental Health is developing the Research Domain Criteria, a new taxonomy for mental disorders that draws from genetics, neuroscience, and behavioral science [103]. Additionally, the DSM-5-TR, which was released in March 2022, includes the addition of prolonged grief disorder; the inclusion of symptom codes for suicidal behavior and nonsuicidal self-injury; refinement of criteria; and comprehensive literature-based updates to the text [104].

GENERALIZED ANXIETY DISORDER

GAD is characterized by excessive and inappropriate worrying that is persistent and not restricted to particular circumstances. Patients have physical anxiety symptoms and key psychologic symptoms. GAD is often comorbid with major depressive disorder, panic disorder, phobia, health anxiety, and OCD [3]. The DSM-5 diagnostic criteria for GAD remain unchanged from previous editions [2; 102]:

- Excessive anxiety and worry (apprehensive expectation) over a number of everyday concerns (e.g., school/work performance)
- Individual finds it difficult to control the worry
- Excessive anxiety and worry are associated with three or more of the following six symptoms, with at least some occurring more days than not for at least six months:
  - Restlessness, feeling "on edge"
  - Easily fatigued
  - Difficulty concentrating
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling or staying asleep, restless sleep)
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Symptoms not better explained by another mental disorder
- The disturbance is not attributable to the physiologic effects of a substance or another medical condition

Patients with GAD in the absence of current or lifetime comorbidity are uncommon, and patients with GAD typically present to primary care with comorbid depression, anxiety disorders, or substance use disorders. The presence of comorbidity complicates diagnosis and treatment [2].

PANIC ATTACKS

Panic attacks are abrupt, unexpected periods of intense fear or discomfort with multiple physical or psychologic anxiety symptoms, often peaking by 10 minutes and lasting around 30 to 45 minutes. Panic disorder is characterized by recurrent unexpected surges of severe anxiety (panic attacks). As noted, most patients develop a fear of having further panic attacks. The extent of anticipatory anxiety between attacks varies, and patients may alter their behavior to reduce the recurrence risk [2; 3].

The essential features of panic attacks are unchanged in the DSM-5, but the complicated DSM-IV terminology for describing different types of panic attacks (i.e., situational-bound/cued, situational-predisposed, and unexpected/uncued) is replaced with unexpected and expected panic attacks. Panic attacks function as a marker and prognostic factor for severity of diagnosis, course, and comorbidity across an array of disorders, including but not limited to anxiety disorders. Hence, panic attack can be listed as a specifier, applicable to almost all DSM-5 disorders [102]. The DSM-5 criteria for panic attacks specify an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and includes four or more of the following symptoms [2]:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feelings of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, light-headed, or faint
- Chills or heat sensations
- Paresthesias (numbness or tingling sensations)
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or going crazy
- Fear of dying

Physical symptoms predominate.

Panic attack is not classified as a mental disorder and does not have a diagnostic code. Instead, an attack can occur with other mental disorders, such as depressive and anxiety disorders, and also be extant with physical disorders. While panic attack is a specifier for both mental and physical disorders, the elements

of panic attack are contained within the criteria for panic disorder, making the specifier unnecessary for that diagnosis.

PANIC DISORDER

Panic disorder in the DSM-5 has an added criterion for unexpected panic attacks. This implies that expected panic attacks exist and that anticipated, situationally triggered panic attacks are somehow less pathologic than spontaneous panic attacks. This assumption is challenged on the basis that panic attacks are inherently pathologic, regardless of context or lack thereof, and individuals with panic disorder can have unexpected and expected panic attacks [18; 105]. Regardless, the DSM-5 diagnostic criteria for panic disorder require [2]:

- Recurrent unexpected panic attacks
- One or more of the attacks followed by at least one month of one or both of the following:
  - Persistent concern or worry about additional panic attacks or their consequences
  - Significant maladaptive change in behavior related to the attacks

The symptoms must not be attributable to substance-related effects, other medical conditions, or other psychiatric disorders. Up to 70% of patients report a history of at least one nocturnal panic attack [106]. Patients may present with symptoms suggestive of heightened sympathetic nervous system activity such as palpitations, increased systolic blood pressure, hyperventilation, sweating, or flushing. Other common symptoms include chest pain and discomfort, dizziness, and paraesthesias, while gastrointestinal symptoms such as nausea and vomiting are more common among men [2; 107].

The severity of distress during panic attacks by patients with panic disorder with or without agoraphobia is increasingly seen as traumatic. Panic attacks are frequently experienced as life threatening, and patients with panic disorder can experience PTSD symptoms in relation to their panic attacks. Patients with panic disorder/agoraphobia or PTSD were found to relive their trauma or panic attacks with equal frequency, report comparable bodily reactions and distress associated with trauma or panic attack memories, and avoid trauma or panic attack reminders (i.e., places and things associated with trauma or panic attacks). Trauma-like symptoms surrounding panic attacks are common, and panic attacks may be processed similarly to trauma in PTSD [108].

Intense, disorganized recollections, a core symptom of PTSD, are thought to result from inadequate processing of trauma information. A first panic attack resembles trauma; both are unexpected, frightening, and subjectively life-threatening events. Like PTSD, panic disorder with agoraphobia also involves fear conditioning after the first event. Therefore, panic attack and trauma processing may be similar, with panic attack and PTSD trauma memories sharing the characteristics of reliving and disorganization. A comparison of panic memories and PTSD trauma memories did not find differences between groups in reliving intensity and disorganization levels, suggesting that panic attacks may affect information processing similarly to a traumatic event [109; 110].

Patients with panic disorder exhibit considerably worse overall mental well-being than individuals with cancer, diabetes, heart disease, arthritis, hypertension, and other chronic physical conditions [111]. Current panic disorder is also related to worse quality of life and physical function and an elevated risk of attempting suicide [112]. These effects are similar to or greater than those associated with major depression. A study found that nearly 33% of these patients in primary care had seen three or more healthcare professionals and almost 20% had visited emergency departments [113]. Another study found that although the majority of individuals with panic disorder first present to the primary care setting, only 38% of those with panic disorder with agoraphobia and 24% of those with panic disorder without agoraphobia were receiving appropriate treatment, and the use of empirically supported interventions was rare [114].

AGORAPHOBIA

Agoraphobia is defined as the fear of panic attacks occurring in places or situations from which escape might be difficult or embarrassing or where help may not be available. These situations can include crowds, going outside the home, or using public transportation and are either avoided or endured with significant personal distress [3]. Agoraphobia can become severely disabling, and more than 33% of patients diagnosed with agoraphobia cannot endure leaving their home environment. Roughly 66% of patients with panic disorder develop agoraphobia [2].

In the DSM-5, agoraphobia was de-aggregated from panic disorder and is now classed as a separate diagnostic entity. The former DSM-IV diagnoses of panic disorder with agoraphobia, panic disorder without agoraphobia, and agoraphobia without history of panic disorder are now replaced by two diagnoses with separate criteria: panic disorder and agoraphobia. Co-occurring panic disorder and agoraphobia are also coded as two diagnoses. This change recognizes that a substantial number of individuals with agoraphobia do not experience panic symptoms, although clinical prevalence is much lower than community prevalence. The diagnostic criteria for agoraphobia are derived from the DSM-IV descriptors, with endorsement of fears from two or more agoraphobia situations now required to more effectively distinguish agoraphobia from specific phobias. The criteria for agoraphobia are also extended to concord with criteria sets for other anxiety disorders [102]. Diagnosis is based on marked fear or anxiety about two or more of the following [2]:

- Public transportation (e.g., traveling in planes, automobiles, buses, trains, ships)
- Open spaces (e.g., parking lots, market places, bridges)
- Being in shops, theatres, or stadiums

- Standing in line or being in a crowd
- Being outside of the home alone in other situations

The individual with agoraphobia fears or avoids these situations due to thoughts that escape might be difficult or help might not be available in the event of panic-like symptoms. These situations almost always provoke fear or anxiety and are actively avoided, require presence of a companion, or are endured with marked fear or anxiety. The fear or anxiety is out of proportion to the actual threat posed by an agoraphobic situation. The fear, anxiety, or avoidance is persistent, typically lasting at least six months, and causes clinically significant distress or impaired functioning. Avoidance symptoms in PTSD differ in that the situations avoided are trauma-associated, such as a park or street where an assault occurred or riding in a car after a motor vehicle accident [2].

Major personality dimensions, such as introversion and neuroticism, have been studied for contribution to the risk of developing agoraphobia and other anxiety disorders. Genetic factors that influence individual variation in extraversion and neuroticism have been found to account entirely for genetic liability in SAD and agoraphobia but not animal phobia, emphasizing the importance of both introversion (low extraversion) and neuroticism as risk factors [115]. Situational avoidance is the most disabling aspect of agoraphobia. Temperament is shown to influence agoraphobia severity, with introverted temperament significantly associated with the presence and severity of agoraphobic situational avoidance [9].

The longitudinal relationship between personality disorder traits and panic disorder (with or without agoraphobia) is important for understanding agoraphobia etiology. A large-scale study that assessed community-dwelling adults at baseline and again 12 to 15 years later found that after excluding participants with baseline panic attacks, baseline timidity with avoidant, dependent, and related traits predicted the onset of panic disorder or panic disorder with agoraphobia during the follow-up period. These results suggest that avoidant and dependent personality traits are predisposing factors, or markers of risk, for panic disorder or panic disorder with agoraphobia, and not simply epiphenomena [24]. Additionally, personality and temperament traits may be potentially related to poor treatment response [116].

SOCIAL ANXIETY DISORDER

SAD is often misconstrued as mere shyness but can be considerably disabling and produce much greater distress and more severe symptoms. SAD is characterized by a marked, persistent, and unreasonable fear of being observed or evaluated negatively by other people in social or performance situations, which is associated with physical and psychologic anxiety symptoms. Feared situations, such as speaking to unfamiliar people or eating in public, are either avoided or are endured with significant distress [3]. Social phobia has been renamed SAD to reflect a new, broader understanding of the condition in a variety of social situations.

Previously, social phobia was primarily diagnosed in patients reporting extreme discomfort or fear when performing in front of others. Research indicates this definition is too narrow, and SAD in the DSM-5 can be diagnosed based on patient response to a variety of social situations. For example, the patient may be so uncomfortable engaging in conversation he or she is unable to talk to others, especially strangers. A patient with anxiety regarding being observed may be unable to go out to dinner over fears of being watched while eating and drinking [102].

The essential features of SAD remain unchanged. However, a number of changes have been made, including deletion of the requirement that individuals older than 18 years of age must recognize that their fear or anxiety is excessive or unreasonable and addition of a duration criterion. A more significant change is that the "generalized" specifier has been deleted and replaced with a "performance only" specifier. The DSM-IV-TR generalized specifier was problematic in that "fears include most social situations" was difficult to operationalize. Individuals who fear only performance situations (i.e., speaking or performing in front of an audience) appear to represent a distinct subset of SAD in terms of etiology, age at onset, physiologic response, and treatment response. The DSM-5 establishes the following diagnostic criteria for SAD [2]:

- Marked fear or anxiety about social situations in which the person may be exposed to scrutiny by others
- Fear that actions or showing anxiety symptoms will cause negative evaluation (e.g., embarrassment, humiliation) or offend others
- The social situation:
  - Almost always provokes fear or anxiety
  - Is actively avoided or endured with marked fear or anxiety
- The fear, anxiety, or avoidance:
  - Is disproportionate to actual threat posed by the social situation
  - Is persistent, typically at least six months
  - Causes significant distress or functional impairment
- If another medical condition is present (e.g., stuttering, obesity), the disturbance is unrelated or out of proportion to it

If the fear is restricted to speaking or performing in public, diagnosis should specify "performance only." Other diagnostic features of SAD include [2]:

- Post-event processing: Tendency to replay social encounters in a negative, self-critical manner
- Attentional bias: Heightened attention to negative evaluative threat cues and lack of attention to positive or benign cues
- Social skills deficits: Poor eye contact, closed stance, quiet tone of speech, and difficulties initiating conversations

Patients with SAD highly inflate perceived social costs from committing hypothetical blunders. Accounting for much of this social cost inflation are concerns about revealing self-flaws and, in particular, concerns over appearing socially incompetent [117].

SPECIFIC PHOBIA

Specific, simple, or isolated phobia describes excessive or unreasonable fear in the presence of phobic stimuli, typically involving specific animals, objects, or situations (e.g., dentists, spiders, elevators, flying, seeing blood). Phobic stimuli are either avoided or are endured with significant personal distress [3]. This fear or anxiety must be markedly stronger than the actual threat of the object or situation (e.g., likelihood of being stuck on a well-maintained elevator) [2]. The core features and different types of specific phobia remain unchanged from the DSM-IV, but the requirement was removed that individuals older than 18 years of age must recognize their fear and anxiety as excessive or unreasonable. The duration requirement of longer than six months now applies to all ages [102].

Specific phobias can develop after a traumatic event or from witnessing traumatic events. The fear or anxiety happens every time the person is exposed to the stimulus and may include panic attack symptoms.

The median age of onset with specific phobia is 13 years [2]. According to the DSM-5, specific phobia is diagnosed when the following criteria are met [2]:

- Marked fear or anxiety about a specific object or situation (e.g., flying, seeing blood)
- Phobic object or situation almost always provokes immediate fear or anxiety and is actively avoided or endured with marked fear or anxiety
- Fear or anxiety out of proportion to the actual danger posed by the specific object or situation
- The fear, anxiety, or avoidance is persistent, typically at least six months
- Marked distress or functional impairment

Specific phobia subtypes are organized by phobia categories:

- Animal: Dogs, snakes, insects
- Natural environment: Storms, heights, dark
- Blood-injection-injury: Injections, blood draws, medical procedures
- Situational: Driving, flying, enclosed spaces
- Other: Choking, vomiting, clowns

Specific Phobia Coding

Approximately 75% of individuals diagnosed with specific phobia fear more than one object. In the past, when this occurred, more than one ICD-10 code was given [2]. However, the ICD-11 eliminated this component. When individuals experience panic attacks in response to their phobia, clinicians should add "with panic attacks" to the diagnosis.

SEPARATION ANXIETY DISORDER

Separation anxiety is a basic human fear and readily observable in children. Being close to nurturing parental figures in infancy is necessary for survival, and forming close relationships throughout life provides support in times of stress. Separation anxiety does not vanish with development and maturation, but prominent separation anxiety in adults becomes less apparent as a problem on its own. Manifestations of pathologic separation anxiety include uncontrollable apprehension over losing important attachment figures, intense fears of leaving home or going out unaccompanied, and nightmares around themes of separation. Persons with SEPAD have substantial impairments in many aspects of community life, although not all individuals show problems in attachment [118; 119].

Pathologic early childhood attachments can have far-reaching consequences in adulthood. These patients often have a grossly impaired ability to experience and internalize positive relationships or to develop mental capacities for self-soothing, anxiety tolerance, affect modulation, and individuation. Adults with SEPAD feel unable to function in the absence of a mother surrogate. Separation anxiety has long been considered the distal antecedent to panic disorder. In adults, separation anxiety may reflect excessive activation of fear circuits in response to separation and over-activation of reward circuits with reunion, likely the result of abnormalities or deficits in underlying social representation and cognition systems [98].

SEPAD is characterized by fear or anxiety concerning separation from those to whom an individual is attached. Common features include excessive distress when experiencing or anticipating separation from home, and persistent and excessive worries about potential harms to attachment figures or untoward events that might result in separation [3].

The core features of SEPAD are mostly unchanged from DSM-IV, but the wording is modified to more adequately represent SEPAD expression in adulthood. For example, attachment figures may include the children of adults, and avoidance behaviors may occur in the workplace as well as at school. Diagnostic criteria no longer require childhood history of SEPAD or onset before 18 years of age, because a substantial number of adults report onset later in life. Adults with the condition include those with adult-onset and those with childhood onset and symptom persistence into adulthood. A duration criterion of six months or longer was added [64; 102]. For a diagnosis of SEPAD, the persistent and excessive anxiety related to separation or impending separation from a major attachment figure (e.g., spouse, close family member) must be evidenced by at least three of the following criteria [2]:

- Recurrent excessive distress when anticipating or experiencing separation
- Persistent and excessive worry about losing a major attachment figure or about possible harm to him or her

- Persistent and excessive worry about experiencing an untoward event (e.g., getting lost, kidnapped, into an accident) that causes separation from a major attachment figure
- Persistent reluctance or refusal to go out, away from home, to school, to work, or elsewhere because of fear of separation
- Persistent and excessive fear of or reluctance about being alone or without a major attachment figure
- Persistent reluctance or refusal to sleep away from home or to go to sleep without major attachment figure near
- Repeated nightmares involving the theme of separation
- Repeated complaints of physical symptoms (e.g., headaches, stomachaches, nausea, vomiting) when separation occurs or is anticipated

To meet the criteria for this disorder, the symptoms must cause clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning. Symptoms must not be better explained by another mental disorder (e.g., delusions or hallucinations concerning separation in psychotic disorders); refusal to go outside without a trusted companion (as in agoraphobia); worries about ill health or other harm befalling significant others (as with generalized anxiety disorder); or concerns about having an illness (as in illness anxiety disorder) [2]. Panic attacks commonly occur with youth and adult SEPAD.

Differential Diagnosis

In the past, adult SEPAD was often diagnosed as panic disorder, and it shares features with other psychiatric conditions. Excessive attachment toward others is a feature of a dependent personality, and avoidance behavior is a predominant feature of agoraphobia. With SEPAD, the focus involves key attachment figures, unlike dependent personality disorder, which is more indiscriminate. Panic and phobic-like behavior in SEPAD is specific to fears of separation from, or harm to, attachment figures and not spontaneous or triggered by other factors. Social and occupational function is frequently impaired, but individuals with SEPAD do not show impaired function in family life compared to controls and often function well in family environments. Borderline personality disorder differs by pervasive mood and relationship instability uncharacteristic of SEPAD [61].

A study exploring whether SEPAD in patients with panic disorder/agoraphobia was a manifestation of anxious attachment, a form of agoraphobia, or a specific condition with clinically significant consequences found that patients with SEPAD had greater panic symptom severity and quality of life impairment than those without separation anxiety. A greater rate of symptoms suggestive of anxious attachment was found among patients with panic disorder and SEPAD versus those without SEPAD. However, the relationship between SEPAD and attachment style was weak, and SEPAD occurred in some patients who reported secure attachment style. There was also little evidence SEPAD was a form of agoraphobia. SEPAD was found to be a distinct condition associated with impairment in quality of life and should be better recognized and treated in patients with comorbid panic disorder [119].

SELECTIVE MUTISM

Separation anxiety disorder and selective mutism were included in the DSM-IV section Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence, but were classed as anxiety disorders and moved to the anxiety disorder section in the DSM-5 [102]. The majority of children with selective mutism are anxious, and while selective mutism is now considered an anxiety disorder, it remains a disorder primarily of childhood and is beyond the scope of this course [102].

ASSESSMENT

Effective anxiety disorder treatment relies on accurate diagnosis. Diagnosis is made when diagnostic criteria are met and the anxiety is not better explained by the effects of other medical conditions, medications, substances, or other mental disorders [2].

The management of patients presenting with anxiety symptoms should initially follow the flow of these five components [120]:

1. Screen for anxiety and related symptoms.
2. Consider differential diagnosis and severity, impairment, and comorbidity.
3. Identify specific or multiple anxiety disorder(s).
4. Initiate psychologic and/or pharmacologic treatment.
5. Perform follow-up.

Evidence suggests that in primary care, patient tendency to ascribe pathologic anxiety symptoms to physical causes contributes to high rates of missed diagnoses and the misdiagnosis of GAD and panic disorder. To offset this requires a broad differential and caution to identify confounding variables and comorbid conditions [121].

SCREENING FOR ANXIETY DISORDERS IN THE PRIMARY CARE SETTING

In primary care settings, panic disorder prevalence is around 10%, with GAD co-occurring in 68% of patients with panic disorder and in 38.6% of those with major depression [34; 122]. The American Academy of Family Physicians states that rates of missed diagnoses and misdiagnosis of GAD and panic disorder are high in primary care, with symptoms often ascribed to physical causes [121]. One study of older patients with GAD found low rates of anxiety symptom recording (34%) and anxiety disorder diagnosis (9%) despite high levels of healthcare utilization [123]. In the current managed care environment, anxiety is usually treated in the primary care setting, and given the increasing time constraints imposed on primary care providers, it is not surprising that anxiety disorders are under-recognized and undertreated [70].

Many patients with anxiety and depressive symptoms do not seek help, and in those who do, anxiety symptoms are often not the presenting complaint. Patients and providers often have difficulty initiating discussion of emotional problems and distress. Primary care providers with greater sensitivity to nonverbal communications have been found more likely to detect and diagnose anxiety, while those tending to "blame" patients make fewer psychologic inquiries and are less accurate in detecting distress [3; 124].

PATIENT SCREENING

The American Academy of Family Physicians suggests using screening and monitoring tools, such as the Generalized Anxiety Disorder 7-Item Scale (GAD-7) and the Severity Measure for Panic Disorder, to help establish diagnosis and monitor therapy response [121]. In theory, patients and providers should benefit from screening tools to detect anxiety disorders. However, use of screening tools requires other changes in practice structure, and it is uncertain whether routine screening and disclosure to "screened positive" patients improves clinical outcomes. One primary care educational intervention using this design did not find patient outcomes improved [3; 125].

In the past, routine screening of anxiety symptoms was not recommended, but in 2022, the U.S. Preventive Services Task Force recommended screening all children older than 7 years of age for anxiety, and in 2023, they expanded their recommendation to include screening all adults, including pregnant and postpartum persons, for anxiety disorders [349; 350]. Primary care providers can improve anxiety detection skills by acknowledging that many patients are reluctant to discuss psychologic problems. This can be offset with greater sensitivity to nonverbal expression of psychologic distress and using repeated patient contact to ask about possible anxiety symptoms if suspected but not confirmed in earlier appointments [3].

Healthcare providers can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health. Symptom presentation is influenced by cultural factors, and in some cultures, anxiety may be expressed through somatic symptoms, such as musculoskeletal pain and fatigue. Providers may consider starting the conversation with the patient by focusing on physical symptoms. The concept of anxiety also varies across cultures, and patients may not seek medical treatment unless symptoms manifest as psychosis, conversion disorders, or significant physical ailments.

IDENTIFYING PATIENTS WHO REQUIRE TREATMENT

The potential chronicity and disability of anxiety disorders indicates that most patients meeting anxiety disorder diagnostic criteria should receive psychologic and/or pharmacologic treatment. Treatment selection is guided by severity, duration, patient distress and impairment, the presence of depression and other comorbid disorders, previous treatment response or contraindication, evidence base, patient preference, provider experience, and treatment availability [3; 126]. However, many patients with anxiety disorders who could benefit do not receive treatment. Fewer than one in five patients with an anxiety disorder receive appropriate medication; this improves to one in three for patients with comorbid depression [127].

Treatment quality is improved with accurate diagnosis and regular monitoring. Inadequate dosage and treatment duration were found common in the primary care treatment of patients with panic disorder, but improved outcomes were more likely with enhanced patient education and follow-up contact than with physician education [3; 128]. Worth noting is the contrast between concerning media reports of medicalization and inappropriate psychotropic prescribing for "normal" anxiety, shyness, or situational stress, and the repeated findings in primary care studies of inadequate or no prescribing and a high level of unmet patient need [3].

SCREENING QUESTIONS

General Screening

Ask patients if they have recently felt excessively nervous, anxious, or on edge, or if they worry uncontrollably. The DSM-5 suggests the following questions for identifying anxiety-related symptoms [2]:

During the past two weeks, how much have you been bothered by the following problems:

- Feeling nervous, anxious, frightened, worried, or on edge
- Feeling panic or being frightened
- Avoiding situations that make you anxious

A positive history of anxiety symptoms should be explored with screening questions for specific anxiety disorders.

Screening for Specific Anxiety Disorders

In addition to the general questions suggested for all patients with complaints of anxiety, it is important to inquire regarding disorder-specific symptoms. This will allow for more specialized assessment and diagnosis.

Generalized Anxiety Disorder

- During the past four weeks, have you been bothered by feeling worried, tense, or anxious most of the time?
- Are you frequently tense or irritable, or do you have trouble sleeping?

Panic Disorder

- Do you have sudden, unexpected episodes/spells/attacks of intense fear or discomfort? If yes, then continue.
- Have you had more than one of these attacks?
- Does the worst part of these attacks usually peak within several minutes?

- Have you ever had one of these attacks and spent the next month or more living in fear of having another attack or worrying about the consequences of the attack?

Agoraphobia

- Do you avoid certain situations or places where panic attacks have occurred or may occur?

Social Anxiety Disorder

- Does fear of embarrassment cause you to avoid doing things or speaking to people?
- Do you avoid activities where you are, or may be, the center of attention?
- Is being embarrassed or looking stupid among your worst fears?

Specific Phobia

- Do you feel intense anxiety or fear when confronted by certain animals, objects, or situations?
- Are you avoiding these animals, objects, or situations because of your fear?
- In what ways has this anxiety or fear interfered with your life?
- How would you react if you were exposed to the animal, object, or situation right now?
- Have you ever fainted or almost fainted around blood, injuries, or needles?

Separation Anxiety Disorder

- Do you feel anxious, fearful, or upset thinking about separation, or being away from, your (spouse, partner, primary support person)?

Positive responses to screening questions is followed by a formal assessment.

PATIENT HISTORY

A patient history is performed to assess patient and family history for clinically relevant information. Patients should be assessed for onset of anxiety symptoms, duration (remission or persistent), association with life events or trauma, level of distress, and effect on current functioning (academic, occupational, relationships, leisure activities, role functioning). Also inquire about a personal history of physical or emotional trauma, anxiety or mood disorders, medications or therapies, and patient response. Family history should be assessed for anxiety, mood, and substance use disorders [2]. Screening for depression is very important, given its high comorbidity rate and associated risk of suicidal behavior [129].

A thorough list of prescribed, over-the-counter, and herbal medications should be obtained [2]. Furthermore, substance use should be assessed, including:

- Current and past tobacco use
- Current and past alcohol use
- Current and past use of illicit drugs (e.g., cannabis, cocaine, heroin, methamphetamine)
- Current and past use of pharmaceutical drugs (e.g., opioids, stimulants, benzodiazepines)
- Current and past use of "legal high" or novel drugs (e.g., club drugs, "bath salts," "synthetic cannabis")
- Having been told their substance use is a problem
- Having received counseling or treatment for a substance use problem

PHYSICAL EXAMINATION

There are usually no objective findings in persons presenting with anxiety disorders, although patients may become noticeably anxious or nervous when discussing their anxiety. Signs reflective of heightened sympathetic nervous system activity may be present (e.g., tachycardia, hyperventilation, sweating, flushing). Vasovagal fainting may also be present, especially when individuals with blood-injection-injury phobia are exposed to medical situations or procedures. These patients should be assessed for other medical conditions associated with fainting risk (including blood glucose levels and orthostatic hypotension) [2].

Diagnosis is made through self-report, clinical interview, and behavioral observation of impairments in personal, social, or occupational domains; no laboratory testing is necessary. Several empirically validated self-report questionnaires are available to assess baseline functioning and track treatment response. Assessment of anxiety symptoms and associated impairments optimally includes key informant interviews with family members or close friends [2].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is performed to eliminate potential underlying causes that, if present, would better account for patient anxiety complaints. As noted, screening for other anxiety, mood, and substance-related disorders should be routinely conducted due to high comorbidity rates.

Other Mental Disorders

To confirm or rule out the presence of comorbid anxiety or related disorders, determine the nature and focus of patient apprehension/anxiety. It may be [2]:

- Diffuse, non-specific (GAD)
- Discrete, intense anxiety episodes (panic disorder)
- Fear of one's panic attacks and avoidance of places or situations where they may occur (agoraphobia)
- Embarrassment in public (SAD)
- Fear of specific objects or situations (specific phobia)
- Attachment figure separation (separation anxiety)
- Contamination (OCD)
- Weight gain (anorexia nervosa)

- Multiple physical complaints (somatization disorder)
- Serious illness (hypochondriasis)
- Strictly trauma-related (PTSD)

A diagnosis of SAD should rule out avoidant personality disorder. Some symptoms of avoidant personality disorder resemble SAD, such as a pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation. However, avoidant personality disorder is distinguished by non-social avoidance that extends to novel situations and positive affect. Roughly 36% of patients with SAD are comorbid for avoidant personality disorder, and some believe avoidant personality disorder is a more severe variant of SAD [130; 131].

Medication or Substance Use

It is important to rule out medication side effects as the underlying cause of anxiety by obtaining a complete list of currently used prescribed, over-the-counter, and herbal medications. Examples of common medications with anxiety side effects are asthma medications (e.g., albuterol, theophylline), herbal medicines (St. John's wort, ginseng, *ma huang*), corticosteroids, and antidepressants [2].

Patients should also be assessed for current use of alcohol, nicotine, stimulants, benzodiazepines, and opioids, because the direct, adverse, or withdrawal effects can mimic anxiety or panic symptoms [132]. Illicit or illicitly used drugs with acute effects most commonly associated with anxiety include cocaine, methamphetamine, prescription amphetamines (e.g., lisdexamfetamine), methylphenidate, and MDMA ("Ecstasy") [2]. Caffeine may also provoke anxiety in sensitive patients, including those with anxiety disorders [28]. Alcohol use disorder is highly prevalent among persons with anxiety disorders. Acute anxiety relief may powerfully reinforce alcohol use, but frequent or heavy drinking commonly exacerbates the anxiety disorder symptoms. When these two disorder co-occur, treatment can be complicated.

Medical Conditions

Careful history taking and physical examination are warranted for all patients to rule out medical causes of anxiety symptoms. Conditions that can mimic or cause anxiety complaints include hyperthyroidism and hypothyroidism, asthma, cardiac arrhythmias, pheochromocytoma, and temporal lobe epilepsy. As noted, screening for depression is very important, given its high comorbidity rate and associated risk of suicidal behavior [129].

Laboratory Tests and Imaging

Although usually negative in the absence of other suggestive evidence, laboratory testing or imaging studies may be indicated to help rule out medical cause. For example, a routine blood panel with thyroid-stimulating hormone and blood glucose levels may help to identify or rule out conditions such as hyperthyroidism or hypoglycemia that may be responsible for intense, persistent anxiety and panic. Toxicology screening may also be indicated to determine whether illicit substances are contributing to the clinical presentation. An electrocardiogram is required in all patients presenting with chest pain (to exclude cardiac causes), and pulmonary function tests are used to rule out pulmonary disease in patients with shortness of breath. It is important to note that cardiopulmonary disorders can co-occur with anxiety disorders [2].

Screening Tools

The Primary Care Evaluation of Mental Disorders (PRIME-MD) was developed as a screening instrument, but its administration time has limited its clinical usefulness. The instrument contains modules on 12 different mental health disorders [133]. The panic screen contains four yes or no questions to assess the presence of panic attacks within the last four weeks. Responding "yes" to all four questions indicates likely presence of panic disorder. The panic screen also includes 11 somatic and cognitive symptoms, with endorsement of at least 4 of these symptoms indicative of likely panic disorder [133]. Developers of the PRIME-MD subsequently created the Patient Health Questionnaire (PHQ), which is a self-administered version of the PRIME-MD. The PHQ contains mood, anxiety, alcohol, eating, and somatoform modules as covered in the original PRIME-MD [134]. The GAD-7 was subsequently developed as a brief self-report measure for assessing anxiety severity in primary care. In total, seven items are scored on a 0 to 3 scale, with a cut score of ≥10 indicative of a likely anxiety disorder. Designed to measure generalized anxiety, the GAD-7 is also sensitive in detecting panic-related symptoms [135].

GENERAL TREATMENT CONSIDERATIONS

Information in this section is derived from published research, meta-analyses, and clinical practice guidelines. The most recent anxiety disorder guideline (on panic disorder) by the American Psychiatric Association was published in 2009. The 2014 Anxiety Disorders Association of Canada (ADAC) guidelines are the most recent and comprehensive North American publication and are emphasized accordingly [120]. Successful treatment requires tailoring options to individuals and may often include a combination of modalities [121].

CBT, which includes an exposure therapy component, is used to address and work through maladaptive beliefs and avoidance behaviors that reinforce pathology surrounding fear-eliciting stimuli. CBT with some variant of exposure is the first-line psychotherapy approach for most pathologically anxious patients. Pharmacotherapy, also a first-line treatment for anxiety disorders, uses various agents to induce rapid anxiolytic effects (e.g., benzodiazepines, some anti-epilepsy drugs) or agents that require prolonged, long-term treatment (e.g., antidepressants) to attenuate symptoms of pathologic fear and anxiety [136].

Advances in anxiety disorder neuroscience have increasingly pointed to the necessary role of fear extinction learning (through exposure therapy) in addressing underlying pathophysiology. While efficacy is shown with CBT and exposure,

patients can have difficulty with the demanding and exhausting therapy process, and many who do manage to complete therapy respond partially and relapse with time. Efforts to improve CBT/exposure outcomes have led to the investigation of augmenting agents. In contrast to standard anti-anxiety drugs, these agents are not anxiolytic but are used to promote and accelerate long-term adaptive changes in brain function initiated by successful exposures [137].

Any review of treatment efficacy for anxiety disorders, and pharmacotherapy in particular, requires a disclaimer. Most treatment outcomes were based on studies using methodologies that excluded those with additional anxiety disorders and comorbid psychiatric or medical disorders. Patients seeking care for anxiety problems in primary care and other real-world settings often differ from carefully screened study participants. The extent that efficacy, response, and remission rates reported in the published research generalize to typically more complex clinic patients has been questioned [138].

Treatment refusal and attrition are significant problems. Patients with anxiety disorders show treatment refusal rates of 25% to 30% and treatment dropout rates of 10% to 82% [139]. Treatment dropout is very high in exposure therapy, as patients repeatedly confront (with graded intensity) the situations or objects that trigger their greatest fear or panic response. The intensity of distress during exposure can overwhelm patients, and with avoidance the hallmark feature of most anxiety disorders, attrition is significant [2; 139]. Attrition can interfere with evaluating treatment efficacy (or the lack thereof), and unless explicit in study reporting, can be misleading. Attrition is also a clear concern in the clinical care of patients with anxiety.

PREDICTORS OF WORSE TREATMENT RESPONSE AND OUTCOMES

SEPAD

Pathologic SEPAD is associated with a pervasive negative influence on treatment response. Comorbid SEPAD is highly correlated with poor treatment response and patient outcomes across a range of anxiety and mood disorders. SEPAD negatively impacts response to major depression treatment and is linked to worse symptom chronicity and quality of life. SEPAD decreases CBT response and predicts worse outcomes in patients treated for panic disorder, GAD, or SAD. SEPAD also predicts nonresponse to selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) in patients with panic disorder with agoraphobia [98; 140].

Chronic Pain

Uncontrolled pain is also increasingly recognized to negatively impact anxiety disorder treatment outcomes. In primary care patients with a GAD or panic disorder diagnosis treated for severe anxiety and followed for one year, patients with moderate or greater pain levels were found to show significantly lower rates of clinical improvement [141]. A cohort of 1,122 individuals with remitted anxiety or depressive disorders were followed up to four years, and pain (but not chronic disease) was associated with recurrence during follow-up [142].

Social Drinking

Problematic, excessive drinking clearly disrupts treatment response, but social drinking can also aggravate panic disorder and probably other anxiety syndromes. The short-acting effects of alcohol wear off rapidly, followed by rebound to a state of hyper-excitability that may be more problematic for patients with anxiety. This can occur with one to two drinks in some patients, who often do not even consider this a contributing factor to their anxiety complaint. Explaining the simple physiology of rebound excitation after profound neuronal inhibition will often convince patients that alcohol may be sensitizing the neural circuits subserving their anxiety and that a trial period of abstinence is indicated [28].

Other Anxiety Disorders

Highly symptomatic panic inhibits benefit from interpersonal psychotherapy, either alone or combined with SSRIs. The presence of any anxiety disorder impairs response to treatment of comorbid major depression [98]. Patients with major depressive disorder and a comorbid anxiety disorder demonstrate longer time to recovery and greater risk of early treatment termination. Patients with comorbid anxiety and depressive disorders generally have worse outcomes than patients with either disorder alone. Patients with comorbid GAD and major depression are significantly more likely to remain symptomatic than those with depression or GAD alone [143]. When anxiety symptoms are present within a dominant depressive disorder, antidepressant drugs are often effective in reducing anxiety [144]. However, depression that follows or is comorbid with an anxiety disorder usually indicates greater severity and worse prognosis [145].

Among treatment-seeking patients with panic disorder, SAD, or GAD followed over two years, symptom changes in GAD were most specifically related to changes in impairment, suggesting that treatment of patients with multiple anxiety disorders should initially focus on GAD symptoms or employ trans-diagnostic modalities [146].

Patients with panic disorder/agoraphobia who display the low-expression allele of the serotonin transporter gene promoter show more favorable exposure therapy response than patients with other 5-HTTLPR genotypes. This genetic contribution to exposure therapy outcome implicates the serotonergic system as a response mediator to exposure treatments [85].

OVERLAPPING PSYCHOLOGIC AND DRUG THERAPY MECHANISMS

Emerging evidence is challenging conventional wisdom by showing that antidepressant therapeutic action may begin with the first dose and that psychologic and drug therapy approaches share common mechanisms. In one study, a single-dose of the norepinephrine reuptake inhibitor reboxetine reduced negative affective bias in depression by increasing the recognition of positive facial expressions and enhancing memory for positive vs. negative information [147]. These early changes in emotional processing reflect changes in frontolimbic circuitry involved in the detection and response to biologically salient information. These findings were replicated following seven

days of escitalopram treatment [148]. Changes in neurocognitive processing that precede clinical improvement predict later antidepressant response [149]. A 2013 study found that single-session CBT for panic disorder/agoraphobia led to reduced threat processing the following day, with magnitude of early effect predicting therapeutic response after four weeks [150]. These findings challenge assumptions that psychologic therapies address conscious thought processes before automatic information processing and suggest a greater similarity between early effects of pharmacologic and psychologic treatments for anxiety than previously thought [149].

PSYCHOTHERAPIES: OVERVIEW

Psychologic treatments play an integral role in the management of anxiety disorders, and efficacy is established for several modalities. Most broadly effective are exposure-based and other CBT approaches. When choosing psychologic treatments for individual patients, the forms of therapy developed for the specific anxiety disorder should be used first.

Cognitive and Behavioral Approaches

Psychotherapy can be as effective as medication for GAD and panic disorder, and CBT has the best level of evidence [121]. CBT is the most extensively evaluated psychologic therapy in anxiety disorders and contains elements of cognitive and behavioral therapy approaches.

Behavior therapy is characterized by the use of exposure to modify dysfunctional behaviors that may contribute to the development and persistence of psychologic symptoms [151]. Cognitive therapy involves cognitive restructuring, a psychotherapeutic process of learning to identify and modify irrational or maladaptive thoughts using strategies such as Socratic questioning, thought recording, and guided imagery [34].

CBT is not a single treatment approach but a process that addresses factors that caused and maintain patient anxiety symptoms. The classic CBT approach involves disorder-specific treatment protocols that target the symptoms and the cognitive, behavioral, and emotional vulnerabilities that underlie development and maintenance of each disorder. This approach reflects the assumption that each form of psychopathology has a distinct cognitive profile, to which CBT is tailored accordingly. Disorder-specific CBT is the standard of care for anxiety and depressive disorders [152]. However, there are common components of CBT used in anxiety disorders (***Table 2***) [120].

There is some debate regarding whether the efficacy of CBT that targets common underlying factors would be comparable to standard diagnosis-tailored CBT. Support for CBT that addresses common underlying factors includes frequent comorbidities in anxious patients, such as major depressive disorder, which some studies found present in close to 50% of patients with anxiety [153]. The frequent co-presence of mood and anxiety disorders, substantial overlap in dimensional symptom ratings, and extensive evidence of shared vulnerability factors led to identification of common underlying factors that represent targets for CBT. These include [152]:

- Motivational enhancement
- Psychoeducation and understanding emotions
- Emotional awareness training
- Cognitive reappraisal
- Attenuation of emotional and behavioral avoidance
- Awareness and tolerance of physical sensations
- Interoceptive and situational exposure
- Relapse prevention

Psychotherapy and drug therapy show similar efficacy in most anxiety disorders. Psychotherapy plus drug (combination) therapy outcomes vary and are conflicting, and current evidence does not support routine combination therapy as initial treatment. However, patients lacking response to CBT or drug therapy may benefit from adding the other modality [120].

Delivery of effective CBT is versatile. Individual or group delivery is effective in most anxiety disorders. A variety of self-directed or minimal intervention formats (e.g., bibliotherapy/self-help books, Internet/computer-based CBT with or without minimal therapist contact) have shown significant improvements in anxiety symptoms, and exposure therapy can be effective using a virtual reality format. These strategies can be very useful when real-life exposure is made difficult by inconvenience or patient reluctance [120].

Third-Wave Therapies

Mindfulness-based cognitive therapy, acceptance and commitment therapy, compassionate mind training, extended behavioral activation, metacognitive therapy, and schema therapy are diverse approaches originating from CBT. These modalities place greater importance on the form rather than content of patient cognitions. These third-wave therapies help patients develop more adaptive emotional responses to situations by focusing on the function of cognition. Mindfulness and acceptance are used in anxiety disorders to help patients observe symptomatic processes without overly identifying with or reacting to them in ways that perpetuate distress [154].

Mindfulness

Mindfulness involves attending to relevant aspects of experience in a non-judgmental manner. The goal of mindfulness is to maintain moment-by-moment awareness; disengage oneself from strong attachment to beliefs, thoughts, or emotions; and develop a greater sense of emotional balance and well-being. An aim of mindfulness practice is to take greater responsibility for one's life choices. Some evidence supports the efficacy of this approach in GAD and panic disorder [155; 156; 157].

Mindfulness versus active control was compared in ability to reduce negative thought intrusions activated by a worry-induction procedure. Negative thought intrusions significantly increased with progressive muscle relaxation and focused attention but not with brief mindfulness meditation, suggesting mindfulness might target anxiety by reducing negative elaborative processes that maintain worry [158].

COMMON COMPONENTS OF CBT USED IN THE TREATMENT OF ANXIETY DISORDERS
Cognitive Strategies
Cognitive restructuring, behavioral experiments, and related strategies target exaggerated perception of danger (e.g., fear of negative evaluation in SAD). Therapy provides corrective information regarding the level of threat and can also target self-efficacy beliefs.
Arousal Management
Relaxation and breathing control skills help control increased anxiety levels.
Exposure
Encourage patients to face fears. Patients learn corrective information through experience. Extinction of fear occurs through repeated exposure. Successful coping enhances self-efficacy.
Safety Response Inhibition and Surrender of Safety Signals
Patients wean from and relinquish use of their usual anxiety-reducing safety signals and behaviors (e.g., presence of a companion, need for reassurance, knowing the location of nearest exit or toilet), which decreases negative reinforcement. Coping with anxiety without using anxiety-reducing behavior enhances self-efficacy, allowing patients to learn adaptive self-efficacy beliefs.
Source: [120] *Table 2*

Acceptance and Commitment Therapy

Acceptance and commitment therapy views psychologic events as a set of ongoing interactions between whole organisms and contexts defined historically and situationally. Acceptance and commitment therapy states that analyzing problematic behaviors but excluding the contexts that participate in the event misses the nature of the problem and pathways for its solution. This approach promotes a conscious posture of openness and acceptance of all psychologic events, including those deemed "negative" or "irrational." In acceptance and commitment therapy, when patients feel frustrated, afraid, angry, or anxious, this represents an opportunity to examine how powerful events in the present can become barriers to growth [159]. Some evidence suggests acceptance and commitment therapy may be as effective as CBT in anxiety disorder treatment, including panic disorder [151; 160; 161].

Acceptance-based skill training differs from traditional coping skills training by de-emphasizing control (over physiology or thoughts) to focus on acceptance of panic-related sensations and cognitions as they occur from moment to moment. Patients learn to pay nonjudgmental attention to thoughts, feelings, images, and bodily sensations. Thoughts are viewed as an ongoing process distinct from self, rather than events with literal meaning (cognitive defusion). Efficacy of acceptance approaches has been shown in patients with panic disorder/agoraphobia [162].

Education and Support

Psychoeducation states that providing information to patients with anxiety about their anxiety symptoms and theories of psychologic therapy may reduce these symptoms. By increasing the patient's sense of control, psychoeducation may reduce catastrophic thoughts and emotions. This is especially relevant in patients with panic disorder, in which cognitive coping mechanisms are disrupted and anticipatory anxiety may cause additional attacks [151].

Supportive psychotherapy is non-specific in nature and uses encouragement, rationalizing/reframing, and anticipatory guidance to reduce symptoms and maintain, restore, or improve self-esteem, ego function, and adaptive skills. This approach views the therapeutic alliance as the most important element. The archetype of supportive psychotherapy is the Rogerian client-centered approach; a warm, empathic, and non-directive therapeutic relationship helps clients become aware of their true feelings and achieve full self-acceptance. This approach may benefit patients with agoraphobia, but efficacy in panic disorder is unclear [151].

Physiologic Therapy

Physiologic therapies involve physical training (e.g., breathing retraining, relaxation techniques, biofeedback) to help patients control physiologic anxiety symptoms. Hyperventilation and hypocapnia are identified factors in panic disorder development and maintenance; panic attacks can be caused by acute hypocapnia states in a positive feedback loop between hyperventilation and anxiety. Breathing training is used to ameliorate panic symptoms, but it shows mixed efficacy in panic disorder [162]. Progressive muscle relaxation teaches patients with panic to reduce general tension and achieve a body state that lowers the risk for panic-inducing stressors. Applied relaxation teaches patients to observe the first signs of a panic attack and apply a rapid and effective relaxation technique to cope with and abort panic symptoms before escalation into a panic attack. Applied relaxation is comparable to progressive muscle relaxation in reducing panic attacks [151].

Psychodynamic Approaches

Psychodynamic therapies are psychologic approaches differing in length and depth, based on Freudian psychoanalysis and later refinements. Psychodynamic psychotherapy views psychologic symptoms as the manifestation of intra-psychic or unconscious conflicts; treatment involves uncovering,

interpreting, and resolving such conflicts through the analysis of unconscious contents, dreams, past experiences, parental relationships, transference, and/or resistances [151]. A brief panic-focused psychodynamic psychotherapy, derived from psychodynamic theories, utilizes emotion-focused therapy, whereby the therapist is viewed as an "emotion coach" who works to enhance emotion-focused coping by helping patients become aware of, accept, and make sense of their emotional experience [163].

One psychodynamic psychotherapy approach proposes that fearful parental dependency in childhood may lead to anger toward the parent. A vicious cycle is created; anger threatens the needed tie to the parent and increases fearful dependency, which promotes further frustration and rage at the parent. This cycle may recur in adulthood when threats to attachment trigger intense feelings of abandonment, anger, and anxiety, promoting the development of pathologic anxiety. The goal is to address such underlying psychologic factors to decrease panic symptoms. Some evidence suggests this approach is a valid therapeutic option, especially when SEPAD is present [98; 151].

Exposure Therapies

Exposure therapy is defined as any treatment that encourages patients to systematically confront feared stimuli, which can be external (e.g., feared objects, activities, situations) or internal (e.g., feared thoughts, physical sensations) [136]. Exposure therapy is an effective, empirically supported treatment modality for anxiety disorders and a core component of CBT. Variants of exposure therapy include:

- In vivo exposure: Exposure that involves real-world confrontation of feared stimuli
- Imaginal exposure: Vividly imagining and describing the feared stimulus, including details about external (sights, sounds) and internal (thoughts, emotions) cues
- Virtual reality exposure: Patient immersion into a software-generated virtual world that allows them to confront their fears

The success of exposure therapy occurs by targeting maladaptive learning and fear conditioning, core mechanisms implicated in anxiety disorder etiology and maintenance. Standard exposure therapy involves exposure to feared objects or situations and gradual elimination of safety behaviors—the subtle avoidance behaviors that temporarily diminish distress in feared situations but interfere with long-term anxiety reduction. Patients are encouraged to continue confronting the feared situations through exposure until substantive reductions in fear occur. Exposure therapies facilitate extinction learning by diminishing the association between the avoided situation and fear and promoting new learning of the true nonthreatening nature of the situation [164; 165].

Exposures are graded in intensity, with the same process used for weaning safety signals. For instance, a patient with panic disorder and agoraphobia can initially practice walking through a congested shopping mall with a family member; on the next exposure, he or she may practice walking separately through the shopping mall, and eventually walk through the congested mall alone. Patients are taught that treatment setbacks are common and to distinguish between expected treatment lapses and relapses. Symptom flare-ups do not mean treatment failure, but instead are opportunities to revisit psychoeducation, cognitive restructuring, or exposure, and work toward regaining progress [166].

A substantial number of patients fail to achieve substantive symptom relief from exposure-based therapies or experience fear relapse following exposure therapy. This results from deficits in the mechanisms considered central to extinction learning (e.g., poor medial prefrontal cortex inhibition of amygdala-generated fear impulses) that contributed to the development of pathologic anxiety and avoidance in the first place. Because of this, effort is underway to optimize exposure therapies to improve significant and durable patient response [167]. This effort includes the therapeutic alliance as a potential prognostic indicator [168].

PHARMACOTHERAPY: OVERVIEW

The first-generation antidepressants monoamine oxidase inhibitors (MAOIs) and TCAs were introduced in the late 1950s and early 1960s, and the first report of antidepressant use in anxiety treatment was published in 1962. In this account, patients with agoraphobia who were given the TCA imipramine showed reductions in panic attacks and improved exposure to feared situations [169]. The benzodiazepine chlordiazepoxide (Librium) was introduced to the U.S. market in 1960. This was followed by diazepam (Valium) in 1963, which became the most prescribed drug in the United States from 1969 to 1982; in 1978, more than 2.3 billion diazepam doses were sold in the United States [170]. Panic disorder was first formalized as a psychiatric disorder in the 1980 DSM-III, and alprazolam (Xanax) became the first U.S. Food and Drug Administration (FDA)-approved drug for panic disorder treatment in 1981, remaining the most-prescribed benzodiazepine to date [171].

In the past two decades, antidepressant drugs have displaced benzodiazepines as the most widely prescribed and recommended anxiety disorder pharmacotherapy. Efforts to improve safety, efficacy, and tolerability led to introduction of the second-generation antidepressants, with trazodone (Oleptro) in 1982, bupropion (Wellbutrin) in 1985, and fluoxetine (Prozac)—the first domestically marketed SSRI—in 1987.

Antidepressants are generally recommended as first-line therapy for panic disorder because, unlike benzodiazepines, antidepressants treat comorbid depression and lack abuse risk and potential side effects of excessive sedation, cognitive impairment, and ataxia. All major antidepressant classes are comparably effective, but SSRIs and, increasingly, serotonin-norepinephrine reuptake inhibitors (SNRIs) are recommended over TCAs and MAOIs due to better safety and tolerability [172].

Tricyclic Antidepressants

Norepinephrine, serotonin (5-HT), and dopamine are termed monoamines. Monoamine reuptake transporters retrieve monoamines released into the synaptic cleft to terminate their activation of post-synaptic monoamine receptors. TCAs act by inhibiting norepinephrine and 5-HT reuptake transporters. This increases synaptic levels of norepinephrine and 5-HT by preventing their clearance, which increases post-synaptic receptor activation and signaling. TCAs generally have greater norepinephrine than 5-HT reuptake transporter potency. TCAs also act as histamine H1/H2, muscarinic acetylcholine, and alpha-adrenergic receptor antagonists, resulting in a range of undesirable side effects associated with patient intolerance and discontinuation, including [173]:

- Anticholinergic: Dry mouth, blurred vision, constipation, urinary hesitancy and retention, confusion, precipitation of glaucoma, delayed ejaculation, sweating
- Alpha-1-adrenoceptor antagonism: Postural hypotension, increased heart rate, dizziness
- Antihistaminergic: Sedation, psychomotor slowness, weight gain
- Cardiac sodium channel blockade: QTc prolongation, decreased cardiac conduction, fatal cardiac arrest in overdose

TCAs have comparable efficacy to SSRIs in panic disorder and GAD [174; 175]. TCAs are lethal in overdose and, compared to SSRIs, have a markedly broader, more problematic, and less tolerable side effect profile [172]. Nonetheless, TCAs may work when first-line agents do not [136]. Also, some patients with panic disorder are sensitive to both beneficial and adverse effects of TCAs, so they cannot tolerate imipramine doses >10 mg/day but may still experience panic blockade [172].

Monoamine Oxidase Inhibitors

MAOIs inhibit MAO, an enzyme that degrades and inactivates 5-HT, norepinephrine, and dopamine, thereby increasing monoamine levels and activity. The earlier MAOIs—phenelzine (Nardil) and tranylcypromine (Parnate)—are characterized by irreversibility and nonselectivity. Irreversibility refers to tenacious drug binding to the MAO enzyme for the 14- to 28-day lifespan of the drug molecule. Nonselectivity refers to phenelzine and tranylcypromine binding to both A and B isoenzymes of MAO. While tyramine and dopamine are metabolized by both MAO-A and MAO-B, MAO-A inhibition is established as the precursor to hypertensive crises [176].

During phenelzine or tranylcypromine therapy, dangerous and potentially fatal hypertensive reactions can result from co-ingestion of drugs with monoamine activity or foods high in tyramine content (e.g., cheese, beer, wine). Concurrent use of serotonergic agents or supplements such as St. John's wort can cause potentially lethal serotonin syndrome. Common side effects include orthostatic hypotension, weight gain, sexual dysfunction, sedation, headache, and insomnia. To avoid drug interactions, washout periods are required before an MAOI is started (≥ 5 days) or stopped before switch to another medication (≥14 days) [136].

Moclobemide is a reversible inhibitor of monoamine oxidase type A (RIMA). With reversibility, MAO enzyme detachment and/or displacement readily occur, greatly improving safety. Compared to tranylcypromine, it takes eight times the tyramine level (8 mg vs. 63 mg) with moclobemide to induce a 30 mm Hg rise in diastolic blood pressure; dietary and co-medication concerns are greatly reduced. No washout period is required for switching anti-depressants. Moclobemide is safe in overdose, and 20,000 mg has been ingested without fatality. Common side effects include nausea, insomnia, tremor, and lightheadedness. Orthostatic hypotension is uncommon, even in the elderly [176]. Moclobemide lacks the cholinergic and histaminergic side effects of TCAs and the sexual side effects of SSRI/SNRIs. Depressive patients more commonly reported improved libido, erection/ejaculation, and orgasm with moclobemide. Weight gain or lowered seizure threshold are not side effects [177]. Moclobemide was slated for introduction in the United States in 1992. It was withdrawn from the application process because SSRI popularity cast doubts on its profit potential. This drug is available in Canada and throughout Europe and Asia [176; 178].

MAOIs and RIMAs are effective for panic disorder and SAD and are thought by some to be superior options for severe, treatment-resistant anxiety disorders. As noted, MAOIs have a substantial side effect profile and impose the greatest safety burden of all antidepressants. Therefore, they are usually reserved as the last treatment option after other drug therapies have failed to achieve remission [179]. Clinicians do not routinely prescribe MAOIs for anxiety disorders, although they are probably not considered often enough in treatment-resistant patients [136].

SSRIs

SSRIs are considered first-line therapy for GAD and panic disorder [121; 172]. SSRI mechanism is thought to involve serotonin transporter (SERT) inhibition at the presynaptic axon terminal of 5-HT neurons. SERT inhibition also occurs at the somatodendritic end of the neuron, where the increase in 5-HT causes 5-HT1A autoreceptors to downregulate, desensitize, and over time lose the ability to inhibit 5-HT release. The resultant increase in synaptic 5-HT level mediates the therapeutic action. SSRIs were termed "selective" because, unlike TCAs, they were believed to have little-to-no interaction with non-serotonin receptors and transporters [136; 180].

It is now recognized that SSRIs differ in pharmacologic effect, including activity beyond SERT inhibition [179; 180]:

- Fluoxetine: Antagonist at 5-HT2C receptors, which enhances norepinephrine and dopamine release. Therapeutic effects may emerge more slowly than other SSRIs.

- Sertraline (Zoloft): A weak dopamine transporter inhibitor, sigma-1 receptor activity. Along with fluoxetine, increases cortex monoamine levels to possibly explain patient reports of improved energy, motivation, and concentration.
- Paroxetine (Paxil): A weak norepinephrine transporter inhibitor, which contributes to antidepressant effects. Muscarinic cholinergic receptor activity may underlie some sedative and anxiolytic effects.
- Fluvoxamine (Luvox): Along with sertraline, has sigma-1 receptor activity that possibly contributes to the anxiolytic effects of both agents.
- Citalopram (Celexa): Mild antihistamine properties not observed with escitalopram.
- Escitalopram (Lexapro): Is considered the only SSRI without pharmacologic activity beyond SERT inhibition.

The atypical SSRIs vilazodone (Viibryd) and vortioxetine (Trintellix) display expanded serotonergic and other monoaminergic activity beyond those of standard SSRIs. Vilazodone and vortioxetine are likely to be treatment options for patients who do not respond to or cannot tolerate typical SSRIs/SNRIs.

Common SSRI side effects include gastrointestinal upset (nausea, vomiting, diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, sleep disturbances), sexual dysfunction (loss of erectile or ejaculatory function in men, loss of libido and anorgasmia in both sexes), headache, fatigue, and weight gain. Many side effects dissipate over time. Sertraline is particularly associated with diarrhea, and paroxetine with weight gain. Discontinuation syndrome from paroxetine is more severe and protracted than other SSRIs [181]. To avoid relapse, medication should be continued for at least 12 months after symptom improvement before tapering [121].

Vilazodone

Approved by the FDA in 2011, vilazodone primarily acts as a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, with modest action as a dopamine and norepinephrine reuptake inhibitor, with 5-HT4 receptor activity [173]. This profile resembles the combination of SSRI and buspirone, and GAD efficacy of both agents suggests a potential role for vilazodone in anxiety disorder treatment. Two eight-week randomized controlled trials of vilazodone treatment of GAD have been published. One using a flexible-dose design found nominal clinical improvement with vilazodone compared with placebo, while the other study using a fixed-dose design found statistically significant reduction in anxiety scores (vs. placebo) with vilazodone 40 mg but not 20 mg [182; 183]. Vilazodone does not appear to improve efficacy over drugs already in use, but it does have advantages of earlier onset of clinical response (beginning by two weeks) and little evidence of sexual dysfunction or weight gain. Vilazodone should be taken with food, which increases its absorption and bioavailability by 72% [184].

Vortioxetine

Approved by the FDA in 2013, vortioxetine is a multimodal antidepressant and potential anxiolytic with activity as an antagonist in 5-HT1D/3A/7 receptors, a 5-HT1A receptor agonist, 5-HT1B partial agonist, serotonin transporter inhibitor, and weak norepinephrine transporter inhibitor. This multiple receptor activity modulates serotonergic, noradrenergic, dopaminergic, and histaminic systems to produce clinical effect [185]. Results from four randomized controlled trials suggest vortioxetine may have potential efficacy in the treatment of severe GAD, but effects in patients with more moderate GAD were minimally improved compared with placebo. Nausea, the most common side effect, was dose dependent [186]. Sexual dysfunction rates were similar to placebo across the 5–20 mg/day dose range, and vortioxetine can be taken without regard for meals [187].

SNRIs

Venlafaxine, the first SNRI approved in the United States, was introduced as immediate release (IR) in 1993 and extended release (XR) in 1997. This was followed by the introduction of duloxetine in 2004, desvenlafaxine in 2008, milnacipran in 2009, and levomilnacipran in 2013. SNRIs increase synaptic concentrations of 5-HT and norepinephrine by blocking reuptake of these neurotransmitters by their respective transporters. SNRIs lack significant affinity for adrenergic, cholinergic, histaminergic, opioid, glutamate, or GABA receptors and transporters [136; 188].

SNRIs differ in proportion of 5-HT/norepinephrine reuptake inhibition. Venlafaxine is the most serotonergic SNRI, followed by duloxetine and desvenlafaxine. Milnacipran shows relatively equal influence on 5-HT and norepinephrine reuptake inhibition, and levomilnacipran is a greater norepinephrine than 5-HT reuptake inhibitor. Such differences suggest that SNRIs are dissimilar from one another. Venlafaxine and duloxetine exhibit dose-related sequential effects on reuptake inhibition, while desvenlafaxine, milnacipran, and levomilnacipran act simultaneously on 5-HT and norepinephrine reuptake inhibition with proportionality intact with dose escalation [189].

Side effects from SNRIs overlap with SSRIs but can also include adrenergic effects of increased pulse rate and blood pressure, dilated pupils, dry mouth, and excessive sweating. Venlafaxine has a greater incidence of nausea and vomiting than SSRIs and may be associated with an increased risk for cardiovascular events [181]. Sexual side effects associated with SNRIs include decreased response to sexual stimuli, loss of interest in sex, anorgasmia, and much less frequently, genital anesthesia. Discontinuation syndrome from venlafaxine is markedly worse than other SNRIs and SSRIs [188].

Relative to SSRIs and TCAs, the SNRIs have relatively short half-lives, and few or no active metabolites for simpler overall pharmacology. In contrast to venlafaxine and duloxetine, desvenlafaxine, milnacipran, and levomilnacipran largely bypass the hepatic cytochrome P450 isoenzyme system, making drug interactions less likely. Of the five available SNRIs, only venla-

faxine has an active metabolite (desvenlafaxine). Dosing with venlafaxine IR and milnacipran is twice daily; the remaining SNRIs are dosed once daily [184].

The impairing effects from synaptic plasticity induced by conditioned psychologic stress were found reversed by SNRI treatment. Long-term venlafaxine and milnacipran use suppressed long-term potentiation in hippocampal CA1 via 5-HT1A receptor and a1-adrenoceptor activity, contributing to reversal in synaptic plasticity-related impairment induced by conditioned fear stress. Increased responsiveness of a1-adrenergic and dopaminergic D3 systems, decreased responsiveness of 5-HT2 systems, and development of adaptive changes occurred despite lack of SNRI affinity for these neurotransmitter receptors [188; 190; 191].

Venlafaxine

Venlafaxine IR was introduced in 1993 but from the outset was plagued with side effects, leading to the 1997 introduction of venlafaxine XR. The XR formulation has become a widely prescribed agent with established efficacy in several anxiety disorders. In addition to the dose-related reuptake inhibition of 5-HT and norepinephrine mentioned, weak dopamine reuptake inhibition may appear at dosages greater than 300 mg/day. This sequential activity is mirrored by the initial predominant serotonergic side effects (headache, nausea, fatigue, sexual dysfunction), with noradrenergic effects at higher doses (activation effects, dry mouth, night sweats) [184].

Desvenlafaxine

Desvenlafaxine (Pristiq) shows a 10-fold higher selectivity for serotonin over norepinephrine reuptake inhibition at 50 mg/day, with selectivity unchanged by dose increase to 100 mg/day [184]. A primary advantage of desvenlafaxine over venlafaxine involves metabolic pathways and drug interactions. Venlafaxine is extensively metabolized by the hepatic CYP2D6 isoenzyme to desvenlafaxine, while desvenlafaxine is metabolized primarily via glucuronidation and minimally through CYP3A4 [178]. Venlafaxine, but not desvenlafaxine, clearance in patients with polymorphic 2D6 can be accelerated or delayed, resulting in non-efficacy or greater side effects/toxicity. This makes desvenlafaxine preferable to venlafaxine for these patients. The desvenlafaxine metabolic pathway also eliminates adverse drug interactions with 2D6 substrates that require consideration with venlafaxine prescribing [188; 192]. However, few trials have evaluated desvenlafaxine in anxiety disorder treatment [184]. A comparison of the efficacy and safety of desvenlafaxine and escitalopram for treatment of depression with anxiety found that both drugs reported similar efficacy, but escitalopram was better tolerated with fewer adverse effects [193].

Duloxetine

Duloxetine (Cymbalta) has greater potency in 5-HT reuptake inhibition than fluoxetine. It has an elimination half-life of roughly 12.5 hours, steady-state is usually achieved after three days, and metabolism occurs mainly through hepatic CYP 2D6 and 1A2 [178; 194]. Common adverse effects of duloxetine include nausea, headache, and weight loss. Certain adverse effects, including xerostomia, drowsiness, and fatigue, are dose related [178].

Milnacipran

Milnacipran (Savella) has been marketed in France since 1997 for the treatment of major depression, but it is indicated for use by the FDA solely for fibromyalgia [178]. Milnacipran is not available in a generic formulation, and the expiration of the patent is not imminent. Anxiolytic effects of milnacipran are at least partially mediated by 5-HT2A receptor agonism [188; 195]. Results of a systematic review were inconclusive regarding the comparative efficacy, acceptability, and tolerability of milnacipran versus other antidepressive agents; however, milnacipran reportedly was more favorable than TCAs in terms of acceptability and tolerability [196].

Levomilnacipran

Levomilnacipran (Fetzima) differs from other SNRIs in that it is a more potent and selective inhibitor of norepinephrine than serotonin, especially at low doses. Alcohol may disrupt the extended-release mechanism to release large amounts of drug over a brief period, and co-ingestion should be avoided. With reports of milnacipran increasing hepatic transaminases to cause fulminant hepatitis, levomilnacipran should be avoided in patients with a history of alcoholism or chronic liver disease. Levomilnacipran is not associated with weight gain [173; 178]. Levomilnacipran ER 40–120 mg daily was found to be effective in preventing relapse in patients with major depressive disorder [197].

Other Antidepressants

Bupropion

Bupropion (Wellbutrin) lacks effect on serotonin neurotransmission either presynaptically (through serotonin release or reuptake inhibition) or postsynaptically (acting on serotonin receptors). Instead, bupropion inhibits the reuptake of norepinephrine and dopamine without affecting release or transport of other neurotransmitters and without binding to other neurotransmitter receptors. This unique pharmacologic profile makes bupropion the only approved antidepressant that increases dopamine neurotransmission in the nucleus accumbens and prefrontal cortex. The side effect profile, distinct from other antidepressants, lacks sexual dysfunction, weight gain, and sedation. The activating effects of bupropion can increase insomnia and anxiety, leading to its infrequent use in anxiety disorders [179; 198].

Trazodone and Nefazodone

The anxiolytic effects of trazodone are mediated by activity as a highly potent 5-HT2A receptor antagonist and moderately potent 5-HT1A partial agonist, with additional activity in SERT and 5-HT2C receptor inhibition. The combined actions of 5HT2A/5HT2C antagonism and SERT inhibition only occur at moderate-to-high doses, with doses lower than effec-

tive for antidepressant action frequently used for the effective treatment of insomnia [178; 179; 199]. Nefazodone (Serzone) is highly similar in pharmacologic activity to trazodone, but it is rarely prescribed due to liver toxicity concerns [179].

Mirtazapine

Mirtazapine (Remeron) is a tetracyclic compound with a unique mechanism of action, leading to description as a noradrenergic antagonist-specific serotonin antagonist antidepressant. Pharmacologically, mirtazapine is a 5-HT1 receptor agonist, and antagonism of 5-HT2A/C receptors increases cortical serotonin, dopamine, and norepinephrine modulation. Inhibition of norepinephrine alpha-2 autoreceptors allows greater norepinephrine release from neuron terminals. Also antagonized are receptors of 5-HT3, 5-HT5, and H1 histamine. This unique profile helps account for earlier onset of action than SSRI/SNRIs. Mirtazapine tends to promote sleep or drowsiness, and the most frequent side effect of daytime sedation can be a beneficial effect in highly anxious patients [178; 179; 188].

Mirtazapine is found beneficial in patients with GAD, SAD, OCD, panic disorder, and PTSD [200]. It is relatively safe in overdose. Mirtazapine is particularly useful in patients with sexual dysfunction from other antidepressants and is a good choice in patients with significant insomnia. Weight gain is a side effect, and if the risks for elevated lipid levels and rare agranulocytosis are a concern, mirtazapine may be reserved as a third-line choice [200; 201].

Agomelatine

Agomelatine is approved for clinical use in Europe, Australia, and a total of 40 countries overall, but not by the FDA. It is discussed in light of its novel mechanism and particular benefit in GAD [202].

Agomelatine is a synthetic melatonin analog with activity as a melatonin MT1/MT2 receptor agonist and 5-HT2C receptor antagonist. Unique to agomelatine, and one of its most important properties, is a sleep-promoting and pro-chronobiologic effect. Its 5-HT2C antagonism promotes dopaminergic firing in the ventral tegmental area, frontal cortex, hypothalamus, hippocampus, medulla, pons, and retina by enhancing norepinephrinergic activity in the locus coeruleus [185; 203].

With a unique non-monoaminergic mechanism of action, clinical trials have shown a low risk of sexual dysfunction, lack of weight gain or withdrawal symptoms, and overall side effect profile similar to placebo. However, reports of liver injury require patients to receive liver enzyme monitoring [204].

Anti-Epileptic Drugs

Gabapentinoids

Pregabalin (Lyrica) and gabapentin (Neurontin) are structurally analogous GABA analogs, with pregabalin more extensively evaluated in anxiety disorders. The anxiolytic, antinociceptive, and antiseizure properties of pregabalin are mediated through binding to presynaptic α2δ subunits of central nervous system (CNS) voltage-gated calcium channels, which decreases calcium influx at presynaptic channels and inhibits neurotransmission of excitatory glutamate, norepinephrine, and substance P [185; 205].

The relative efficacy and early onset of effect of pregabalin versus benzodiazepines may represent a new therapeutic intervention for GAD as mono- and augmentation therapy. Pregabalin has a low risk of drug interactions, lacks withdrawal or physical dependence risk, is associated with minimal adverse effects (e.g., dizziness, weight gain, insomnia), and is safe and well tolerated. A potential role for pregabalin in patients with GAD tapering off long-term benzodiazepine therapy has been suggested [185].

Benzodiazepines have been the only anxiolytic agents that rapidly reduce anxiety, but trials conducted in the last decade have also found this effect with pregabalin. In 89 patients with moderate-to-severe dental anxiety (without anxiety disorder diagnosis) given single-dose pregabalin 150 mg, alprazolam 0.5 mg, or placebo four hours before a dental procedure, the onset of anxiolytic effects began within three to four hours after pregabalin and within two hours after alprazolam. The magnitude of anxiety reduction and tolerability were equivalent between pregabalin and alprazolam [206].

Common GAD comorbidities of insomnia, gastrointestinal symptoms, and depression do not impair efficacy and are specifically improved by pregabalin. Pregabalin is generally well tolerated; the adverse event profile includes dizziness, somnolence, incoordination, dry mouth, headache, and weight gain. Risk of withdrawal symptoms is low when tapered over one week [205].

Levetiracetam (Keppra) is an analog of the nootropic drug piracetam and structurally unrelated to other anti-epileptic drugs. It has a novel mechanism of action that involves binding to synaptic vesicle protein SV2A, a protein that modulates neurotransmitter release including GABA. Metabolism has no effect on the cytochrome P450 enzyme system. The most common side effects include somnolence, dizziness, and weakness [207]. In one study, adjunctive levetiracetam (mean: 1,969 mg/day for 9.3 weeks) in highly symptomatic patients with treatment-refractory anxiety disorders led to clinically and statistically significant improvement in illness severity [208]. Further research involving patients with panic disorder with or without agoraphobia given levetiracetam for 12 weeks showed significant improvement in panic attack frequency, anxiety, and global severity ratings. Clinical benefits were apparent by one to two weeks for most patients, and side effects were minimal [209]. Patients with SAD initially administered levetiracetam 250 mg/day and flexibly titrated up to 3,000 mg/day over eight weeks showed significant improvements on measures of social anxiety, overall anxiety, and illness severity [210]. In contrast to the anti-epileptic agents zonisamide and topiramate, levetiracetam has not shown decrements in neuropsychologic performance on tests of cognitive impairment in patients with seizure disorder [211].

Atypical Antipsychotics

Olanzapine, risperidone, aripiprazole, and quetiapine are dopamine D2 receptor antagonists, as with all antipsychotic drugs, but differ from typical (first-generation) antipsychotics by also acting as 5-HT2A receptor antagonists (minimizing development of extrapyramidal effects), 5-HT1A receptor partial agonists (producing anxiolytic effects), and histamine receptor antagonists (further augmenting sedative and anxiolytic effects) [185].

Quetiapine

Quetiapine (Seroquel) is the most-studied atypical in anxiety disorder treatment and has greatest efficacy in GAD. A review of quetiapine in GAD found efficacy and tolerability in all acute and long-term monotherapy trials and statistically significant changes in anxiety and symptom severity in three of five adjunct therapy studies. Quetiapine is a treatment option for patients unresponsive to first-line therapy, and potential benefits may outweigh risks with appropriate monitoring and side effect management [212]. While the unique efficacy of quetiapine monotherapy in GAD is supported by a Cochrane review, quetiapine was denied FDA approval for GAD, likely due to its tendency for inducing lipid abnormalities, weight gain, and glucose intolerance, and concerns over widespread use in primary care without careful consideration of alternatives or monitoring adverse metabolic effects during follow-up [136; 213].

Buspirone

Introduced in 1986, buspirone (BuSpar) was the first anxiety-specific medication unrelated to benzodiazepines or barbiturates in pharmacology, effect, and abuse potential. The 5-HT1A receptor partial agonism mediates the anxiolytic effects. Buspirone acts as a weak presynaptic dopamine D2, D3, and D4 receptor antagonist and alpha-1 agonist [214]. Buspirone is primarily used in the treatment of GAD and to augment antidepressants for improved response.

Hydroxyzine

Hydroxyzine (Vistaril) acts mechanistically as a potent H1 receptor inverse agonist, and as a 5-HT2A, D2, and alpha-1-adrenergic receptor antagonist. The serotonergic activity of hydroxyzine is more potent than its dopaminergic and adrenergic activity and likely accounts for its anxiolytic efficacy, as other antihistamines lacking this property have not been effective in the treatment of anxiety [215; 216]. Hydroxyzine efficacy in anxiety disorders is limited to GAD, for which anxiety-reducing efficacy is demonstrated [217; 218; 219].

Benzodiazepines

Since their introduction in the early 1960s, benzodiazepines have been the most prescribed drugs for anxiety over the majority of the past half-century. Although SSRI/SNRI agents have replaced benzodiazepines as the top-prescribed anxiolytics, benzodiazepine prescribing remains common. In 2018, alprazolam and lorazepam were among the top 25 most frequently prescribed psychotropic medications in the United States; alprazolam ranked second, and lorazepam ranked 10th [220; 221].

Pharmacology and Short-Term Effects

Numerous benzodiazepines are available and have similar pharmacodynamic properties and clinical actions; they mainly differ in pharmacokinetic properties (absorption, distribution, metabolism, elimination). Benzodiazepines bind to a specific receptor site in the GABA-A receptor complex. GABA is the primary inhibitory neurotransmitter in the CNS, and benzodiazepines cause non-selective GABA-A inhibitory effects throughout the brain that include drowsiness, cognitive impairment, dampening of fear and anxiety, memory impairment, anticonvulsant actions, and impairment of balance, motor control, muscle tone, and coordination. Adverse reactions to alprazolam also include amnesia, aggression, mood changes, and hostility. The newer Z drugs (e.g., zolpidem, zopiclone) have similar actions to benzodiazepines but are marketed for insomnia due to their pharmacokinetic profile, with high doses required for anxiolytic effects. There is evidence the Z drugs share similar risks to benzodiazepines [222; 223].

Meta-analyses suggest alprazolam, lorazepam, and diazepam are effective but comparable in GAD efficacy, while clonazepam shows much greater efficacy in the treatment of panic disorder than alprazolam, lorazepam, and diazepam, which all have modest efficacy [224].

Appropriate Prescribing

Benzodiazepine treatment of anxiety disorders is controversial. While effective in rapid anxiety reduction, the potential drawbacks with long-term use are substantial. These agents are indicated when potent, short-term anxiolytic effects are necessary to permit infrequent exposure to feared stimuli and potentially severe anxiety, such as airplane travel [121; 129; 136]. Clonazepam, lorazepam, and alprazolam are effective for short-term use in panic disorder, GAD, and SAD, but ineffective for, and potentially worsening, comorbid depression [28]. The rapid anxiolytic effects make benzodiazepines highly appealing to patients with anxiety, but aside from this specific context, benzodiazepine prescribing for as-needed use is discouraged [136; 225; 226]. Benzodiazepines can reinforce pill taking, serve as a safety signal that undermines self-efficacy, and become incorporated into conditioned fear responses; these concerns are heightened with as-needed use. On-demand dosing links pill taking to rapid anxiety reduction, powerfully reinforcing avoidance in anxiety-provoking situations and encouraging longer-term reliance on the drug. This iatrogenic effect also contributes to poor CBT response.

The current recommended prescribing is for time-dependent use, instead of panic response-dependent use, to minimize the risks [121]. This would also seem to maximize risk of withdrawal syndrome from uninterrupted versus intermittent drug exposure.

Benzodiazepines are also useful in the initial weeks of SSRI/SNRI initiation, to rapidly reduce anxiety and possible early anxiogenic medication side effects before the onset of SSRI/SNRI anxiolytic effects [121; 129; 136]. However, patients may discontinue the antidepressant when co-prescribed a rapidly effective benzodiazepine, believing the benzodiazepine's symptom relief makes the SSRI/SNRI unneeded. Supportive therapy with regular visits or phone contacts may also help patients remain adherent until the delayed onset of antidepressant benefits appears or early antidepressant side effects lessen [227].

Another indication for benzodiazepine use is for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress. Perhaps the greatest prescribing challenge with benzodiazepines is preventing short-term use from insidiously developing into long-term use. Patients with the most severe anxiety may obtain the greatest relief and become most hesitant to discontinue use [228]. In many cases, clinicians ignore the recommended two- to four-week prescribing limit, mainly because alternative options with superior anxiolytic effects are not available [229]. Clinicians intending to prescribe alprazolam should carefully consider the likelihood that its use will remain restricted to the very short term—a few days to a couple weeks—to see the patient through a crisis [228].

Benzodiazepines may be prescribed to augment SSRI/SNRI therapy for improved response in select patients with significant residual anxiety or non-response. In one study, patients with SAD and sertraline nonresponse after 10 weeks were given sertraline plus clonazepam (≤3 mg/day), venlafaxine (≤225 mg/day), or sertraline plus placebo for 12 weeks. Those with sertraline augmented by clonazepam showed greatest reduction in SAD symptoms and a better overall response rate than comparator groups, although remission rates did not differ significantly [230]. These agents are third- or fourth-line treatment in patients unresponsive or intolerant to other anxiolytic drugs who remain highly symptomatic [121; 129; 136]. Generally, patients with a history of substance abuse, personality disorder, or chronic pain should not be treated with benzodiazepines because of the high risk for overuse of these medications [129]. While benzodiazepines should usually be reserved for patients lacking response to at least two treatments (i.e., non-response to an SSRI/SNRI and a psychologic treatment), concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing, and impairing anxiety symptoms [231].

It seems the most appropriate guidance for benzodiazepine prescribing involves occasional, context-specific use or cautious use during SSRI/SNRI initiation [3; 231]. Otherwise, benzodiazepines should be reserved for patients lacking response to three or more treatments, such as an SSRI, an SNRI, and a psychologic intervention, who remain highly symptomatic.

Risks/Drawbacks

While alprazolam remains the most-prescribed benzodiazepine for anxiety disorders, evidence suggests that relative to other benzodiazepines, alprazolam is no more effective and may have specific drawbacks [171]. Alprazolam may have greater potential for dependence than other benzodiazepines due to its rapid onset of anxiolysis and short half-life. With the short half-life, persons prescribed fixed-interval alprazolam (e.g., every six to eight hours) can experience morning withdrawal symptoms following the last nighttime dose. This is frequently mistaken as relapse in anxiety for which the drug was originally prescribed, confirming the continuing need for the drug [228]. The alprazolam product monograph states that such emergence of interdose symptoms reflect insufficient plasma levels, best managed by adding the same dose for four times daily administration (but breakthrough anxiety and alprazolam withdrawal are not differentiated). The document also states that alprazolam treatment of panic disorder differs from sub-syndromal anxiety, in that recommended dosing is as close to around-the-clock as possible, or three or four times per day [232].

Long-term benzodiazepine use can result in added symptoms during stable-dose maintenance, including increasing anxiety and withdrawal-associated symptoms such as perceptual disturbances and paresthesia. This emerging withdrawal syndrome despite ongoing benzodiazepine use is much more likely with highly potent and rapidly eliminated alprazolam or lorazepam and is temporarily alleviated by dose escalation. As craving, dysphoria, and other withdrawal symptoms develop over time between doses, the motivation to continue benzodiazepine use for anxiolysis gradually merges with the need to avoid withdrawal symptoms [233].

Benzodiazepine prescriptions are associated with nonmedical use and the development of benzodiazepine use disorder unrelated to co-occurring drug use or anxiety disorder diagnosis/severity [221]. Acute cognitive-impairing side effects are drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. In one study, long-term use of an average 17 mg/day diazepam equivalent led to substantial cognitive decline that did not resolve three months after cessation [234]. Motor vehicle accident risks during benzodiazepine therapy are comparable to driving with a blood alcohol concentration of 0.050% to 0.079% [235]. Hip fracture risk is increased by ≥ 50% in older persons who take benzodiazepines; with zolpidem, the risk is increased 200% in persons older than 65 years of age [236]. The risk of overdose is particularly great when benzodiazepines are combined with sedative drugs such as opioids or alcohol.

Personality traits associated with long-term use, emotional dependence, and more severe/protracted benzodiazepine withdrawal have been described. Long-term benzodiazepine users often have poor stress coping abilities. Benzodiazepines compensate for these deficits, but their use interferes with learning stress coping strategies, including behavioral therapy for agoraphobia. Passive-dependent personality traits and lack of internal and external stress coping resources increases vulnerability to withdrawal symptoms and motivation for continued use. In these patients, benzodiazepine deprivation

renders them unprotected from stress and re-exposes their coping deficits. Chronically anxious people have been found innately hypersensitive to punishing stimuli and punishment; benzodiazepines can be described as "depunishing" drugs [233].

Withdrawal

Withdrawal symptoms following benzodiazepine cessation are appropriately concerning and a liability of this drug class that all prescribers should understand. In patients with panic disorder discontinuing alprazolam following 1.5 to 22 months of treatment, 33% to 100% were unable to completely taper [181]. These data did not include the 50% of long-term benzodiazepine users who do not consent to withdrawal studies or who later quit the study. The experience of benzodiazepine withdrawal is known to deter patients from future attempts [237]. An estimated 25% to 76% of patients prescribed benzodiazepines are long-term users. Defining high-dose benzodiazepine varies, but users of high-dose benzodiazepines commonly have comorbid disorders and are unlikely to benefit from current discontinuation and withdrawal strategies that expose them to greater risk of impairment and injury [237].

Despite comparable dosing, patients with panic disorder often show greater difficulty tapering than patients with GAD. Problems during alprazolam tapering are most severe during the last half of the taper. Patients with panic disorder receiving diazepam or alprazolam had fewer problems during taper of the top 50% of daily dose. However, with abrupt discontinuation of the remaining dose, alprazolam caused significantly more anxiety, relapse, and rebound. This may reflect greater problems withdrawing from short half-life, high-potency benzodiazepines like alprazolam [181].

The patient experience of benzodiazepine withdrawal was studied in 41 high-dose benzodiazepine-using inpatients deciding to withdraw (median dosage: 70 mg/day diazepam equivalent; median duration: six years) [237]. Driving this decision were health concerns of cognitive and physical impairments; feeling addicted; belief benzodiazepine use was a moral burden that limited autonomy; and pressure or coercion by relatives or institutional or governmental bodies to change benzodiazepine consumption patterns. The patients had long histories of repeated unsuccessful attempts to stop taking benzodiazepines and disappointment and frustration by the outcomes. However, many wanted to withdraw completely, with abstinence the goal. Most subjects described benzodiazepine withdrawal symptoms as severe, unpredictable, diverse in manifestation, and of duration difficult to anticipate. Common symptoms included chills, weakness, headache, muscle pains, abdominal pain, nausea, vomiting, diarrhea, tachycardia, dizziness, vision disorders, irritability, nervousness, restlessness, difficulties sleeping, depression, anxiety, tickling sensations, dissociation, complete loss of appetite, and epileptic seizures. Most experienced prolonged post-withdrawal symptoms. Many initially tried withdrawing by abruptly stopping benzodiazepine usage at home; most stated this resulted in perceived epileptic seizures. All favored gradual, long-term tapering over abrupt withdrawal [237].

Normally used to reverse benzodiazepine overdose and post-surgery sedation, flumazenil has shown effects that diminish benzodiazepine withdrawal severity and duration and improve abstinence rates. Dosage and infusion rates vastly differ between these two indications [238]. Flumazenil requires IV or subcutaneous infusion, because its brief half-life and extensive gastric metabolism prohibit oral use [239].

In a study of flumazenil IV infusion, 29 patients stopped benzodiazepines and began flumazenil 1.6 mg/day and oral clonazepam 2 – 6 mg/day. Antidepressants were started three weeks before the trial or were maintained. Clonazepam was tapered during outpatient follow-up. No patient dropped out, withdrawal severity showed significant linear reduction through the seven-day infusion, and 53% remained free of clonazepam and other benzodiazepines at six-month follow-up [240]. In patients with protracted withdrawal at 47 weeks, IV flumazenil significantly reduced aggression and hostility compared with placebo [241].

In research focused on subcutaneous infusion of flumazenil, patients were switched to oxazepam, began a 48-hour taper, and started flumazenil 16 mg over 96 hours. Subcutaneous infusion significantly reduced psychologic distress and benzodiazepine withdrawal symptoms during treatment. Patients with the highest initial withdrawal severity showed greatest improvement. Patients reported high treatment comfort, willingness to receive the treatment again, and likelihood to recommend it to a friend [239].

Flumazenil attenuates chronic benzodiazepine withdrawal symptoms by up-regulating benzodiazepine receptor binding sites to reverse uncoupling between benzodiazepine and GABA binding sites on the GABA-A complex. This reversal of GABA-A functional alteration helps explain its effect on benzodiazepine withdrawal and reports of positive effects on mood, memory, cognition, and motor performance [229].

CLINICAL ISSUES

Poor Treatment Response or Nonresponse

An estimated 30% to 60% of patients with anxiety disorders do not achieve meaningful symptom reduction or remission with initial therapy [242]. Decades of psychopharmacologic research have yielded safer, more tolerable side-effect profiles, but without improved efficacy in anxiety disorders. With poor or non-response, clinicians and patients then must decide how treatment should proceed, but research that best informs this clinical dilemma is only beginning to emerge. Given the limitations of SSRIs and benzodiazepines, investigators are pursuing novel treatment approaches and molecular targets [136].

With apparent patient nonresponse to treatment, clinicians should explore other factors before deciding the next therapy approach. The two broad causes of treatment resistance are pseudo-resistance and true treatment resistance [28].

Treatment Pseudo-Resistance

Pseudo-resistant patients have not actually received sufficient treatment, because of ineffective treatment matching for the anxiety diagnosis, insufficient medication dose or psychotherapy delivery, or patient non-adherence. Treatment pseudo-resistance may be the result of ineffective drug therapies, such a bupropion, beta-blockers (except in performance anxiety), buspirone and trazodone (except in GAD), and TCAs in SAD. Insufficient dosages and waiting an inadequate period for onset are also factors. The time for treatment onset is often longer for anxiety than depression. Patients may not fully respond until 8 to 12 weeks, and response may further increase in the second 6 months. Waiting an adequate time for response may be difficult for patients and healthcare providers, who may feel a need to change prescriptions or the regimen if a patient is distressed over his or her continued anxiety symptoms [28].

Poor patient adherence may also present as apparent treatment resistance. Only half of patients refill their first prescription, and many patients discontinue their drug in the first six months of treatment [136; 185]. Nonadherence may result from medication intolerance or side effects. Even if patients with troubling side effects do not stop the drug, the inherent distress avoidance and anticipatory anxiety with anxiety disorders can delay achieving adequate dose or taking medication long enough for response. Therapeutic skills can help to gain patient trust and overcome their anxiety of medication; adherence improves with medication counseling [136; 185]. Medication beliefs or attitudes that contribute to poor adherence include [28]:

- Unrealistic expectations
- Negative beliefs of perceived harmful effects
- Stigma
- Not "buying in" to treatment rationale or difficulty believing that treatment will work
- Psychologic conflicts over dependence and fear of becoming "addicted" to the medication
- Preference for psychotherapy over medication (as patients are less likely to adhere to a treatment modality they prefer less)

Following adherence and remission or large improvement, some patients will become non-adherent, and relapse follows. This may be addressed by explaining that the disorder requires ongoing treatment, like diabetes or any other chronic disease.

Overlooked Diagnosis, Comorbid Conditions, or Psychosocial Contributors

When established that adequate treatment was delivered and received, factors contributing to treatment resistance can include misdiagnosis or overlooked comorbidities or psychosocial factors. The following should be revisited [28]:

- Primary diagnosis accuracy
- Presence and contribution of unrecognized substance use disorder, psychiatric comorbidity, and/or complicating medical condition
- Psychosocial or lifestyle factors (e.g., caffeine overuse, sleep deprivation, interpersonal or family conflict)

Necessary Treatment Duration for Evidence of Response or Dose Escalation

With initiation of SSRI/SNRI treatment is the uncertainty over how long treatment should continue without signs of improvement before concluding a response is unlikely. With duloxetine and escitalopram, response is unlikely without clinical effect by four weeks of initiation. With pregabalin, onset of clinical effect within two weeks is associated with a 5.3-fold increased likelihood of treatment response; 25% of patients not showing clinical effect at two weeks will ultimately respond to treatment. A pregabalin dosage of 150 mg/day is suboptimal; a dose-response effect usually requires 300 – 600 mg/day [243].

In clinical trials of venlafaxine XR, therapeutic benefits usually separated from placebo at four to six weeks. However, the percentage remitted from panic disorder in one trial increased from 18% at 6 weeks to 50% at 12 weeks [244].

SSRIs/SNRIs usually take two to six weeks to show an initial "partial" response, often defined as ≥25% improvement (i.e., beyond random noise or natural symptom fluctuations). Full benefit may not appear for another four to six weeks or longer. Data from patients with depression, and some uncontrolled data with anxiety, suggest that about 20% of patients may need 10 to 12 weeks or longer before responding. Thus, dose escalation to highest level tolerated is recommended for patients with incomplete response before adequate time has passed [245]. In contrast to depression, antidepressant efficacy in anxiety disorders appears to be lost soon after stopping, with anxiety recurrence being the rule rather than the exception [228].

Patient Education

Successful medication treatment often involves dosage adjustments and/or trials of a different medication at some point in order to maximize response and minimize side effects. Because patient adherence is the essential pre-condition for maximum clinical benefit, the following messages should be communicated to the patient to encourage and support ongoing medication adherence [246]:

- Side effects often precede therapeutic benefit and typically recede over time.
- It is important to expect some discomfort prior to the benefit.
- Successful treatment may involve dose adjustments and/or trials of different medications to maximize response and minimize side effects.
- Most people must be on medication at least 6 to 12 months after adequate response, and patients may show improvement at two weeks but need a longer length of time to really see response and remission.
- It is important to take the medication as prescribed, even after feeling better, because early discontinuation is associated with high rates of relapse/recurrence.

- Do not stop taking the medication without calling the provider.
- Side effects can often be managed by changing the dose or dosage schedule.

A novel approach to improve patient understanding of their anxiety disorder and treatment rationale incorporates anxiety neuroscience. A core concept is that anxiety disorders/symptoms with amygdala origin (e.g., panic disorder, phobias) require different approaches than anxiety of cortical origin (e.g., SAD, GAD). Educating patients of the brain-based source of their anxiety can improve treatment adherence and empower patients to modify these areas of brain function. For example, patients with cortex-related symptoms such as obsessions, perfectionism, and chronic worry benefit from an approach termed "Question Your Cortex." They can be encouraged to identify anxiety-generating thoughts in the cortex and use cognitive restructuring methods to exploit cortical neuroplasticity by modifying their thoughts. However, cortex-based interventions are not effective at reducing or managing anxiety with amygdala-mediated symptoms; for these patients, exposure to feared situations is stressed. Most patients benefit from a combination of cortex- and amygdala-focused interventions, with the rationale and order of interventions differing by disorder and individual patient [247].

Antidepressant Withdrawal

In the SSRI literature, "withdrawal syndrome" has been largely replaced by the term "discontinuation syndrome" with industry support to convey the message that SSRIs do not cause addiction, dependence, or a syndrome similar to that experienced following benzodiazepine cessation. This has been challenged, given the potential seriousness of SSRI post-cessation symptoms, as a false dichotomy that minimizes the vulnerabilities induced by SSRIs. For the purposes of this course, the term "withdrawal syndrome" will be used [248]. Clinicians should be aware of these withdrawal syndromes, as misdiagnosis may result in inappropriate diagnostic tests and treatment and unnecessary patient distress and morbidity [248].

A 2015 meta-analysis found SSRI withdrawal symptoms can occur with any SSRI but are exceedingly more frequent with paroxetine [248]. Common symptoms include dizziness, nausea, headache, confusion, low energy, weakness, sleep disturbance, flu-like symptoms, restlessness, agitation, anxiety, panic, anger, and irritability. Less common and more severe symptoms include electric-shock sensations, vertigo, paresthesias, intensified suicidal ideation, aggression, derealization, depersonalization, and visual/auditory hallucinations. Symptoms do not greatly differ between patients with anxiety versus mood disorders. The authors concluded that the typical SSRI withdrawal syndrome begins within a few days of cessation and lasts two to three weeks [248]. Variations include late onset and protracted duration up to one-year follow-up. Several cases of persistent postwithdrawal disorders induced by paroxetine have been described.

Gradual tapering is a reasonable strategy but does not prevent the onset of SSRI withdrawal [248]. Patient characteristics that predict increased vulnerability are not known. Recognition of withdrawal symptoms requires careful exploration, as they can be misidentified as signs of impending relapse. Even when withdrawal symptoms are recognized, clinical management is hindered by the lack of research.

SSRI cessation may trigger complex phenomena related or unrelated to the onset of withdrawal, such as hypomania, mania, and persistent postwithdrawal disorders. Iatrogenic comorbidity describes the lasting effects from treatment well beyond their time of administration, such as mood instability and high reactivity to environmental stimuli in persistent postwithdrawal disorders [248].

Among 20 patients with remitted panic disorder with agoraphobia followed over one year after SSRI cessation, nine experienced SSRI withdrawal syndrome that subsided within one month [249]. Exceptions were three patients taking paroxetine, who experienced worsened mood, fatigue, and emotional lability with trouble sleeping, irritability, and hyperactivity. One patient prescribed clonazepam after three months of symptom persistence improved considerably but was later unable to discontinue clonazepam. A second patient did not improve with clonazepam or fluvoxamine, and symptoms subsided only with paroxetine reinstatement. In a third patient, clonazepam had little benefit, paroxetine reinstatement was refused, and symptoms persisted unchanged over one year [249].

Following SSRI/SNRI cessation, the rates of withdrawal syndrome range from 17.2% to as high as 78% (with venlafaxine). Among SSRI/SNRIs, venlafaxine XR may have the worst withdrawal syndrome. In addition to serotonergic withdrawal symptoms, palinopsia (persistent visual images) and sensory disturbances are frequently reported. These symptoms are described as sensations affecting the brain and head that feel like electrical shocks or the sensation of the brain shivering. This sensory disturbance, often accompanied by dizziness, headache, and disorientation, is distressing to patients and has been reported to persist for months after venlafaxine XR cessation [244; 250]. Other unexpected withdrawal symptoms that may emerge include gait difficulties, delirium, suicidal ideation, and hypomania or mania. The onset of withdrawal is usually one to four days post-venlafaxine XR cessation; dose reduction can also trigger withdrawal [251].

The etiology and treatment of these highly distressing sensory symptoms are unknown. However, contribution from noradrenergic dysregulation is suggested theoretically and by reports of positive treatment response to noradrenergic agents. Abrupt cessation of venlafaxine XR 37.5 mg led to a sensation that "felt like the brain was shaking inside the skull," with anhedonia, anxiety, tinnitus, headache, nausea, and increased noise sensitivity. A trial of the norepinephrine transporter inhibitor atomoxetine 40 mg/day led to immediate improvement in "brain shivers" two to three hours from the first dose [250]. Post-venlafaxine XR electric shock-like sensations and dizziness were greatly reduced by low-dose clonidine (0.05 mg twice/day), a central α-2 adrenergic agonist. The positive response suggests an underlying noradrenergic rebound mechanism [244].

Interdose withdrawal symptoms have been reported with venlafaxine XR, probably resulting from the "ultrarapid metabolizer" genetic variant of 2D6, the hepatic cytochrome P450 isoenzyme that metabolizes venlafaxine. Occurring in 3% to 5% of white individuals, this polymorphism accelerates venlafaxine elimination, causing interdose withdrawal [251].

Antidepressant Lethality in Overdose

In some patients with anxiety disorder, and especially those with depressive comorbidity, consideration of overdose fatality is necessary when deciding on therapy options. Lethality rates from intentional overdose involving single medication ingestions of agents commonly prescribed for depression and anxiety were calculated from data obtained during the period 2000–2014 [252]. TCAs remain the most lethal antidepressants, with fatality rates from 31–142 per 10,000 ingestions. Amitriptyline is associated with the greatest lethality in overdose and alone accounted for 37% of all deaths from antidepressants [252]. Lithium, bupropion, venlafaxine, quetiapine, and valproic acid had rates of 6.9–12.0 per 10,000 ingestions, while citalopram and fluvoxamine had rates of 3.9–4.1 per 10,000. Fluoxetine, sertraline, paroxetine, and escitalopram had the lowest overdose lethality rates at 0.79–1.34 per 10,000 ingestions [252].

Substance Use Disorder

Anxious patients often use alcohol or anxiolytics to regulate general anxiety, distressing panic symptoms, or social anxiety and social skills deficits. Substance use disorder is highly prevalent in patients with anxiety disorders and interferes with treatment response and leads to poor outcomes [28]. More than 33% of patients with GAD have an alcohol use disorder, and patients with SAD have a lifetime substance use disorder prevalence of roughly 40%. Nicotine dependence is also disproportionately high among patients with panic disorder [253; 254; 255].

Self-medication of anxiety disorder symptoms has been conclusively identified as a significant predictor for later development of alcohol or drug dependence. This is consistent with the self-medication hypothesis, which posits that the specific substance used for anxiety relief/control tends to be the substance to which the person develops a substance use disorder [256]. Ongoing substance use problems are abundantly linked to worse outcomes in comorbid anxiety disorders. Long-term effects of substance use negatively interact with anxiety symptoms, and quitting substances may improve anxiety in some patients. A trial of abstinence will usually answer this question. The duration must be several months to evaluate the link between anxiety and substance use, and there should be ongoing treatment, preferably in a 12-step program. Twelve-step programs have been shown to have anxiolytic effects themselves due to the support and empowerment they offer. Residual anxiety then should be treated with either medication or CBT [28].

If substance use is suspected, patients should be screened during diagnosis. A motivational interviewing approach is recommended to frame the rationale for substance abuse in a non-judgmental manner and explore patient desire and readiness for change. For patients initiating efforts to decrease substance use, concurrent treatment with an SSRI or venlafaxine is reasonable; benzodiazepines should be avoided due to the abuse liability [257]. Detoxification from alcohol or benzodiazepines is indicated if signs of substance withdrawal appear, and referral to a formal substance abuse treatment is recommended. Recognition and treatment of underlying substance abuse is an essential component in the overall treatment plan [13; 28].

Anxiety Disorder Treatment Effect Sizes

A 2015 meta-analysis of panic disorder, GAD, and SAD assessed treatment efficacy [224]. Studies published through 2012 were used to calculate medication, psychologic, or combination treatment efficacy. Effect sizes were calculated from pre- versus post-treatment and treatment versus control comparisons (***Table 3***) [224]. A significantly higher average pre-post effect size was found for medication outcomes than psychotherapy outcomes. Side effects, contraindications, drug interactions, and efficacy should all guide drug selection. Benzodiazepine abuse, dependence, and withdrawal potential; TCA side effects; and quetiapine metabolic risks make these agents second- to fourth-line options and not first-line options, as suggested by effect sizes alone [224].

TREATMENT OF GENERALIZED ANXIETY DISORDER

The primary goals of GAD treatment are reduction of anxiety symptoms and reduction or elimination of disability. Pharmacotherapy and CBT or cognitive therapy are equal as first-line options. CBT/cognitive therapy may be preferred by patients who are pregnant or who cannot tolerate or wish to avoid medication [258]. GAD is associated with specific biases for mood-congruent information. Patients with GAD are vigilant for threatening stimuli and tend to misinterpret ambiguous information as threat. These cognitive biases diminish with successful psychologic or drug treatment [243].

PSYCHOTHERAPY

First-Line Options

CBT

The use of CBT in patients with GAD usually combines psychoeducation, worry exposure, relaxation, applied relaxation, problem solving, cognitive re-structuring, and interpersonal psychotherapy. Meta-analyses clearly demonstrate that CBT significantly reduces GAD symptoms and is markedly more effective than placebo or wait-list control conditions [120]. Sessions should occur at least weekly over 6 to 12 weeks and involve 12 to 20 sessions. While fewer than eight sessions is as effective as eight or more sessions for anxiety symptoms, more intense regimens are more effective in improving worry and depression symptoms [258; 259; 260]. Individual and group

EFFECT SIZES OF TREATMENTS FOR PANIC DISORDER, GENERALIZED ANXIETY DISORDER, AND SOCIAL ANXIETY DISORDER	
Treatment Modality	**Effect Size[a]**
Medications	
SNRIs	2.25
Benzodiazepines	2.15
SSRIs	2.09
Tricyclic antidepressants	1.83
Psychotherapy	
Mindfulness therapies	1.56
Relaxation	1.36
Individual CBT/exposure therapy	1.30
Group CBT	1.22
Psychodynamic therapy	1.17
Internet and self-directed therapies	1.11
Eye movement desensitization and reprocessing	1.03
Interpersonal therapy	0.78
Other approaches	
CBT/drug combination therapy	2.12
Exercise	1.23
[a]An effect size greater than 0.80 is considered large, indicating that the treatment is effective. CBT = cognitive-behavioral therapy, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin re-uptake inhibitor.	
Source: [224]	*Table 3*

CBT seem equally effective in anxiety symptom reduction, but individual therapy may lead to earlier improvement in worry and depression symptoms [120].

Cognitive Therapy

Cognitive therapy teaches patients to evaluate their anxious thoughts objectively. Variants include pure cognitive therapy, cognitive restructuring, meta-cognitive therapy, and uncertainty intolerance therapy. Cognitive therapy typically involves 15 to 20 individual sessions [261].

As discussed, effective cognitive therapy/CBT treatment helps patients develop new, alternative strategies to manage worries and habits and cope with life stressors, which reduces the symptoms of anxiety. Cognitive therapy/CBT helps patients to understand [261]:

- They cannot control their fears, but can control their worrying behavior as a fear response.
- Worrying has no protective value, reinforces negative thinking, and increases the risk of escalating anxiety levels in the future.
- Worrying does not assist in managing negative future scenarios, and patients are equipped to handle whatever future challenges appear.

Cognitive therapy/CBT techniques may be especially helpful for generalized anxiety in later life [120].

Internet-Based CBT

Internet-based CBT is delivered by patient-administered media interventions. Components include cognitive restructuring, exposure, problem solving, and applied relaxation, usually over six to eight sessions [261; 262]. Efficacy is demonstrated, with benefits maintained at long-term follow-up. A peer-to-peer cognitive self-therapy program has been found as effective as treatment-as-usual, with a decreased need for therapist contact [120].

Applied Relaxation

Applied relaxation teaches the patient a coping skill that will enable him or her to relax rapidly, in order to counteract and eventually abort the anxiety reactions. This therapy is different from simple relaxation alone, which is not helpful. Applied relaxation entails having patients relax in actual anxiety-provoking situations. Effective applied relaxation involves around 15 individual sessions [261].

Second-Line Options

Acceptance and commitment therapy and mindfulness are CBT variants with promising initial results. They teach patients to focus on the present moment and follow actions guided by their values rather than by emotions and anxiety. Effective acceptance and commitment therapy usually involves 10 to 15 individual sessions [261].

Short- and long-term psychodynamic psychotherapy has shown efficacy and may be used with unavailability of CBT/cogni-

tive therapy. Specific psychotherapy targets in GAD include intolerance of uncertainty, poor problem-solving confidence, and positive and negative metacognitive beliefs concerning the value or utility of worry [263].

Adjunctive Approaches

Additional modalities can be added to psychotherapy and/or drug therapy. Exercise is not widely studied in GAD, but available data have shown reduction in anxiety symptoms [264]. Meditation training is an option for patients unable or unwilling to receive psychotherapy [265]. Applied relaxation is effective as adjunctive therapy and uses relaxation techniques that are self-monitoring without the use of in-depth psychotherapy [266]. In addition, physical activity has been noted as a cost-effective treatment for GAD [121].

Sleep disturbances are highly prevalent in patients with GAD. Sleep hygiene education can be a useful tool in primary care, used with CBT in GAD to ensure the best possible sleep efficiency and quality. Patients can be counseled to improve sleep hygiene by going to bed and waking up at the same time each day, eliminating alcohol after 6 p.m., avoiding caffeine after 3 p.m., and getting out of bed if unable to fall asleep to avoid development of negative associations with the bed environment [267; 268]. Long-term follow-up data from a meta-analysis and randomized controlled trials suggest that benefits of psychologic treatments are maintained one to three years following treatment [120].

PHARMACOTHERAPY

In addition to efficacy, selection of initial drug therapy for GAD is based on illness severity and degree of distress, medical and psychiatric comorbidities, substance abuse profile, patient preference, and side effect profile.

First-Line Options

The ADAC and the Anxiety and Depression Association of America (ADAA) have created guidelines for the selection of appropriate pharmacotherapy in the treatment of GAD with differing recommendations regarding first- and second-line medications [120; 261]. The ADAC recommends agomelatine, pregabalin, venlafaxine XR, duloxetine, escitalopram, paroxetine, or sertraline as first-line options, while the ADAA suggests venlafaxine XR, duloxetine, paroxetine, escitalopram, sertraline, or fluoxetine [120; 261].

Pregabalin

Two randomized, placebo- and active comparator-controlled, double-blind studies evaluated the efficacy of pregabalin versus lorazepam for the treatment of GAD. The pregabalin and lorazepam groups experienced greater reductions in Hamilton Anxiety Rating Scale (HAM-A) score by week 4 compared with placebo, with no observed statistically significant differences among the active-treatment groups. Relative to placebo, pregabalin 600 mg significantly reduced psychic and somatic anxiety, while lorazepam significantly reduced somatic anxiety symptoms only. Anxiety reduction with pregabalin and lorazepam was evident within one week [185].

A four-week trial randomized 451 patients with GAD to alprazolam 1.5 mg/day; pregabalin 300, 450, or 600 mg/day; or placebo. As measured by HAM-A scores, psychic anxiety symptoms were significantly reduced (vs. placebo) with all pregabalin doses and alprazolam by weeks 1 and 4. Somatic anxiety symptoms were significantly reduced by 300 and 600 mg pregabalin, but not by 450 mg pregabalin or 1.5 mg alprazolam (vs. placebo). Pregabalin produced an early onset (≤1 week) of clinically relevant anxiety reduction comparable to alprazolam and anxiety reduction over a broader range of GAD symptoms than alprazolam by four weeks [269].

Data was combined from six placebo-controlled trials of patients with GAD randomized to pregabalin 150 mg, 300 – 450 mg, or 600 mg; lorazepam 6 mg/day; alprazolam 1.5 mg/day; or placebo. Pregabalin 300 – 600 mg significantly improved HAM-A psychic and somatic anxiety factor scores, but pregabalin 150 mg showed significance in psychic anxiety only. Of the 14 HAM-A items, significant improvement was shown on 13 with pregabalin 300 – 450 mg, 10 with pregabalin 600 mg, and 5 with benzodiazepines. A dose-response effect was evident for pregabalin [270].

Along with SSRIs/SNRIs, pregabalin is considered a first-line agent for long-term GAD treatment by the World Federation of Societies of Biological Psychiatry. Head-to-head studies with SSRIs/SNRIs are lacking, but pregabalin augmentation of SSRI/SNRI therapy has been found more effective than SSRI/SNRI alone [205].

Sleep dynamics were evaluated in healthy volunteers randomized to pregabalin (150 mg three times per day), alprazolam (1 mg three times per day), or placebo for three days. Pregabalin and alprazolam modestly but significantly reduced sleep-onset latency (compared with placebo). Pregabalin significantly increased the proportion of slow-wave sleep to total sleep period, and the slow-wave sleep duration of stage 4 sleep. Alprazolam significantly reduced slow-wave sleep. Rapid eye movement (REM) sleep latency with pregabalin did not differ from placebo and was significantly shorter than with alprazolam. Pregabalin and alprazolam similarly reduced the REM sleep proportion to total sleep (vs. placebo), while pregabalin significantly reduced the number of awakenings longer than one minute. Ease in getting to sleep and sleep quality were subjectively rated as improved with both active treatments. Pregabalin effects on sleep and sleep architecture were distinct from benzodiazepines. Enhancement of slow-wave sleep was relevant to frequent reports of reductions in slow-wave sleep in patients with fibromyalgia or GAD [271].

Clinical trials have reported euphoria, which emphasizes the need for careful and continuing evaluation of any potential for abuse. Reports of pregabalin abuse have appeared, usually involving individuals with a history of psychotropic medication abuse [243]. Discontinuation symptoms were reported after abruptly stopping pregabalin and were more prominent with higher daily doses. However, significantly fewer withdrawal symptoms were found after stopping pregabalin compared with lorazepam, and when tapered over one week, pregabalin

withdrawal symptoms are minimal. Tentative evidence suggests pregabalin may be beneficial in withdrawal from benzodiazepines and related compounds [243].

Agomelatine

Agomelatine studies have mostly investigated its efficacy in GAD. Three randomized controlled trials have been performed. One trial with an escitalopram arm found that agomelatine led to comparable efficacy in GAD and significantly improved sleep restoration with fewer side effects and no discontinuation symptoms compared with escitalopram [202]. The low discontinuation rate reflected good tolerability, and laboratory results showed a low incidence of transient elevations in liver enzymes. Another trial that measured therapeutic response as 50% or greater reduction in HAM-A score found response rates of 66.7% with agomelatine, compared with 46.6% with placebo. Agomelatine was noted to improve sleep quality, with a lack of sexual side effects or discontinuation syndrome. Dizziness (8%) and nausea (5%) were more frequent than placebo [202; 272]. Agomelatine was superior to placebo in symptom reduction beginning at six weeks and in relapse prevention at six-month follow-up [203].

Second-Line Options

In patients for whom SSRIs/SNRIs are ineffective or intolerable, alternative agents with demonstrable efficacy include the TCA imipramine, the second-generation antipsychotic agent quetiapine, and pregabalin. Pregabalin is also effective for augmenting other first- and second-line agents in patients showing partial response. Internationally, pregabalin is regarded as a first-line option for GAD, but U.S. guidelines have not yet integrated this agent into the first-line tier [185].

Several options as second-line agents have efficacy in GAD comparable to first-line agents but possess potential side effects or other risks that preclude first-line use [120]. Benzodiazepines would be considered first in most cases, except where there is a risk of substance abuse, while bupropion XL would likely be reserved for later. Quetiapine XR remains a good choice in terms of efficacy, but given the metabolic concerns associated with this atypical antipsychotic, it should be reserved for patients who lack response or cannot tolerate antidepressants or benzodiazepines [120]. It is important to note that drugs such as beta-blockers (e.g., propranolol) prescribed to address the physical symptoms of anxiety are ineffective in the treatment of GAD [243].

Quetiapine

In three 10-week randomized controlled trials of patients with GAD, quetiapine monotherapy showed clinically and statistically significant improvements in anxiety reduction and remission rates versus placebo [185]. Meaningful separation from placebo in anxiety reduction began as early as four to seven days after initiation of treatment. Somnolence, dizziness, and fatigue were more frequent with quetiapine, and sexual function improved slightly in quetiapine groups. Quetiapine has shown decreased symptom recurrence and improved sleep quality during maintenance treatment. However, quetiapine is not recommended for patients with nonresponding GAD because efficacy is inconsistent [185]. One literature review included three studies that evaluated the use of quetiapine extended-release (XR) as monotherapy for acute GAD treatment, one study that evaluated quetiapine XR monotherapy for maintenance treatment of GAD, and five studies that evaluated quetiapine (2 XR, 3 immediate release) as adjunct therapy for acute GAD treatment [273]. Quetiapine displayed both efficacy and tolerability in all monotherapy trials evaluating its use for acute and long-term treatment of GAD. Despite limitations to and heterogeneity among the five adjunct therapy studies, three studies showed that quetiapine resulted in statistically significant changes in the HAM-A scores [273].

Imipramine

While TCA use has become disfavored because of tolerability and safety issues, compelling support of imipramine efficacy in GAD came from a landmark study comparing the anxiolytic effects of imipramine, trazodone, diazepam, and placebo in non-depressed patients with GAD. Imipramine resulted in moderate-to-marked improvement between weeks 2 and 8 of therapy in 73% of patients, compared with 69% for trazodone, 66% for diazepam, and 44% for placebo [274].

Vortioxetine

Multiple randomized controlled trials involving patients with GAD found clinical improvement and symptom reduction with vortioxetine marginally greater or similar to placebo. With vortioxetine, discontinuation from side effects was modestly greater than placebo, with incidence of sexual dysfunction comparable. Patients with severe baseline GAD did show significantly greater benefit from vortioxetine [186; 275; 276].

Comorbid Major Depression

With a few caveats, treatment of GAD is generally the same whether comorbid major depression is present or absent. Use of buspirone and pregabalin is not recommended, while duloxetine has shown efficacy in comorbid anxiety disorder and major depressive disorder [277]. Patients with comorbid major depression and GAD prescribed benzodiazepines, sedating medications, or TCAs should be monitored for suicide risk; those with severe depression and suicidal ideation may require hospitalization while therapy is initiated [278].

Relapse Prevention

Relapse-prevention studies randomized patients showing response to acute treatment to placebo or the same medication/dose. Results in GAD showed significant advantages with continuing the active medications agomelatine, duloxetine, escitalopram, paroxetine, quetiapine, venlafaxine, or vortioxetine versus switching to placebo for periods of 6 to 18 months [243].

TREATMENT OF PANIC DISORDER

A meta-analysis found sufficient evidence that combined treatment is superior in panic disorder, with effects of combined psycho- and pharmacotherapy treatment versus placebo about twice as large as pharmacotherapy alone versus placebo [279]. The results also suggest that the effects of pharmacotherapy and psychotherapy are largely independent from each other and roughly equal in contribution to the effects of combined treatment. The effects remain strong and significant up to two years post-treatment. As such, monotherapy may not constitute optimal care [279].

PSYCHOTHERAPY

Behavior Therapy

With panic disorder, behavior therapy consists of graded exposure to the body sensations that accompany panic (interoceptive exposure), to situations perceived as threatening (in vivo exposure, imagery exposure, virtual reality exposure), or both, in order to progressively reduce apprehensive reaction toward them by the patient. Although exposure strategies alone can be effective in the treatment of panic disorder, they do not appear to be a valid alternative to CBT as a first-line treatment [151].

Cognitive Therapy

In cognitive therapy for panic disorder, panic attacks are thought to result from the catastrophic misinterpretation of certain bodily sensations. The patient perceives the sensations of normal anxiety response as much more dangerous than they are, such as palpitations viewed as evidence of impending heart attack. Cognitive therapy identifies these negative interpretations of the bodily sensations experienced in panic attacks, suggests alternative non-catastrophic interpretations, and helps the patient test the validity of these alternative interpretations. While cognitive therapy is often combined with behavioral techniques, there is some evidence that training in cognitive procedures in isolation from exposure and behavioral procedures is efficacious in reducing some aspects of panic [151; 280; 281; 282; 283].

CBT

CBT assumes that cognitions, behaviors, and emotions are interrelated and combines behavior therapy and cognitive therapy to reduce emotional distress and psychologic symptoms. CBT usually includes psychoeducation, breathing retraining, progressive muscle relaxation, cognitive restructuring, behavioral experiments, interoceptive exposure, and in vivo exposure. A fairly consistent body of evidence supports the efficacy of CBT for panic disorder in individual or group sessions. There is also growing evidence that supports CBT efficacy when therapist-supported and self-administered via the Internet [151; 284; 285]. A network meta-analysis found that the most effective combination of CBT components for treatment of panic disorder were face-to-face and interoceptive exposure components, while muscle relaxation and virtual-reality exposure were the least effective components [286].

Patient Education

An essential step after diagnosis of panic disorder is to review with patients their fears of medical illness and expectations of medical testing and treatment. More than 80% of patients with panic disorder present with a medical symptom, and most are fearful of having a serious condition, such as a stroke. Clinical experience suggests that patients benefit from education about panic disorder as the cause of their symptoms and the mechanism by which a mental disorder may provoke physical symptoms. Educational materials for patients may be obtained from the ADAA (at https://adaa.org) and the National Institute of Mental Health (https://www.nimh.nih.gov) [129].

PHARMACOTHERAPY

The first-line drugs recommended for the treatment of panic disorder are SSRIs or venlafaxine XR [120]. Research suggests that the largest effect size is found with clonazepam, followed by venlafaxine and fluoxetine [224]. Despite a sizeable number of pharmacologic options, less than 50% of patients with panic disorder experience full and sustained remission to first-line medication therapy [287].

SSRI/SNRI

The SSRI safety/side effect profile relative to TCAs, MAOIs, and benzodiazepines led to their recommendation as first-line drug options for patients with panic disorder. SSRI side effects occur early in treatment before the therapeutic effects. Many patients with panic disorder are highly sensitive to side effects, and SSRIs should be started at low doses, with dose titration every five to seven days, as tolerated [129].

Following 10 weeks of venlafaxine treatment for panic disorder, patients with few dissociative symptoms during panic attacks showed significantly greater treatment response than patients with greater presence of panic attack-associated dissociative symptoms. These findings suggest that dissociative symptoms accompanying panic disorder negatively impact pharmacologic treatment response. Re-evaluation of dissociative symptoms at the beginning and end of treatment would help in personalizing therapy [288].

Benzodiazepines

A meta-analysis was performed of randomized controlled trials comparing alprazolam to other benzodiazepines in the treatment of panic disorder with or without agoraphobia [289]. In the pooled results, there were no significant differences in efficacy between alprazolam and comparator benzodiazepines on improvements in panic attack frequency, anxiety rating scores, or proportion of patients panic attack-free at final evaluation. To date, the evidence fails to demonstrate alprazolam superiority to other benzodiazepines for panic disorder treatment [289]. Additionally, while alprazolam is one of the most widely prescribed benzodiazepines for the treatment of panic disorder, its clinical use is contentious due to its potential for misuse [290].

TREATMENT OF AGORAPHOBIA

Almost all agoraphobia studies reported treatment outcomes of patients with co-occurring panic disorder, as they were not separated into distinct diagnostic entities until the DSM-5 was published in 2013.

PSYCHOTHERAPY

CBT is the most empirically supported psychosocial treatment for panic disorder with agoraphobia, with a central focus of repeated exposure to feared situations and sensations and application of skills learned in therapy. These include cognitive skills to control negative thoughts and somatic skills to control dysregulated physiology during exposure. While CBT has clearly been established as an effective treatment for panic disorder with agoraphobia, the effect sizes are smallest among the anxiety disorders and a large percentage of treatment completers are not panic free or do not reach responder status after treatment. The largest randomized controlled trial to date for panic disorder with agoraphobia found only 32% of those assigned to CBT alone demonstrated strong treatment response at 12 months post-treatment [162]. A small 20-year follow-up of patients with panic disorder with agoraphobia found that completion of medication-free, integrated exposure and psychodynamic treatment resulted in excellent very long-term outcomes for these patients [291].

The relevance of process variables in patient response and outcomes with CBT have been studied. Among 301 patients with panic disorder/agoraphobia, changes in panic symptoms were preceded by changes in catastrophic appraisal and agoraphobic avoidance in all treatment phases, anxiety sensitivity during generalization and follow-up, and psychologic flexibility during exposure therapy. Changes in functioning were preceded by changes in agoraphobic avoidance and psychologic flexibility in all treatment phases, fear of bodily symptoms during generalization/follow-up, and anxiety sensitivity during exposure. The effects of process variables on outcomes differed across treatment phases and outcomes. Agoraphobic avoidance and psychologic flexibility should be therapeutically targeted in addition to cognitive variables [292].

Low remission rates in patients with panic disorder/agoraphobia following CBT-based therapies has led to the development and evaluation of novel psychotherapies, adjunctive drug therapies, and cognitive enhancer drugs to improve exposure therapy response and remission rates.

Novel Psychotherapies

The intervention for patients with panic disorder/agoraphobia who are nonresponsive to CBT has generally been pharmacotherapy, with few studies evaluating a switch to psychotherapy. In one study, patients with previous unsuccessful state-of-the-art treatment were randomized to immediate acceptance and commitment therapy or four-week waiting list with delayed acceptance and commitment therapy; they were then followed for up to six months. Significantly greater changes in functioning and symptomatology were found in patients who received immediate acceptance and commitment therapy versus those on the waiting list, and medium-to-large effect sizes were maintained for six or more months. Acceptance and commitment therapy may be a viable treatment option for treatment-resistant panic disorder with agoraphobia [293].

A long-term study of patients with panic disorder and agoraphobia found catastrophic beliefs to be an important mediator of change. Of 46 patients with panic disorder/agoraphobia randomized to cognitive or guided mastery therapy, 31 (67.4%) medication-free patients who completed treatment were followed up to 18 years post-treatment. Both groups showed a large effect size for avoidance of situations when alone, and 56.5% no longer met diagnostic criteria for panic disorder or panic disorder with agoraphobia. Patient outcomes between the two treatments were comparable, although guided mastery was associated with greater beneficial changes in catastrophic beliefs and self-efficacy. Greater reduction in panic-related beliefs about physical and mental catastrophes predicted lower anxiety level at follow-up [294].

Combination Therapy

Following paroxetine plus CBT (once weekly for 12 weeks), paroxetine plus CBT and virtual reality exposure (four sessions), or paroxetine only, the six-month follow-up of 99 patients with panic disorder/agoraphobia showed reduced anxiety levels in all three groups and greatest reduction in both CBT groups. The virtual reality exposure group showed greater improvement in confronting agoraphobic stimuli, although medication cessation and dropout were high [295].

The one-year follow-up of patients with panic disorder with and without agoraphobia treated with CBT, SSRI, or CBT and SSRI found that panic attack frequency significantly declined in all groups and both SSRI groups improved significantly faster than CBT [296]. The SSRI gains were maintained after tapering. Panic frequency in patients with moderate-to-severe agoraphobia decreased more rapidly with CBT plus SSRI than either sole treatment. With CBT alone, improvement was slower than with SSRI or CBT plus SSRI. SSRI monotherapy was concluded sufficient for patients with panic disorder with no or mild agoraphobia, while patients with panic disorder and moderate-to-severe agoraphobia should receive CBT plus SSRI [296].

PHARMACOTHERAPY

An efficacy analysis of drug therapy trials in the treatment of panic disorder with agoraphobia was published in 2011 [86]. It concluded that panic attack recurrence worsens agoraphobic behaviors in panic disorder with agoraphobia and disrupts agoraphobia remission. This suggests that using panic attack-blocking medication in patients with panic disorder/agoraphobia at risk of panic attack recurrence is more appropriate than CBT alone.

The meta-analysis also found that paroxetine displayed high efficacy in panic and phobic symptoms and agoraphobia severity reduction. This efficacy was similar to CBT in reducing

agoraphobic behaviors and superior to CBT in reducing panic attacks during acute treatment phase [86]. Adding paroxetine to CBT in patients with poor CBT response is significantly more effective in improving agoraphobic behaviors than adding placebo, so it is strongly suggested to add paroxetine for patients lacking adequate response or panic attack reduction with CBT [86]. Sertraline, citalopram, and escitalopram are also effective in the treatment of panic disorder/agoraphobia.

A randomized controlled trial compared treatment with an SSRI (paroxetine or citalopram) to continued treatment with CBT in a sample of 68 individuals with panic disorder (with or without agoraphobia) who had not responded to an initial course of CBT [297]. Participants were randomized to three months of treatment and then followed for an additional nine months. Those who responded to treatment after 3 months were maintained on the treatment until 12-month follow-up. Participants receiving an SSRI showed significantly lower panic disorder symptoms compared with continued CBT at three months, suggesting a greater improvement in panic disorder symptoms when patients are switched to an SSRI after failure to respond to an initial course of CBT [297].

The TCA clomipramine has similar panic/phobic efficacy to paroxetine and sertraline. Imipramine is more effective than placebo in long-term maintenance, but less effective than sertraline in short-term outcomes. Venlafaxine is effective in reducing panic and phobic symptoms [86]. Reboxetine is more effective in the treatment of panic/phobia than placebo. It has similar efficacy to paroxetine in phobic avoidance and anticipatory anxiety, but lower efficacy in reducing panic attacks.

Fluvoxamine has only inconsistent efficacy in the treatment of panic disorder/agoraphobia, and while fluoxetine may be used to address panic attacks, it has limited efficacy for panic disorder/agoraphobia [86].

These results suggest noradrenergic system involvement in modulating panic disorder with agoraphobia avoidance behaviors, but serotonergic system targeting is important to decrease panic attacks. Re-analysis of prior pharmacologic randomized controlled trial data found higher efficacy with sertraline and clomipramine in reducing agoraphobic symptoms than paroxetine, fluvoxamine, or citalopram. This may reflect the added dopaminergic modulation of these agents beyond their primary serotonergic activity [86].

A novel treatment approach is based on multiple findings of balance system dysfunction in patients with panic disorder/agoraphobia. An open study found citalopram influenced the balance system in these patients by improving postural stability, as measured by static posturography. Compared with baseline scores, most patients whose balance system function improved were no longer agoraphobic, while those whose posturography scores remained abnormal continued to be agoraphobic. These findings suggest the involvement of balance system dysfunction in panic disorder with agoraphobia and serotonergic system relevance in mediating the connection between balance and agoraphobia [298]. The authors suggest that real abnormal body functioning (primarily involving cardiorespiratory and balance systems), which leads to reduced overall physical fitness, may be a primary cause of panic disorder and that the anxiety and fear it induces is sustained by repeated signals of impaired body functioning [299].

In one study, patients with panic disorder/agoraphobia received alprazolam plus exposure, alprazolam plus progressive muscle relaxation, placebo plus exposure, or placebo plus progressive muscle relaxation. The highest rate of improvement at follow-up was observed in the placebo/exposure (71%) and alprazolam/exposure (71%) groups; alprazolam/progressive muscle relaxation (51%) and progressive muscle relaxation/placebo (25%) groups were less improved [300]. Alprazolam showed no benefit over placebo when added to exposure therapy as treatment for panic disorder/agoraphobia [300].

CONTRIBUTING FACTORS TO PANIC DISORDER WITH AGORAPHOBIA TREATMENT RESPONSE

Pronounced safety behaviors during exposure therapy, but not at baseline, have been associated with poor treatment response in patients with panic disorder/agoraphobia. This underscores the importance of rigorous safety behavior assessment during therapy [301].

During 13 to 21 years post-treatment follow-up, major depression at baseline predicted worse improvement in agoraphobic avoidance in the first year. Employment and marriage/cohabitation at baseline predicted greater improvement at 1-year, 2-year, and 13- to 21-year follow-up [302].

A substantial number of patients with panic disorder/agoraphobia fail to improve following CBT. Agoraphobic avoidance is the most consistent predictor of decreased improvement, followed by low expectancy for change, high levels of functional impairment, and Cluster C personality pathology [303].

TREATMENT OF SOCIAL ANXIETY DISORDER

PSYCHOTHERAPY

CBT is the criterion-standard psychologic treatment for SAD. Cognitive techniques that address SAD include restructuring and challenging maladaptive thoughts, and the behavioral component typically involves exposure therapy. The efficacy of CBT is supported by many randomized controlled trials, with outcomes that vary but are typically similar to pharmacotherapy. Some reports suggest that, after treatment discontinuation, gains achieved with CBT may persist longer than those achieved with pharmacotherapy. CBT for SAD can be administered in group or individual formats. Although some studies have reported that individual CBT is superior to group CBT, meta-analyses have failed to find significant differences in efficacy between the two modalities. There is evidence to support the effectiveness of exposure therapy alone, but efficacy compared with CBT is equivocal [120].

Several CBT variants have been examined. Videotaped feedback was not shown to enhance the effects of exposure-based

treatment. However, CBT with virtual reality exposure was found more effective than wait-list control and as effective as CBT with imaginal or in vivo exposure according to two meta-analyses [120].

A form of CBT focused on interpersonal behavior found similar improvements in social anxiety compared to standard CBT and also increased relationship satisfaction and social approach behaviors. Evidence to support interpersonal therapy in SAD is conflicting; while some results are negative, interpersonal therapy is probably more effective than wait-list control, but less effective than traditional CBT [120].

With Internet CBT for SAD, patients with an avoidance and depression profile showed lower remission after treatment, higher levels of social anxiety at follow-up assessments, and typically remained highly symptomatic. In patients with SAD, high levels of social avoidance and depressive symptoms constitute a risk profile for poor treatment response [304].

PHARMACOTHERAPY

Pharmacotherapy of SAD is effective but varies considerably, with room for further improvement [305]. The ADAC recommends escitalopram, fluvoxamine (immediate- or controlled-release), paroxetine (immediate- or controlled-release), pregabalin, sertraline, or venlafaxine XR for first-line treatment of SAD [120]. Citalopram has less evidence but is likely as effective as other SSRIs. Phenelzine efficacy is established in multiple randomized controlled trials but is recommended as a second-line option due to concerns over dietary and medication restrictions that, if not strictly adhered to, can lead to hypertensive crisis [120].

Abnormalities in brain GABA and glutamate systems have been studied in patients with SAD, including whether these changed following eight weeks of levetiracetam. Compared to healthy controls, patients with SAD at baseline showed significantly higher whole brain levels of glutamate and glutamine (but not GABA) and significantly higher thalamic glutamine and lower GABA levels. Following treatment, these patients showed significant reduction in thalamic glutamine. These findings support the role of impaired GABAergic and overactive glutamatergic function in SAD and may explain the anxiolytic effects of levetiracetam [306].

TREATMENT OF SPECIFIC PHOBIA

Patients with specific phobias generally do not consult medical professionals when able to avoid the specific feared situations or objects. Exposure therapy is effective in treating specific phobia and is the favored approach.

PSYCHOTHERAPY

Exposure-based therapies are the treatments of choice and show a high degree of successful remission for all phobias. In vivo exposure and virtual reality exposure can be effective, with in vivo exposure superior to imaginal and virtual reality exposure at post-treatment but not at follow-up [307].

The effectiveness of exposure-based therapy is enhanced when exposure sessions are grouped closely together; when exposure is prolonged, real (not imagined), and provided in different settings; and when there is some degree of therapist involvement instead of being entirely self-directed. A greater number of sessions have been shown to predict more favorable outcomes. There is no evidence that flooding is more effective, and patients usually find graded, progressive exposures more tolerable [307].

A variety of psychotherapeutic options have been found effective for the treatment of specific phobias, with some approaches recommended for particular phobias (***Table 4***) [120]. For blood-injection-injury phobias, an effective approach is combining exposure therapy with muscle tension exercises (applied tension) designed to prevent fainting. Using stress-reducing medical devices, such as decorated butterfly needles and syringes, has significantly reduced needle phobia and stress in pediatric and adult patients. With dental phobias, use of CBT can reduce avoidance of oral injections and decrease patient anxiety [120; 307].

Long-term treatment of specific phobia is rare. CBT and exposure therapies show sustained benefits at long-term follow-up assessments following a time-limited course of treatment [120].

PHARMACOTHERAPY

Pharmacotherapy has a minimal role in specific phobia treatment, largely from the lack of drug therapy research and the success of exposure therapies. Alprazolam benefit was studied in 28 women with flying phobia during two air travel exposures, one week apart. Compared with subjects given pre-flight placebo for both flights, those receiving alprazolam before the first flight had less anxiety and symptoms but greater heart and respiratory rates. Those given alprazolam had a substantial increase in panic attacks during the second flight compared with the first flight (71% vs. 7%), greater overall anxiety, and further elevation in heart rate. Alprazolam increased physiologic activation under acute stress conditions and hindered the therapeutic effects of exposure therapy for flying phobia [120; 308]. These findings require replication to determine clinical utility.

Some benefit is suggested by small trials of paroxetine or escitalopram. However, there is too little evidence to recommend any drug treatment of specific phobias [224].

A NOVEL APPROACH COMBINING MEDICATION AND EXPOSURE THERAPY

In 2015, a potential landmark study of 45 subjects with spider phobia was published. A pre-treatment two-minute tarantula exposure was followed four days later by randomization to propranolol without exposure or to exposure and then propranolol 40 mg or placebo (within 10 minutes). All three groups went through tarantula exposure 9 days, 16 days, 90 days, and one year later [309].

After nine days, all exposure/propranolol subjects touched the tarantula, while the other two groups barely touched its

PSYCHOLOGIC TREATMENTS EFFECTIVE IN SPECIFIC PHOBIA	
Treatment Approach	**Phobia(s)**
Exposure-based treatments	All specific phobias
Virtual reality exposure	Heights, flying, spiders, claustrophobia
Computer-based self-help programs	Spiders, flying, small animals
Applied muscle tension (i.e., exposure with muscle tension exercises)	Blood-injection-injury type
Cognitive therapy and exposure	Dental, flying
Source: [120]	*Table 4*

container. By 16 days, all exposure/propranolol subjects further progressed in approach, while the two other groups did not progress. Approach behavior remained stable for all three groups throughout one year. Most interestingly, significant reduction in self-reported spider fear lagged several months behind the instant behavioral transformation in the exposure/propranolol group [309].

This study is the first to identify optimal drug and timing for durable remission of phobic anxiety and avoidance. The results challenge the fundamental tenet of CBT that changes in cognition are necessary for behavioral change. Such a novel approach is clearly needed, and similar trials enrolling subjects with agoraphobia and social phobia are expected in the future [309].

TREATMENT OF SEPARATION ANXIETY DISORDER

PSYCHOTHERAPY

As mentioned, the presence of pathologic separation anxiety has a pervasive negative influence on treatment response in patients with diverse anxiety and mood disorders receiving standard therapies. Patients with SEPAD show poor response to standard CBT and exposure-based therapies. This poorer treatment response may reflect the difficulties these patients experience forming and maintaining attachments, including therapeutic relationships. Growing evidence points to the incompatibility in applying the prevailing fear extinction model of anxiety to patients with SEPAD. This pathophysiologic model emphasizes desensitization to threatening stimuli. While theoretically and empirically supported in other anxiety disorders, this model does not consider the role of earlier childhood SEPAD in adult panic disorder and other anxiety disorders [98].

The unmet need for SEPAD-specific treatment has led to psychotherapies that focus on relationships and separation anxiety. These approaches use the therapist-patient relationship to recapture and better understand important elements of earlier pathologic parent-child relationships. Panic-focused psychodynamic psychotherapy is an affect-focused therapy that specifically targets separation anxiety as a core component of panic disorder. Preliminary efficacy is shown in patients with prominent separation anxiety symptoms across different anxiety and mood disorders. High separation anxiety levels constitute a central organizing element in patient self-perception as incompetent and unable to manage developmentally normative tasks without the presence of their central attachment figures. Panic-focused psychodynamic psychotherapy emphasizes free association, centrality of transference, unconscious thoughts that underlie physical sensations of panic, and difficulty with separation and autonomy. The therapist focuses on these processes as they relate to panic symptoms. Common themes of difficulty with separations and unconscious rage inform interpretive interventions. The pre-determined 24-session, 12-week time limit enhances the opportunity to work with separation anxiety and permits the re-experiencing and better understanding [98].

PHARMACOTHERAPY

With adult SEPAD becoming formalized in 2013 as a distinct diagnostic entity and anxiety disorder, little pharmacotherapy research has been performed specifically addressing this condition.

EMERGING THERAPIES AND NOVEL TREATMENT APPROACHES

NEUROENHANCING AGENTS TO AUGMENT EXPOSURE THERAPY

Some neuroenhancers, especially D-cycloserine (DCS), are promising for treating anxiety disorders because these agents improve extinction learning efficacy, integral in exposure therapy. They facilitate learning new memories through habituation and extinction, and these safe memories will over-ride the previous fear memories. Use of neuroenhancers to augment CBT represents a promising translational effort—taking neuroscience discovery into clinical practice. In contrast, use of anxiolytics and CBT in anxiety disorders did not originate from a theoretical basis for the mechanism of action, and overall effectiveness leaves substantial room for improvement [164].

D-Cycloserine

The most extensively studied exposure augmentation agent is DCS, an *N*-methyl-D-aspartate (NMDA) receptor partial agonist. Findings that extinction learning is modulated, in part, by the glutamatergic NMDA receptor complex prompted interest in the role of glutamatergic transmission in anxiety disorders. Clinical trials began to study the potential efficacy of low-dose DCS for enhancing memory consolidation and effectiveness

of exposure therapies for anxiety disorders [165]. DCS studies of patients with specific phobia (e.g., heights, snakes), OCD, panic disorder with agoraphobia, PTSD, or SAD have been published. Following promising early findings, more recent studies have reported inconsistent results, including findings that DCS resulted in faster rates of improvement but not higher response or remission rates in SAD and even more symptoms at post-treatment in PTSD. These inconsistent trials have informed the understanding of limitations and indications of DCS augmentation of exposure therapy [310; 311; 312; 313].

Dosing and dose timing of DCS is essential. Most trials reporting positive results used low-dose DCS (50–250 mg) one to two hours before three to five exposure sessions. Studies with negative results often used higher doses (≥ 250 mg), chronically (before 12 exposures), and more than one to two hours before an exposure. Higher-dose DCS shows weaker NMDA partial agonist or antagonist effects. Key extinction learning processes occur hours following exposure, and DCS blood concentration peaking at four to six hours makes it more effective taken within one to two hours before exposure for peak activity to coincide with key extinction processes. Repeated DCS use can desensitize the NMDA receptor complex, leading DCS to effectively work as an NMDA antagonist. Long-term antidepressants can induce neurochemical changes at the glycine binding site of the NMDA receptor complex, which alters the action of DCS. Therefore, use of DCS should consider the narrow therapeutic window and the need to be administered without concomitant medication, acutely, and at low doses one to two hours pre-exposure [310].

DCS is associated with serious risks. DCS not only enhances cognitive processes during fear extinction learning but also during fear memory reconsolidation, thus improving good exposures and worsening bad exposures. If fear-inducing stimulus re-exposure during fear memory reactivation is too brief relative to the strength of fear conditioning or if fear decrease during exposure is inadequate, little extinction is induced and DCS can augment the process of fear memory reconsolidation to worsen symptoms [310].

These findings led to DCS administered post-exposure, contingent on the level of fear reduced (i.e., extinction learning achieved) by the end of the exposure session. Preliminary evidence shows that this approach may be effective in capitalizing on the benefits while minimizing the risks of DCS use to augment exposure therapy [310].

Yohimbine Hydrochloride

Yohimbine hydrochloride (YOH) is a selective competitive alpha2-adrenergic receptor antagonist currently only approved for veterinary use. This compound increases extracellular norepinephrine in humans by blocking autoreceptor inhibition of norepinephrine release. This mechanism potentially facilitates extinction learning in exposure therapies. Placebo-controlled trials have been performed in specific phobia and SAD. Subjects with claustrophobia given YOH 10.8 mg before two 60-minute exposures of sitting in a closed, dark chamber showed more robust reductions in claustrophobia symptoms. Patients with SAD given YOH 10.8 mg before four exposure sessions showed accelerated treatment improvement and lower levels of social anxiety symptoms. More research is needed, but these results suggest YOH may have a role in augmenting exposure therapy [164].

Glucocorticoids

Glucocorticoids have shown enhancement of virtual reality-based exposure therapy for fear of heights and were investigated for possible outcome enhancement in exposure-based group therapy for spider phobia. In one randomized controlled trial, cortisol 20 mg or placebo was orally administered one hour before each therapy session and patients were assessed at one-month post-therapy follow-up. Compared to placebo, cortisol led to significantly greater reduction in fear of spiders at follow-up but not immediately post-treatment, as measured psychometrically and by exposure to live spiders. Groups did not differ in phobia-unrelated state-anxiety before and after exposure sessions and at follow-up [314].

Another randomized controlled trial investigated the role of hydrocortisone as an adjunct to brief CBT for specific (spider) fear [315]. Spider-fearful participants were randomized to receive either 20 mg hydrocortisone or placebo one hour prior to single-session, predominantly computerized, exposure-based CBT. Participants' fear of spiders was assessed using self-report and approach behaviors measured at baseline and at one-day and one-month follow-up. Threat processing was assessed at baseline and at one-day follow-up. Cortisol and cortisone levels from hair and saliva samples were analyzed at baseline. All measures improved following CBT. Augmentation with hydrocortisone resulted in greater improvement in self-reported fear and approach behavior but not threat bias. Neither threat bias nor endogenous glucocorticoids predicted symptom change. Evidence indicates that higher hair cortisone predicts a stronger threat bias reduction [315].

Methylene Blue

Methylene blue is a nitric oxide synthase inhibitor, central MAO inhibitor, and cerebral metabolic enhancer. A placebo-controlled trial of subjects with severe claustrophobic fear found that participants displaying low fear at the end of extinction training showed significantly less fear at follow-up if they received methylene blue post-training relative to placebo. In contrast, participants displaying moderate-to-high levels of post-training fear tended to fare worse at follow-up with methylene blue compared with placebo. Similar to the profile of DCS, methylene blue enhanced memory and retention of fear extinction when administered after a successful exposure session, but it may have deleterious effects on extinction when administered after an unsuccessful session [316].

CAPNOMETRY-ASSISTED RESPIRATORY TRAINING

Panic disorder and sensitivity to increased carbon dioxide (CO_2) levels common in patients with panic disorder may represent pathologically amplified survival mechanisms. Panic disorder reflects a "fight-or-flight" response, and CO_2 hypersen-

sitivity is an evolutionary carry-over from when alarm response to dwindling oxygen helped ensure survival. Panic attacks that awaken people at night only occur during non-REM sleep, when deep relaxation and slowed breathing lead to rising CO_2 levels that trigger a false suffocation alarm [317].

Capnometry-assisted respiratory training (CART) is an intervention that addresses CO_2 fluctuation and its role in panic attacks for some people. CART targets respiratory dysregulation and hypocapnia through a four-week training using immediate feedback of end-tidal CO_2 pressure (PCO_2). Patients are taught how to raise subnormal PCO_2 levels (caused by hyperventilation) to control dysfunctional respiratory patterns and related panic symptoms of shortness of breath and dizziness. CART uses novel technologies that allow precise assessment and monitoring of core respiratory variables. A portable capnometer offers breath-by-breath feedback of expired CO_2 and breathing rate, as measured via nasal cannula.

In one study, four weeks of CART led to reductions in panic symptom severity and frequency comparable to standard CBT, maintained at 12-month follow-up. Patients with panic disorder/agoraphobia randomized to four weeks of CART or cognitive therapy showed significant and comparable reductions in panic symptom severity and panic-related cognitions [281]. Across studies in patients with panic disorder with agoraphobia and asthma, compliance with the 17-minute, twice-daily exercises was high, and compliance correlated with the extent of panic symptom reduction [281; 318]. Changes in PCO_2 mediated and preceded changes in fear of panic sensations, cognitive reappraisal of symptoms, and perceived control. Reductions in respiration rate were unrelated to outcome [281; 319]. These findings strengthen the idea that panic symptom reduction can be achieved through different mechanisms [162].

NEUROMODULATION THERAPIES

Brain stimulation (also referred to as neuromodulation, neurostimulation, or somatic therapy) for the treatment of neuropsychiatric disorders was developed as an option for patients with severe disorders refractory to multiple treatments. Electroconvulsive therapy, introduced more than 75 years ago, has been historically the only widely used somatic treatment of psychiatric disorders. This was changed by the development and FDA approval of several minimally or non-invasive brain stimulation modalities with much greater specificity than electroconvulsive therapy. Other modalities are undergoing evaluation and possible market entry [320]. This approach shifts the treatment focus from altering synaptic neurotransmission to altering or modulating the function of entire neural circuits, the dysfunction of which underlies anxiety disorders [120].

Repetitive Transcranial Magnetic Stimulation

The most studied neurostimulation approach in the United States is repetitive transcranial magnetic stimulation (rTMS). As discussed, patients with panic disorder often lack response or only partially respond to drug or psychologic treatments, which increases the risk of the disorder becoming chronic and disabling. Transcranial magnetic stimulation delivers non-invasive stimulation to the cerebral cortex, with currents induced by powerful, extremely brief magnetic fields. Administration in a rhythmic, repetitive form is rTMS. Modulation of cortical excitability uses high-frequency rTMS to increase cortical excitability or low-frequency rTMS to inhibit cortical excitability of targeted areas. rTMS can also affect remote brain areas connected to the stimulated site [321].

Early studies of rTMS in anxiety disorders often found no difference between active vs. sham rTMS, reflecting the inability to stimulate brain regions deeper than superficial cortical layers and inadequate treatment duration or post-treatment follow-up [322]. Subsequent technical refinements show treatment efficacy.

A randomized controlled trial treated 28 patients with panic disorder and major depression with active or sham rTMS to the right dorsolateral prefrontal cortex. Response was defined as reduction by ≥40% in panic disorder severity and ≥50% in depression ratings. After four weeks, panic disorder response rate was 50% with active and 8% with sham rTMS, with no difference in depression. After eight weeks of active rTMS, response rates were 67% for panic and 50% for depressive symptoms. Significant improvements occurred in panic disorder, major depression, clinical global impression, and social adjustment. Clinical improvements were maintained at six months post-treatment. While four weeks of rTMS was sufficient to significantly reduce panic symptoms, a longer course led to better outcomes for both panic disorder and major depression. These data suggest that inhibitory rTMS to the right dorsolateral prefrontal cortex affects symptom expression in comorbid anxiety and depressive disorder [323]. Another study found that inhibitory rTMS to the left dorsolateral prefrontal cortex showed therapeutic effects in patients with major depressive disorder [324].

NEW OR NOVEL ANXIOLYTIC AGENTS

Cannabidiol

Cannabidiol is the second most abundant cannabinoid in *Cannabis* plants and lacks the consciousness-altering effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in *Cannabis*. Cannabidiol is a pharmacologically broad-spectrum drug that has drawn increasing interest as a treatment for a range of neuropsychiatric conditions, including anxiety disorders. Preclinical evidence supports cannabidiol as a treatment for GAD, panic disorder, SAD, OCD, and PTSD when administered acutely, but few studies have investigated chronic cannabidiol dosing. Randomized controlled trials showed that, relative to placebo, cannabidiol significantly reduced anxiety in patients with SAD and GAD [136; 325].

In a series of randomized controlled trials using fear-conditioning paradigms, subjects who received cannabidiol (vs. placebo) all showed successful conditioning, extinction, and recall. When given after resolution of symptoms, cannabidiol enhanced consolidation of extinction learning. Cannabidiol administered pre- or post-extinction reduced the reinstatement of autonomic contextual responding. No acute effects

of cannabidiol were found on extinction. These results are the first evidence that cannabidiol may enhance consolidation of extinction learning in humans, suggesting cannabidiol may have potential as an adjunct to extinction therapies for anxiety disorders [326].

Brain imaging cannabidiol trials in patients with GAD or SAD consistently showed changes in functional activity in limbic and paralimbic cortical areas implicated in anxiety pathophysiology, with effects in the left para-hippocampal gyrus, the hippocampus, and the right posterior cingulate gyrus. Cannabidiol was found safe and tolerable, with few side effects and without major side effects during acute treatment. Cannabidiol administered chronically in oral doses of 10–1,280 mg/day to healthy volunteers and patients with schizophrenia, bipolar affective disorder, Parkinson disease, or Huntington disease did not find significant side effects or induction of any new neurologic, psychiatric, or general clinical conditions [136; 327]. Overall, evidence indicates cannabidiol has considerable potential as a treatment for several anxiety disorders, with further study of chronic and therapeutic effects in relevant clinical populations needed [325; 328].

Etifoxine

Etifoxine (also known as etafenoxine) is a non-benzodiazepine anxiolytic and anticonvulsant not yet approved in the United States. Clinical effects are mediated by GABA-Aα2 receptors, similar to benzodiazepines, and etifoxine appears to produce anxiolytic effects directly by binding to β2 or β3 subunits of the GABA-A receptor complex. The effects of etifoxine are not completely reversed by the benzodiazepine antagonist flumazenil. Etifoxine also stimulates neurosteroid production, which contributes to anxiolytic and neuroprotective effects. Several randomized controlled trials comparing etifoxine to lorazepam found vigilance, psychomotor performance, and free recall significantly impaired by lorazepam but not etifoxine. Superior anxiolytic effect and memory recall were noted with etifoxine, with fewer withdrawal symptoms than with lorazepam. Etifoxine appears promising as a non-benzodiazepine anxiolytic agent that lacks many shortcomings with benzodiazepines and SSRIs, although acute liver toxicity has been reported [329; 330].

Asenapine

Asenapine is a newer atypical antipsychotic drug. Its dominant mechanism of action is mediated through 5HT2A and D2 receptor antagonism and also by antagonism of 5HT2B, 5HT2C, 5HT6, and 5HT7 serotoninergic; α1A, α2A, α2B and α2C adrenergic; and D3/D4 dopaminergic receptors [178]. Clinical efficacy in anxiety and mood disorders is predicted by its serotoninergic profile. This agent lacks affinity for muscarinic receptors and induces fewer anticholinergic side effects than other second-generation antipsychotics [331]. Asenapine is FDA-approved for schizophrenia and bipolar disorder; its use for anxiety disorders is off-label [178].

Tandospirone

Closely related to buspirone, tandospirone (also known as metanopirone) is a 5-HT1A receptor partial agonist used in China and Japan. Its efficacy was compared to sertraline in an eight-week randomized controlled trial in adolescents with SAD. Both drugs significantly improved anxiety scores from baseline, showed similar overall response and anxiety symptom-specific response rates (≥50% reduction), and resulted in significant and comparable improvements in social phobia symptoms. Tandospirone appeared non-inferior to sertraline treatment of SAD in adolescents. The drug is not FDA-approved [332].

COMPLEMENTARY/ ALTERNATIVE THERAPIES

HERBAL PRODUCTS AND SUPPLEMENTS

Myo-Inositol

Myo-inositol is a glucose isomer and essential component of the phosphatidylinositol second messenger system critically linked to several CNS receptor-signaling systems [333]. Myo-inositol anxiolytic and antidepressant activity is mediated by a serotoninergic 5-HT2A/5-HT2C receptor-signaling pathway [334].

Several randomized controlled trials have been conducted using placebo or active controls. In 21 patients with panic disorder with or without agoraphobia given inositol 12 g/day or placebo for four weeks, significant decreases were found in the frequency and severity of panic attacks and agoraphobia severity with inositol relative to placebo [335]. Another randomized controlled trial compared myo-inositol 18 g/day with fluvoxamine 150 mg/day in patients with panic disorder with or without agoraphobia. Both drugs led to significant but comparable improvements in anxiety symptoms/severity, agoraphobia symptoms/severity, and global impression. In the first month, reduction in the number of panic attacks per week was significantly greater with inositol than fluvoxamine (4.0 vs. 2.4). Nausea and fatigue were significantly more common with fluvoxamine [336].

Other randomized controlled trials found that myo-inositol 12 g/day in 28 patients with major depression significantly reduced Hamilton Depression Rating Scale scores (vs. placebo) after four weeks; and 18 g/day given to patients with OCD for six weeks led to significant reductions in OCD symptom scores (vs. placebo) [335]. A review of supplements and herbal therapies with purported anxiolytic efficacy concluded myo-inositol was one of very few with demonstrated effectiveness [337]. The published research needs larger trials but is intriguing in light of a study in which patients with severe depression receiving treatment with rTMS showed significantly elevated prefrontal cortex myo-inositol levels, and this elevation correlated with extent of clinical improvement [338]. A meta-analysis of inositol for depression and anxiety disorders found that the agent may be particularly beneficial for treatment of depression [339].

The effective dose is 12–18 g per day, and inositol is free of side effects other than loose stools and drowsiness [335]. A drawback is the large amount required for therapeutic benefit, necessary to compensate for poor blood-brain barrier penetration. An Italian pharmaceutical company has developed a more

concentrated myo-inositol formulation, with dose comparability to standard myo-inositol at 25% the dose level [338].

Overall, inositol is a natural compound with few side effects and may be an attractive option for patients with panic disorder who are ambivalent about taking psychiatric medication [336]. Myo-inositol is one of nine inositol isomers, but unless another inositol isomer is specified, inositol sold at retail is almost always myo-inositol.

Kava

Kava (*Piper methysticum*) extract has been used for anxiolytic effects, mediated through GABA channel modulation and weak GABA binding, β-adrenergic downregulation, and MAO-B inhibition. Efficacy studies in GAD showed superiority to placebo and comparability to buspirone. However, distribution and use of kava dropped off when reports of liver toxicity surfaced in the early 2000s [340; 341; 342].

Lavender Oil

A six-week randomized controlled trial compared silexan, a lavender oil capsule preparation, with lorazepam in GAD treatment efficacy. Both treatment groups showed similar reductions on the primary anxiety measure (HAM-A) and similar and comparable reductions on measures of somatic anxiety, psychic anxiety, anxiety self-rating, impression of illness severity, sleep quality, and other scales. Silexan appears to be an effective and well-tolerated alternative to benzodiazepines for GAD treatment [343]. A 10-week randomized controlled trial compared silexan with paroxetine and placebo in GAD treatment efficacy. Participants received 80 mg or 160 mg silexan, 20 mg paroxetine, or placebo once daily for 10 weeks [344]. The primary outcome measured was HAM-A total score reduction between baseline and treatment end. A total of 60.3% of participants in the silexan 160 mg group showed a HAM-A total score reduction greater than 50% of the baseline value compared with 51.9% in the silexan 80 mg group, 34.1% in the paroxetine group and 37.8% in the placebo group. Silexan additionally showed a pronounced antidepressant effect and improved general mental health and health-related quality of life. Rates of adverse effects were comparable among the silexan and placebo groups and lower for the paroxetine group [344].

EXERCISE THERAPY

Resistance exercise (i.e., strength training) includes a broad group of activities that evoke repeated muscle action against resistances above those encountered in daily life. A growing body of literature has identified anxiolytic effects of resistance exercise after both single sessions and long-term training. This research has shown that resistance training at a low-to-moderate intensity produces the most reliable and robust decreases in anxiety. Higher intensity has shown either no change or increased anxiety from baseline. One caveat is most of this research involved participants with state (not trait) anxiety [345].

YOGA

Yoga is an ancient mind/body practice that involves different techniques in physical postures, controlled breathing, deep relaxation, and meditation that have positive and specific influences. Research on yoga has demonstrated significant improvements in emotional self-regulation with consequent reductions in depression, stress, and anxiety levels and improvements in mood, quality of life, and well-being [346]. Several studies have found significant anxiolytic effects with yoga in patients with GAD or panic disorder, and it is considered the complementary therapy with strongest evidence of safety and efficacy in anxiety disorders.

One randomized controlled trial compared patients with panic disorder who received yoga or CBT plus yoga weekly over two months. Both treatment groups showed significant decreases from baseline in anxiety levels associated with panic disorder, panic-related beliefs, and panic-related body sensations, although the CBT/yoga combination group led to greater reductions over yoga alone [346].

A group of patients with GAD lacking response to pharmacotherapy received a five-day, 22-hour yoga course. Compared with baseline, follow-up at four weeks found a 73% response rate and 41% remission rate and significant reductions in HAM-A total score and psychic subscale score. Attrition was 25% [347].

Combining yoga with CBT integrates yoga and meditation with traditional and alternative CBT methods to enhance restructuring of the destructive cognitive and emotional patterns associated with physical and psychologic anxiety symptoms. Given in 90-minute sessions once per week for six weeks, CBT/yoga consisted of yoga/meditation, instruction and experiential cognitive restructuring using traditional and alternative CBT interventions, and group discussion with processing. In a group of patients with GAD receiving CBT/yoga, post-treatment scores were compared to baseline. The patients showed significant improvements on measures of state and trait anxiety, depression, panic, suicidality, sleep disturbance, sexual function, and quality of life [348].

CONCLUSION

In the primary care setting, anxiety disorders are often underrecognized and undertreated because many patients present with and report distress from the physical symptoms of anxiety. The prevalence, patient distress and impairment, potential comorbidity, and treatment complexity associated with anxiety disorders underscore the importance of greater understanding of the signs and symptoms, differential diagnosis, and appropriate treatment selection in these patients.

COURSE TEST - #86182 ANXIETY DISORDERS

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 Hour activity must be completed by June 30, 2026.

1. Safety behaviors and safety signals are most accurately described as
- A) *isolation and social withdrawal.*
- B) *self-medication of panic attacks.*
- C) *over-compensation by risk taking in anxiety-provoking situations.*
- D) *people, objects, or behaviors used by those with anxiety disorders to diminish distress in anxiety-evoking situations.*

2. Which of the following statements regarding safety behaviors and safety signals is TRUE?
- A) *They may be counter-therapeutic when persistently used.*
- B) *They lessen acute anxiety but may perpetuate long-term anxiety.*
- C) *They may be helpful early in exposure therapy by making it more tolerable.*
- D) *All of the above*

3. All of the following are classed as anxiety disorders in the DSM-5, EXCEPT:
- A) *Agoraphobia*
- B) *Social anxiety disorder (SAD)*
- C) *Separation anxiety disorder (SEPAD)*
- D) *Post-traumatic stress disorder (PTSD)*

4. Annually in the United States, the number of adults experiencing DSM-5 anxiety disorders plus PTSD and obsessive-compulsive disorder (OCD) is
- A) *22 million.*
- B) *42 million.*
- C) *62 million.*
- D) *82 million.*

5. Which of the following anxiety disorders has a later age of onset?
- A) *SEPAD*
- B) *Specific phobia*
- C) *Elective mutism*
- D) *Generalized anxiety disorder (GAD)*

6. Which of the following demographic factors is associated with a higher risk of anxiety disorder diagnosis?
- A) *Male sex*
- B) *Age 45 to 54 years*
- C) *Low annual income*
- D) *College graduate education level*

7. Anxiety disorders are highly prevalent comorbidities in all of the following conditions, EXCEPT:
- A) *Schizophrenia*
- B) *Major depression*
- C) *Substance use disorder*
- D) *Antisocial personality disorder*

8. What is the annual incidence of panic disorder in the United States?
- A) *0.2%*
- B) *2.4%*
- C) *6.8%*
- D) *24%*

9. Primary prevention by recognizing excessive childhood fearfulness and behavioral inhibition, and appropriate intervention, may prevent future
- A) *SAD.*
- B) *GAD.*
- C) *SEPAD.*
- D) *specific phobia.*

Test questions continue on next page →

10. Children with separation anxiety disorder are more likely to develop which of the following in adulthood?
- A) *Depression*
- B) *Panic disorder*
- C) *Alcohol use disorder*
- D) *Substance use disorder*

11. In several anxiety disorders, an underlying pathophysiology is thought to involve
- A) *disinhibited cerebellar function.*
- B) *disrupted basal ganglia function.*
- C) *impaired prefrontal function and hyper-responsive amygdala.*
- D) *impaired amygdala and hyper-responsive prefrontal function.*

12. The underlying neurotransmitter abnormality in many anxiety disorders involves only
- A) *serotonin.*
- B) *norepinephrine and dopamine.*
- C) *gamma-aminobutyric acid (GABA).*
- D) *The inter-relationship and contribution is complex.*

13. Patients with panic disorder/agoraphobia
- A) *show impaired sensitivity to light or brightness stimuli.*
- B) *display greater balance control reliance on vestibular cues.*
- C) *experience greater balance system reactivity to central visual stimulation.*
- D) *have shown subclinical balance system abnormalities that seem to influence agoraphobia severity and contribute to dizziness and disorientation symptoms.*

14. Hyperactivity in all of the following brain regions is believed to be the underlying pathophysiology of specific phobia, EXCEPT:
- A) *Insula*
- B) *Amygdala*
- C) *Nucleus accumbens*
- D) *Anterior cingulate cortex*

15. The DSM-5 diagnostic criteria for which anxiety disorder remains unchanged from previous editions?
- A) *SAD*
- B) *GAD*
- C) *Agoraphobia*
- D) *Panic disorder*

16. Fear of one's panic attacks, and avoidance of places or situations they may occur, best describes
- A) *PTSD.*
- B) *SEPAD.*
- C) *agoraphobia.*
- D) *specific phobia.*

17. A core fear in patients with SAD is
- A) *a specific object or situation.*
- B) *selective attention to positive evaluation.*
- C) *revealing self-flaws and especially appearing socially incompetent.*
- D) *fear of social limitations causes avoidance of replaying social interactions.*

18. Which of the following is NOT a common feature of adult SEPAD?
- A) *Persistent and excessive fear of being in large crowds*
- B) *Excessive worries about potential harms to attachment figures*
- C) *Excessive distress when experiencing or anticipating separation from home*
- D) *Persistent and excessive worries about untoward events that might result in separation*

19. All of the following statements regarding anxiety disorder recognition and diagnosis in primary care settings are true, EXCEPT:
- A) *In many patients with anxiety problems, anxiety is not the presenting complaint.*
- B) *Rates of missed diagnoses and misdiagnosis of GAD and panic disorder are high.*
- C) *Primary care providers with greater sensitivity to nonverbal communications are less likely to detect and diagnose anxiety.*
- D) *Time constraints imposed on primary care clinicians in the current managed care environment contribute to under-recognition.*

20. Avoidant personality disorder should be ruled out in the differential diagnosis of
- A) *SAD.*
- B) *GAD.*
- C) *SEPAD.*
- D) *Agoraphobia.*

21. Which of the following medications/ supplements has anxiety side effects?
- A) *Ginseng*
- B) *Albuterol*
- C) *Antidepressants*
- D) *All of the above*

22. Addressing the underlying pathophysiology in anxiety disorders requires
- A) *self-efficacy.*
- B) *pharmacotherapy.*
- C) *interpersonal psychotherapy.*
- D) *fear extinction learning through exposure therapy.*

23. When present as a comorbidity to an(other) anxiety disorder, which condition highly predicts worse symptom chronicity and poor treatment response and patient outcome?
- A) *GAD*
- B) *SEPAD*
- C) *Dysthymia*
- D) *Specific phobia*

24. Which of the following is a component of CBT used for anxiety disorders?
- A) *Safety signals*
- B) *Cognitive restructuring*
- C) *Analysis of parental relationships*
- D) *Acceptance of panic-related thoughts*

25. Which of the following most accurately reflects anxiety disorder outcome research?
- A) *Evidence supports routine combination therapy as initial treatment.*
- B) *Psychotherapy and drug therapy show divergent efficacy across anxiety disorders.*
- C) *Patients lacking response to CBT or drug therapy may benefit from adding the other modality.*
- D) *Psychotherapy plus drug (combination) therapy outcomes are consistently superior to either monotherapy.*

26. Although all major antidepressant classes are comparably effective against anxiety disorders, which of the following is recommended due to better safety and tolerability?
- A) *Tricyclic antidepressants (TCAs)*
- B) *Monoamine oxidase inhibitors (MAOIs)*
- C) *Selective serotonin reuptake inhibitors (SSRIs)*
- D) *None of the above*

27. The only SSRI believed to lack pharmacologic activity beyond serotonin reuptake transporter inhibition is
- A) *sertraline.*
- B) *fluoxetine.*
- C) *paroxetine.*
- D) *escitalopram.*

28. The benzodiazepine with greater efficacy in panic disorder is
- A) *diazepam.*
- B) *lorazepam.*
- C) *alprazolam.*
- D) *clonazepam.*

29. Which of the following reflects inappropriate benzodiazepine prescribing?
- A) *As-needed for ongoing treatment of chronic mild-to-moderate anxiety*
- B) *Short-term (two to four weeks) use in patients with severe anxiety and unacceptable distress*
- C) *For infrequent use, to permit exposure to situations evoking severe anxiety (e.g., plane travel)*
- D) *In the initial weeks of SSRI/SNRI initiation to quickly reduce anxiety before the onset of SSRI/SNRI anxiolytic effects*

30. Which of the following statements regarding SSRI/SNRI withdrawal syndrome is TRUE?
- A) *Paroxetine withdrawal is complete in one to two days.*
- B) *Gradual tapering prevents the onset of SSRI withdrawal.*
- C) *Venlafaxine XR has the least severe withdrawal syndrome of all SSRI/SNRIs.*
- D) *With SSRIs, a two- to three-week duration is common, but durations longer than one year have been reported.*

31. The anxiety disorder medication with greatest lethality in overdose is
- A) *quetiapine.*
- B) *citalopram.*
- C) *venlafaxine.*
- D) *amitriptyline.*

Test questions continue on next page →

32. In the treatment of generalized anxiety disorder, which of the following is NOT a treatment option?

A) CBT
B) Pregabalin
C) Propranolol
D) Venlafaxine XR

33. Which of the following is a first-line drug recommended for the treatment of panic disorder?

A) Propranolol
B) Cannabidiol
C) Amitriptyline
D) Venlafaxine XR

34. Which of the following statements regarding the psychologic treatment for SAD is TRUE?

A) Group CBT is superior to individual CBT.
B) CBT is the criterion-standard psychologic treatment for SAD.
C) Interpersonal therapy is as effective as traditional CBT for SAD.
D) Videotaped feedback enhances the effects of exposure therapy.

35. Which of the following statements regarding the treatment of specific phobia is TRUE?

A) Pharmacotherapy plays a key role.
B) Flooding is more effective than graded exposure.
C) Exposure therapy is more effective with imagined (versus real) exposure.
D) Exposure outcomes are improved by therapist involvement (versus self-directed).

36. Which of the following psychologic treatment approaches has been identified as effective in the treatment of phobia specific to small animals?

A) Virtual reality exposure
B) Applied muscle tension
C) Individual psychotherapy
D) Computer-based self-help programs

37. Panic-focused psychodynamic psychotherapy is best described as

A) a form of CBT useful for separation anxiety.
B) a form of CBT useful for all anxiety disorders.
C) affect-focused therapy that targets panic attacks in agoraphobia.
D) affect-focused therapy that targets separation anxiety in panic disorder.

38. In exposure augmentation using D-cycloserine (DCS),

A) sedation from DCS should be monitored.
B) repeated administration increases DCS efficacy.
C) it works best when combined with benzodiazepines or antidepressants.
D) it may amplify effects from positive and negative exposures if taken pre-exposure.

39. Myo-inositol was found beneficial in randomized controlled trials for all of the following, EXCEPT:

A) OCD
B) PTSD
C) Panic disorder
D) Major depression

40. The complementary therapy with strongest evidence of safety and efficacy in anxiety disorders is

A) yoga.
B) kava.
C) lavender oil.
D) exercise therapy.

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