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Continuing Education for Certified Nurses

Child, Adolescent, and Adult Immunization Schedules
Ischemic Stroke
Optimizing Opioid Safety and Efficacy

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CONTINUING EDUCATION FOR CERTIFIED NURSES

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# Child, Adolescent, and Adult Immunization Schedules

Includes 4 Pharmacotherapeutic/Pharmacology Hours

<table>
<thead>
<tr>
<th>Audience</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Course Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Learning Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upon completion of this course, you should be able to:</td>
</tr>
<tr>
<td>1. Discuss the regulation of vaccines and identify the child, adolescent, and adult immunization schedules.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>3. State contraindications to the administration of specific vaccines.</td>
</tr>
<tr>
<td>4. Explain recent safety data regarding vaccines.</td>
</tr>
<tr>
<td>5. Identify barriers to timely vaccination.</td>
</tr>
<tr>
<td>6. Describe methods for maximizing vaccination coverage.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Faculty</th>
</tr>
</thead>
<tbody>
<tr>
<td>John J. Whyte, MD, MPH, is currently the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research. Previously, Dr. Whyte served as the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. In this role, Dr. Whyte developed, designed and delivered educational programming for both a medical and lay audience. (A complete biography appears at the end of this course.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Faculty Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Division Planner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jane C. Norman, RN, MSN, CNE, PhD</td>
</tr>
</tbody>
</table>
#91741 Child, Adolescent, and Adult Immunization Schedules

**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 2013, the incidence of acute hepatitis B declined in all age groups, though decreases appear to have plateaued in 2011. In 2013, the rate was highest among persons 30 to 39 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) had 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 should be covered. For childhood vaccines, the Healthy People 2020 goal is 90% coverage within five years of a new vaccine being added to the immunization schedule. 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 19 to 35 months of age [4]. However, certain vaccines remain significantly underutilized. For children 19 to 35 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 82.9% in 2014, with no significant improvements since 2010 [4]. In 2014, coverage with the hepatitis A vaccine (HepA) for all young children, was approximately 57.5%. Coverage with vaccines against rotavirus was approximately 71.7% [4]. The human papillomavirus (HPV) vaccine is too new to expect coverage to have met the national goal of 90%, and ongoing effort will be needed to ensure that goals are reached.

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 multiple studies confirm that it can reduce the risk of IPD in this population. Yet according to early estimates from the 2015 National Health Interview Survey, only 62.8% of adults in this age group have been vaccinated [7]. Similarly, only about 47.6% of adults 50 to 64 years of age and about 71.4% 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 2016, the rationale for the addition of new vaccines and for several potential new

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Subgroup</th>
<th>Percent Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>50 to 64 years of age</td>
<td>47.7%</td>
</tr>
<tr>
<td></td>
<td>65 years of age and older</td>
<td>71.5%</td>
</tr>
<tr>
<td>Pneumococcal disease</td>
<td>19 to 64 years of age, high risk</td>
<td>20.3%</td>
</tr>
<tr>
<td></td>
<td>65 years of age and older</td>
<td>61.3%</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Women 19 to 26 years of age</td>
<td>40.2%</td>
</tr>
<tr>
<td></td>
<td>Men 19 to 26 years of age</td>
<td>8.2%</td>
</tr>
<tr>
<td>Varicella zoster (shingles)</td>
<td>60 years of age and older</td>
<td>27.9%</td>
</tr>
<tr>
<td>Tdap booster</td>
<td>19 years of age and older</td>
<td>62.2%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>19 to 49 years of age</td>
<td>12.1%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>19 to 49 years of age</td>
<td>32.2%</td>
</tr>
</tbody>
</table>

Td=tetanus-diphtheria toxoids, Tdap=diphtheria and tetanus toxoids and pertussis.

Source: [9]

Table 1

U.S. ADULT IMMUNIZATION RATES, 2014
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 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 16 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

According to the 2018 immunization schedule, what are the recommended vaccine doses for a healthy, 2-month-old infant with no special risks or contraindications who is up-to-date on vaccinations so far?

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 doctor 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).
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo.</th>
<th>2 mos.</th>
<th>4 mos.</th>
<th>6 mos.</th>
<th>9 mos.</th>
<th>12 mos.</th>
<th>15 mos.</th>
<th>18 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>HepB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>RV</td>
<td>RV</td>
<td>RV&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diptheria, tetanus, pertussis</td>
<td>DTap</td>
<td>DTap</td>
<td>DTap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV13)</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza (IIV)</td>
<td></td>
<td>IIV (yearly, 1 or 2 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td></td>
<td></td>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td></td>
<td>VAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td></td>
<td>HepA&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19–23 mos.</th>
<th>2–3 yrs.</th>
<th>4–6 yrs.</th>
<th>7–8 yrs.</th>
<th>9–10 yrs.</th>
<th>11–12 yrs.</th>
<th>13–15 yrs.</th>
<th>16–18 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diptheria, tetanus, pertussis</td>
<td>DTap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza (IIV)</td>
<td>IIV (yearly, 1 or 2 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IIV (yearly, 1 dose)</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>VAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>HepA&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Initiate the 2-dose HepA vaccine series for children aged 12 through 23 months; separate the 2 doses by 6 to 18 months.

<sup>d</sup> Minimum age: 9 months for Menactra (MenACWY-D), 2 months for Menveo (MenACWY-CRM).

<sup>e</sup> 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.

---

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, 2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for Dose 1</th>
<th>Minimum Interval Between Doses</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose 1 to 2</td>
<td>Dose 2 to 3</td>
<td>Dose 3 to 4</td>
<td>Dose 4 to 5</td>
</tr>
<tr>
<td><strong>Children 4 months through 6 years of age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>4 weeks</td>
<td>8 weeks and at least 16 weeks after first dose. Minimum age for final dose: 24 weeks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>6 mos.</td>
<td>6 mos.</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td>6 weeks</td>
<td>4 weeks (if dose before 1st birthday) OR 8 weeks (as final dose) if first dose at 12 to 14 mos. If first dose at ≥15 mos., no further doses needed.</td>
<td>4 weeks (if current age &lt;12 mos. and first dose administered at &lt;7 mos. and at least one previous dose was PRP-T or unknown) OR 8 weeks and age 12 mos. through 59 mos. (as final dose) if current age is &lt;12 mos. and first dose administered between 7 and 11 mos.; if current age is 12 through 59 mos. and first dose administered before 1st birthday and second dose &gt;15 mos.; or both doses were PRP-OMP and administered before 1st birthday. If previous dose at ≥15 mos., no further doses needed.</td>
<td>8 weeks (as final dose), but only necessary for children age 12 through 59 mos. who received 3 doses before 1st birthday.</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>6 weeks</td>
<td>4 weeks (if first dose before 1st birthday) OR 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.</td>
<td>4 weeks (if current age &lt;12 mos. and previous dose given at &lt;7 mos.) OR 8 weeks (as final dose for healthy children if current age ≥12 mos. and previous dose given at 7-11 mos.). No further doses needed for healthy children if previous dose at ≥24 mos.</td>
<td>8 weeks (as final dose), but only necessary 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.</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 continues on next page
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for Dose 1</th>
<th>Minimum Interval Between Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1 to 2</td>
<td>Dose 2 to 3</td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>6 weeks</td>
<td>8 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>12 mos.</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Varicella</td>
<td>12 mos.</td>
<td>3 mos.</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>12 mos.</td>
<td>6 mos.</td>
</tr>
<tr>
<td>Persons 7 through 18 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria; tetanus, diphtheria, pertussis</td>
<td>7 years</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>9 years</td>
<td>Routine dosing intervals are recommended.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>—</td>
<td>6 mos.</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>—</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>—</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>—</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>—</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Varicella</td>
<td>—</td>
<td>3 mos. if age &lt;13 years OR 4 weeks if age ≥13 years</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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.<br>

<sup>b</sup> Administer the second dose 4 weeks after the first dose and the third dose 12 weeks after the second dose.

Source: [12] Table 3
Major changes to the annually published childhood schedule in the last decade have included [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.

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

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### RECOMMENDED ADULT IMMUNIZATION SCHEDULE BY VACCINE AND AGE GROUP, 2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19–21 years</th>
<th>22–26 years</th>
<th>27–49 years</th>
<th>50–64 years</th>
<th>65 years and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (IIV or RIV)</td>
<td>1 dose annually&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis</td>
<td>One dose of Tdap, then boost with Td every 10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Td or Tdap)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>2 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (female)</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (male)</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses RZV or 1 dose ZVL&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>1 or 2 doses (if born 1957 or later)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal 13-valent conjugate</td>
<td>1 dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(PCV13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide</td>
<td>1 or 2 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(PPSV23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td></td>
<td></td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
<td></td>
<td>3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal 4-valent conjugate</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MenACWY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal B (MenB)</td>
<td></td>
<td></td>
<td></td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Hib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>For all patients in this category who lack evidence of immunity.

<sup>b</sup>Recommended if other risk factor is present.

**Source:** [19] 

Table 4
### VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS, UNITED STATES, 2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Pregnancy</th>
<th>Immuno-compromised conditions (excluding HIV)</th>
<th>HIV infection</th>
<th>Men who have sex with men (MSM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD4+ &lt;200 cells/mcL</td>
<td>CD4+ ≥200 cells/mcL</td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td or Tdap)</td>
<td>1 dose Tdap each pregnancy</td>
<td>1 dose Tdap, then boost with Td every 10 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (female)</td>
<td>—</td>
<td>3 doses through 26 years of age&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (male)</td>
<td>—</td>
<td>3 doses through 26 years of age&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Contraindicated</td>
<td>2 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td>ZVL Contraindicated</td>
<td>—</td>
<td>2 doses RZV or 1 dose ZVL&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>Contraindicated</td>
<td>1 or 2 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td>1 dose annually&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
<td>1, 2, or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1, 2, or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1, 2, or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)</td>
<td>—</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal 4-valent conjugate (MenACWY)</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Meningococcal B (MenB)</td>
<td>—</td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)</td>
<td>—</td>
<td>3 doses post-stem cell transplant recipients only&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> For all patients in this category who lack evidence of immunity. 
<sup>b</sup> Recommended if other risk factor is present.

### VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS, UNITED STATES, 2018 (Continued)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Heart disease, lung disease, chronic alcoholism</th>
<th>Asplenia, complement deficiencies</th>
<th>Chronic liver disease</th>
<th>Diabetes, end-stage renal disease, hemodialysis</th>
<th>Healthcare personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)</td>
<td>1 dose Tdap, then boost with Td every 10 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 dose annually&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (female)</td>
<td>2 or 3 doses through 26 years of age&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (male)</td>
<td>2 or 3 doses through 21 years of age&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>2 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td>2 doses RZV or 1 dose ZVL&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>1 or 2 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>1 dose annually&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
<td>1, 2, or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)</td>
<td>1 dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Meningococcal 4-valent conjugate (MenACWY)</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 or 2 doses, then booster every 5 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Meningococcal B (MenB)</td>
<td>2 or 3 doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 or 3 doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)</td>
<td>1 dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 dose&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>For all patients in this category who lack evidence of immunity. 
<sup>b</sup>Recommended if other risk factor is present.

Source: [19]

Table 5
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.

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
- 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 age 60 years and older.

The U.S. Public Health Emergency for 2009 H1N1 influenza expired in June 2010. At that time, the ACIP recommended annual influenza vaccination for all persons in the United States 6 months of age and older. Annual vaccination continues to be recommended for all persons 6 months of age and older. The 2017–2018 influenza vaccine contained an H1N1-like antigen as well as H3N2 and 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.

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 2017–2018 season, use of live attenuated influenza vaccine (LAIV) is not recommended [12].

Recommendation for Adults: Vaccination is recommended annually for all adults without a contraindication with inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV). Other options include high-dose or adjuvanted IIV for adults 65 years of age or older and intradermal IIV for adults 18 to 64 years of age. IIV or RIV should be used for age-appropriate persons with severe egg allergy (i.e., involving symptoms other than hives). Women who are or may become pregnant may receive any licensed, recommended, age-appropriate vaccine [19; 20].

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]. However, data from the 2015–2016 flu season found an only 3% efficacy rate with LAIV (compared with 63% with IIV), and LAIV is not recommended for the 2017–2018 season [19; 20].
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.


Level of Evidence: Expert Opinion/Consensus Statement

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. Td 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 between Tdap is encouraged unless pertussis protection is specifically needed [12].

Recommendation for Adults: Td booster every 10 years. Tdap replaces one Td dose for adults who have not already received Tdap [19]. (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]. Reported cases of pertussis have been increasing since the 1980s. In 2014, 32,971 cases were reported—an increase of more than 40% since 2011—and 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; more than half require hospitalization. Adolescents 11 to 19 years of age and adults 20 years of age and older accounted for approximately 51.5% of reported cases in 2014; cases among children 7 to 10 years of age accounted for approximately 17% 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 MenA,C,W,Y, because of an association between frequent doses of such vaccines and a risk of increased local and systemic reactogenicity [23].

HUMAN PAPILLOMAVIRUS

According to the ACIP recommendations, and considering healthy patients without special risk factors or contraindications, who should receive the HPV vaccine?

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 [12]. Children 9 to 10 years of age may also be vaccinated.

Recommendation for Adults: HPV vaccine is recommended for adult women up to 26 years of age who have not completed the vaccine series. HPV vaccine is also recommended for men up to 21 years of age and older men (up to 26 years of age) if a desired or risk factor is present [19].

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 [26; 27].

Statistics regarding HPV infection and cervical cancer illustrate the rationale behind the vaccine itself. About 13,000 cases of cervical cancer are diagnosed in the United States each year, and more than 4,000 die from the disease [28]. The CDC estimates that 26,000 new cancers attributable to HPV occurred each year between 2004 and 2008 [16].

There are three licensed HPV vaccines available in the United States: Cervarix, Gardasil, and Gardasil 9. Cervarix is a bivalent vaccine covering HPV types 16 and 18; however, this vaccine is no longer used in the United States [12]. Gardasil and Gardasil 9 are recommended for girls 11 and 12 years of age, women 13 to 26 years of age not previously vaccinated, and boys and men 9 to 26 years of age [29; 108]. Gardasil is a quadrivalent vaccine covering types 6, 11, 16, and 18 [30; 31]. In 2014, a 9-valent HPV recombinant vaccine (Gardasil 9) was approved that adds protection to HPV types 31, 33, 45, 52, and 58 in addition to those types covered by the original Gardasil [108]. Three-fourths of cervical can-
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 14 million new infections among people 15 to 59 years of age each year. Teens and young adults are particularly at risk; 40% of health care visits for young women are related to HPV infection, but they tend to be milder. As such, vaccination is recommended for young adult women takes into account the fact that many will already be sexually active and many have been exposed to one or more types of HPV. Young women who are not yet sexually active can receive the full benefit of vaccination. 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 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 adult women takes into account the fact that many currently are sexually active and may have 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, but not after, reflects the safety and efficacy testing on which the vaccines' approvals were based [30; 31; 37]. Use in older women is being studied.

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 [12].

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: MCV 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 [12].

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 [19].

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 three vaccines are Hib-MenCY (6 weeks to 55 years), MenACWY-D (9 months to 55 years), and MenACWY-CRM (2 months to 55 years) [19]. While the Hib-MenCY vaccine, approved in 2012, is an option for infants, it provides coverage of only serotypes C and Y [107]. The serogroup most common in infants, serogroup B, is not covered by any currently licensed vaccine [43]. MenACWY covers 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.

In 2010, the novel quadrivalent meningococcal conjugate vaccine, MenACWY-CRM, was licensed by the FDA as a single dose for use in patients 11 to 55 years of age. The ACIP also recommends vaccination with MenACWY-CRM for persons 2 months of age and older who are at increased risk for meningococcal disease [45].

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 routine use in persons older than 10 years of age who are at increased risk for serogroup B meningococcal disease [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 MenACWY vaccine but at a different anatomic site, if feasible [19].

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 if immunity is desired [12].

Recommendation for Adults: HepA is recommended for certain risk groups [19].

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.

**HERPES ZOSTER**

**Recommendation for Adults:** Zoster vaccine is recommended for individuals 50 years of age and older [19].

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 yet 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 for adults 50 years of age and older [19].

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 the vaccine to placebo, the incidence of herpes zoster was reduced by 51.3% in vaccinated patients, and pain associated with shingles was substantially reduced [51]. The incidence of PHN (defined as persistent pain for 90 days) was reduced by 66.5%.

Of note, the zoster vaccine is recommended whether or not the patient has had a prior episode of shingles [19; 63]. The zoster vaccine is not recommended for patients who have received VAR.

**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) [12].

**Recommendation for Adults:** PPSV is recommended for individuals 65 years of age and older and for younger adults in certain risk groups. One-time revaccination recommended after five years for people in certain risk groups and for those 65 years and older who were first vaccinated before 65 years of age [19]. PCV13 is recommended for adults 65 years of age or older or 19 years of age and older with certain risk factors.

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 [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 current 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]. The effect of this broader vaccine on incidence of IPD remains to be seen.

Of note, PPSV, the 23-valent vaccine included on the adult immunization schedule, protects against 12 of the 13 serotypes in PCV13. PPSV 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.
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 [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; 56]:

- Mild acute illness, with or without low-grade fever, or recovering from illness
- Mild-to-moderate local reaction after a prior dose
- 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
- Pregnancy of mother or household contact

The prescribing information for VAR does not list 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 prescribing information for zoster vaccine contains a similar caution, recommending that patients be informed of the possibility of transmission [58].

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

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 [56]. (A fully definitive list is beyond the scope of this course.)

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 [56]. 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, IIV is preferred over LAIV [56].

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 [56]. The prescribing information, however, includes hypogammaglobulinemic and dysgammaglobulinemic states as contraindications [57]. If a first-degree relative has congenital 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 6 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.)

The zoster vaccine, another live-virus vaccine, is also contraindicated in many forms of immunodeficiency. According to CDC recommendations, it may be administered to people with impaired humoral immunity such as hypogammaglobulinemia, although in the prescribing information, a history of primary or acquired immunodeficiency is listed as a contraindication [56; 58]. As with VAR, it is noted that transmission of the vaccine virus to susceptible contacts may rarely occur.

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 [56]. The zoster vaccine should also be avoided, although with the current age indication it is unlikely a patient would be pregnant. 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; 56]. 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 and VAR should not be given, due to a theoretical risk of exacerbating the disease [56]. The zoster vaccine should also be deferred in patients with untreated, active tuberculosis.

**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 [56]. 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.

The CDC recommends that MCV not be used in patients with a history of GBS, and this is a contraindication in the prescribing information [56; 64]. However, the benefit of MCV may outweigh the risk in specific situations, such as patients at high risk of exposure [64]. DTaP, Tdap, and Td all require caution if GBS occurred in a patient within 6 weeks after a previous dose of a vaccine containing tetanus toxoid, and the vaccine for the Hib booster also mentions this caution, as certain Hib vaccines contain a tetanus toxoid component [21; 23; 64; 65]. Similarly, IIV requires caution.

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<tr>
<th>Hypersensitivity</th>
<th>Vaccine</th>
<th>CDC Recommendation</th>
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<tbody>
<tr>
<td>Yeast</td>
<td>HepB HPV</td>
<td>Do not use</td>
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<tr>
<td>Eggs</td>
<td>Influenza (LAIV)</td>
<td>Do not use&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Latex</td>
<td>Rotavirus (RV1), HepA</td>
<td>Check packaging to see if latex is used and for guidance</td>
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<tr>
<td>Gelatin</td>
<td>MMR</td>
<td>Use extreme caution if administering</td>
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<td></td>
<td>Varicella</td>
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<td>Zoster</td>
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<td>Neomycin</td>
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<td>Polymyxin B</td>
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<td>Thimerosal</td>
<td>Some brands/formulations, including certain DTaP, influenza (IIV), Td, DT</td>
<td>Check package insert</td>
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</tbody>
</table>

<sup>a</sup>Protocols have been devised for administering IIV to patients with egg allergies.

Source: [20; 29]  
Table 6
if GBS occurred within 6 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 Neurological 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; 56]. 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 [56].

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; 56]. 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; 56]. 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 [56]. 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 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.
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. About 12% come from state immunization programs and about 7% from vaccine recipients or their parents or guardians. Reporting forms are available at the VAERS website, http://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) Network 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 [95]. A large outbreak in 2014–2015 was linked to unvaccinated children visiting Disneyland [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].

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.

THIMERSAL 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]. IIIV is an exception. Thimerosal-free preparations of IIIV are available, however, in limited quantities.

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–mid-2011 indicate a slightly increased risk of intussusception after the first dose (but not after subsequent doses) [38]. A 2010 FDA update continues to support the safety of the vaccine [91]. 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 [92].

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]. Composite safety data has 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 6 weeks of vaccination with MCV [94]. This is likely similar to the background rate, and causality has not been established. However, the CDC and FDA have noted that the timing in relation to vaccination is reason to pursue the question further and to gather more information. Providers are asked to report any cases of GBS that may be vaccine-related 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 this vaccine.

HPV VACCINE AND ADVERSE EVENTS

As of 2018, what is known about HPV and problems following vaccination?

Clinical trials and the post-licensure monitoring data of both Cervarix and Gardasil show that both vaccines are safe [29]. Since the licensure of the HPV vaccines, both the CDC and the FDA have monitored HPV vaccine safety through VAERS, VSD, and CISA systems. 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). 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 [29].
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 [29]. 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 several years, news reports 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 uncertainty about vaccines [97]. For those who ultimately decided to allow timely vaccination, assurances or information provided by a healthcare provider according to instructions. Except for 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.

The Institute for Clinical Systems Improvement recommends that clinicians educate patients (or parents, if applicable) regarding the importance of infant, childhood, and adolescent immunizations and age-appropriate vaccines.


Strength of Recommendation: Strong

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, Td, and Td vaccines, available combination products include:

- DTaP and Hib
- HepB and Hib
- HepB and HepA
- DTaP and IPV
- DTaP, IPV, and HepB
- DTaP, IPV, and Hib
- MMR and varicella

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 2011 General Recommendations on Immunization, the ACIP recommended the use of combination vaccines whenever possible to reduce the number of injections [100].
The 2016 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

In addition to those enrolled in Medicaid, which children are eligible for free vaccines under the Vaccines for Children program?

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, and Medicaid funding covering young adults 19 and 20 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.

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, http://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

What is the primary reason adults miss recommended vaccinations?

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 2014 surveillance data, racial/ethnic disparities exist for all seven vaccines the CDC is tracking [9]. The gap is most marked for black adults, whose vaccination rate averaged 30% lower than their white counterparts with respect to seasonal influenza, tetanus (with pertussis), and hepatitis B [9].

“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 “MISSING 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].

REMEMBER SYSTEMS FOR ADULT PATIENTS

Telephone calls and mailed 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.

RESOURCES

Centers for Disease Control and Prevention Vaccines and Immunizations
https://www.cdc.gov/vaccines

Immunization Action Coalition
http://www.immunize.org

Vaccine Adverse Event Reporting System (VAERS)
https://vaers.hhs.gov

Vaccines for Children Program (VFC)
https://www.cdc.gov/vaccines/programs/vfc/index.html

FACULTY BIOGRAPHY

John J. Whyte, MD, MPH, is currently the Director of Professional Affairs and Stakeholder Engagement at the FDA’s Center for Drug Evaluation and Research. Previously, Dr. Whyte served as the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. In this role, Dr. Whyte developed, designed and delivered educational programming for both a medical and lay audience.

Prior to this, Dr. Whyte was in the Immediate Office of the Director at the Agency for Healthcare Research Quality. He served as Medical Advisor/Director of the Council on Private Sector Initiatives to Improve the Safety, Security, and Quality of Healthcare. Prior to this assignment, Dr. Whyte was the Acting Director, Division of Medical Items and Devices in the Coverage and Analysis Group in the Centers for Medicare & Medicaid Services (CMS). CMS is the federal agency responsible for administering the Medicare and Medicaid programs. In his role at CMS, Dr. Whyte made recommendations as to whether or not the Medicare program should pay for certain procedures, equipment, or services. His division was responsible for durable medical equipment, orthotics/prosthetics, drugs/biologics/therapeutics, medical items, laboratory tests, and non-implantable devices. As Division Director as well as Medical Officer/Senior Advisor, Dr. Whyte was responsible for more national coverage decisions than any other CMS staff.

Dr. Whyte is a board-certified internist. He completed an internal medicine residency at Duke University Medical Center as well as earned a Master’s of Public Health (MPH) in Health Policy and Management at Harvard University School of Public Health. Prior to arriving in Washington, Dr. Whyte was a health services research fellow at Stanford and attending physician in the Department of Medicine. He has written extensively in the medical and lay press on health policy issues.
Ischemic Stroke

Includes 5 Pharmacotherapeutic/Pharmacology Hours

**Audience**
This course is designed for nurses, physicians, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.

**Course Objective**
The early identification and management of the risk factors for ischemic stroke can lead to substantial improvement in health and reductions in cost. However, research has documented gaps between healthcare professionals’ knowledge and practice with respect to prevention, with data on adherence to evidence-based or guideline-endorsed recommendations demonstrating underuse or ineffective use of all interventions for primary and secondary prevention. The purpose of this course is to provide needed information about the roles of diagnosis and screening, evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.

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

1. Describe the primary types of cerebrovascular disorders and their causes.
2. Discuss differences in prevalence, morbidity, and mortality according to age, sex, and race/ethnicity.
3. Identify the nonmodifiable and modifiable risk factors for ischemic stroke.
4. Implement primary prevention strategies according to evidence-based guidelines.
5. Discuss the need for education at the community and patient levels.
6. Apply models of predicting risk of ischemic stroke.
7. Select the appropriate tools for screening, diagnosis, and early management of ischemic stroke.
8. Describe the elements of stroke systems of care and a comprehensive stroke center.
9. Discuss evidence-based treatment options for ischemic stroke.
10. Describe the benefits and components of a specialized stroke rehabilitation team.
11. Outline the aspects of patient assessment for stroke rehabilitation.
12. Discuss evidence-based recommendations for secondary prevention of ischemic stroke.

**Faculty**
Lori L. Alexander, MTPW, ELS, MWC, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the American Medical Writers Association (AMWA) Journal, the peer-review journal representing the largest association of medical communicators in the United States. Ms. Alexander earned a Master’s degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

**Faculty Disclosure**
Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

**Division Planner Disclosure**
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.
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This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

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

AACN Synergy CERP Category A.

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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

Cerebrovascular disease is associated with significant morbidity and mortality in the United States. Stroke occurs in approximately 795,000 individuals each year, of which 610,000 are first-time strokes and 185,000 are recurrent [1]. Stroke is the leading cause of long-term disability in adults; 65% of stroke survivors have some degree of impairment [1; 2]. The effect of stroke on mortality is illustrated by the fact that cerebrovascular disease is the fourth leading cause of death in the United States, with an age-adjusted mortality rate of 37.0 per 100,000 population as of 2013 [1; 3]. This represents a 28.7% decrease in the mortality rate and a 11.3% decline in actual deaths since 2004 but still indicates a substantial healthcare issue, with one of every three deaths being attributable to stroke [3]. In addition, the financial cost associated with cerebrovascular disease poses a substantial economic burden, with an estimated direct and indirect cost of $316.6 billion in 2012 [1]. Despite the considerable progress being made in the areas of prevention, management, and rehabilitation, it appears that stroke will increasingly cause death and disability in the coming decades as the population ages [4]. By 2030, the total direct medical costs of cerebrovascular disease are projected to increase to approximately $918 billion [1].

The two primary types of stroke are ischemic and hemorrhagic, and ischemic strokes account for the majority (87%) of cerebrovascular disorders [1]. There are several risk factors for ischemic stroke, and predicting risk is an important element in prevention. In predicting risk, consideration should be given not only to comorbidities but also to age, sex, and race/ethnicity, as disparities in prevalence, morbidity, and mortality have been attributed to these patient characteristics [5; 6; 7; 8]. Evidence-based guidelines for primary and secondary prevention have been developed and should be implemented [9; 10].

Among the most important risk factors for ischemic stroke is a transient ischemic attack (TIA); approximately 15% of ischemic strokes are preceded by a TIA [1]. The greatest risk for post-TIA stroke is within the first 48 hours, and the risk continues beyond 48 hours to 3 months [1; 11]. Improved understanding of TIAs among both clinicians and patients is needed. A survey of 200 primary care physicians showed that 88% could not correctly identify the typical symptoms and duration of a TIA, and studies have indicated that half of individuals who have a TIA do not report the event to their primary care clinician [1; 12].

The early identification and management of the risk factors for ischemic stroke can lead to substantial improvement in health and reductions in cost [13]. For example, the incidence of stroke has been reduced by 30% to 40% with the appropriate use of antihypertensive therapy [10]. Yet, research has documented gaps between physicians’ knowledge and practice with respect to prevention, with data on adherence to evidence-based or guideline-endorsed recommendations demonstrating underuse or ineffective use of all interventions for primary and secondary prevention [11; 14; 15]. Evidence-based guidelines have also been developed for the early management of stroke and for rehabilitation after stroke and should be followed to provide optimum care [16; 17; 18].

The focus of this course is ischemic stroke, due to its overwhelming prevalence. Advances have been made in tools for the screening and diagnosis of ischemic stroke, and a better understanding of the options for patients at risk is needed. This course explores the role of the physical examination and history, laboratory studies, and imaging techniques in screening and diagnosis. Also discussed are evidence-based guidelines for the prevention and early management of ischemic stroke, as well as emerging treatment options. Because data have shown that outcome is improved by care provided in comprehensive stroke centers and by early rehabilitation, these topics are addressed as well [17; 19; 20; 21]. The importance of a multidisciplinary rehabilitation team, appropriate patient assessment, and an exercise program is emphasized.

OVERVIEW OF CEREBROVASCULAR DISEASE

Although “cerebrovascular disease” is often used interchangeably with the term “stroke,” the disease encompasses any neurological disorder that exists in the presence or absence of an ictus (e.g., carotid artery stenosis, arteriovenous malformations). Despite advances in understanding the pathophysiology of cerebrovascular diseases, the term “stroke” (also known as cerebrovascular accident or brain attack) is inconsistently defined. Stroke has been classically characterized as an injury to the central nervous system (CNS) by a vascular cause. Because this definition is mainly clinical and not inclusive of advances in science and technology, the American Heart Association (AHA)/American Stroke Association (ASA) convened a writing group to develop an updated definition of stroke. The AHA/ASA recommend that the term “stroke” be broadly used to include a variety of definitions (Table 1).

TYPES OF CEREBROVASCULAR DISORDERS

The multiple sources, pathophysiologic mechanisms, and sequelae of stroke are reflected in the diverse types of cerebrovascular disorders. The World Health Organization classifies cerebrovascular diseases under “Diseases of the circulatory system” in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), the international standard diagnostic classification for all general epidemiologic purposes and many health management purposes (Table 2) [22]. Although TIAs, traumatic intracranial hemorrhage, and vascular dementia pertain to cerebrovascular disorders, they are excluded from the cerebrovascular disease category in the ICD-10. Their exclusion illustrates the heterogeneity of stroke and its sequelae.
AHA/ASA DEFINITION OF STROKE

<table>
<thead>
<tr>
<th>Injury/Episode</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>CNS infarction</td>
<td>Brain, spinal cord, or retinal cell death attributable to ischemia, based on:</td>
</tr>
<tr>
<td></td>
<td>• Pathologic, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or</td>
</tr>
<tr>
<td></td>
<td>• Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction</td>
</tr>
<tr>
<td>Silent CNS infarction</td>
<td>Imaging or neuropathologic evidence of CNS infarction, without history of acute neurologic dysfunction attributable to the lesion</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>Focal collection of blood within the brain parenchyma or ventricular system, not caused by trauma</td>
</tr>
<tr>
<td>Stroke caused by intracerebral hemorrhage</td>
<td>Rapidly developing clinical signs of neurologic dysfunction attributable to focal collection of blood within brain parenchyma or ventricular system, not caused by trauma</td>
</tr>
<tr>
<td>Silent cerebral hemorrhage</td>
<td>Focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathologic examination, not caused by trauma and without history of acute neurologic dysfunction attributable to the lesion</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Bleeding into subarachnoid space</td>
</tr>
<tr>
<td>Stroke caused by subarachnoid hemorrhage</td>
<td>Rapidly developing signs of neurologic dysfunction and/or headache because of bleeding into the subarachnoid space, not caused by trauma</td>
</tr>
<tr>
<td>Stroke caused by cerebral venous thrombosis</td>
<td>Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.</td>
</tr>
<tr>
<td>Stroke, not otherwise specified</td>
<td>Episode of acute neurologic dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above</td>
</tr>
</tbody>
</table>

CNS = central nervous system.


TIAs are classified under “Diseases of the nervous system: Episodic and paroxysmal disorders.” Traumatic intracranial hemorrhage is listed under “Injury, poisoning, and certain other consequences of external causes: Injuries to the head,” and vascular dementia, a common sequela of stroke, is categorized under “Mental and behavioral disorders: Organic, including symptomatic, mental disorders.”

As noted, the two primary types of stroke are ischemic and hemorrhagic. In the United States, approximately 87% of all strokes are ischemic; 10% are hemorrhagic strokes [1]. An ischemic stroke occurs when any artery that supplies the brain with oxygen becomes stenosed or occluded, resulting in infarction [23]. In the case of hemorrhagic stroke, bleeding occurs below the arachnoid, the location of the brain’s blood supply, allowing blood to directly contact and damage brain tissue. Although ischemic stroke is the focus of this course, a brief overview of hemorrhagic strokes will help to provide context and comparison of the clinical features of both types of stroke. In addition, TIAs are discussed here, as they are often a precursor to ischemic stroke.

Hemorrhagic Strokes

Hemorrhagic stroke is associated with a higher risk of fatality than ischemic stroke, and roughly one-third of patients die within 30 days after the event [1; 24]. Hemorrhagic strokes are categorized by the location of the hemorrhage, either intracerebral or subarachnoid, with the former being more common.

Approximately 87% of hemorrhagic strokes are due to intracerebral hemorrhage (ICH), and because of this, the term hemorrhagic stroke often refers to ICH [25]. ICHs are characterized by bleeding directly into the brain parenchyma [25; 26]. Intraventricular hemorrhage describes bleeding that extends into the ventricles [26; 27]. Nontraumatic ICH is categorized as primary (unrelated to congenital or acquired lesions), secondary (caused by a congenital or acquired condition), or spontaneous (unrelated to trauma or surgery) [26].
The signs and symptoms of ICH include headache, vomiting, seizures, depressed consciousness, meningeal irritation, and blood-tainted cerebrospinal fluid. The onset of symptoms may occur within seconds to minutes after the start of an ICH. Individuals with this type of stroke often feel more ill than those with an ischemic stroke.

ICH is the least treatable type of stroke [28]. Functional independence is regained within 6 months in approximately 20% of survivors [29]. The morbidity and mortality depend on the volume and location of the hematoma. The 1-year mortality rate varies according to anatomic location, with the highest mortality rate (65%) associated with ICH in the brainstem; the rate is 57% for lobar hemorrhage, 51% for deep hemorrhage, and 42% for cerebellar hemorrhage [30]. Overall, 46% of patients with ICH survive one year and 29% survive five years [31].

As many as 80% of primary ICHs occur after small vessels are compromised by chronic hypertension [32]. Hypertension is associated with ICH originating in the periventricular deep white matter, deep subcortical structures, pons, and cerebellum [33]. In individuals older than 70 years of age, cerebral amyloid angiopathy, a condition that leads to amyloid protein infiltration into the cortical arterioles, is responsible for approximately 20% of ICHs [34]. Other causes of ICH include anticoagulant and antiplatelet use, drug use (e.g., cocaine, phenylpropanolamine), and other bleeding diathesis [28; 35]. Fewer than 15% of all cases of ICH are secondary to congenital vascular abnormalities and malignant brain lesions [26].

Subarachnoid hemorrhages occur less frequently than ICHs. The hallmark of subarachnoid hemorrhage is the immediate onset of a severe headache with signs of meningeal irritation [36]. Individuals may describe this headache as their “worst ever.” Nausea, vomiting, neck pain, and photophobia are also classic symptoms, although they are not always present [36]. Neurologic deficits may be acute or may manifest hours to days after the onset of bleeding.

Nontraumatic subarachnoid hemorrhages are subcategorized as aneurysmal or non-aneurysmal [37]. Aneurysmal subarachnoid hemorrhage is associated with higher rates of morbidity and mortality than non-aneurysmal hemorrhage. Among patients who live 3 months after the event, the risk of death is 8.7% within 5 years and 17.9% within 10 years [38]. In contrast, non-aneurysmal subarachnoid hemorrhages are associated with better outcomes and are less likely to cause death [39].

Most nontraumatic subarachnoid hemorrhages involve rupture of an intracranial aneurysm or cerebral arteriovenous malformation. Congenital arteriovenous anomalies are more likely to cause stroke in adolescents and young adults [40]. The incidence of perimesencephalic subarachnoid hemorrhage, a non-aneurysmal type, is increasing. Although the cause remains unknown, increased use of antithrombotic medications may be a factor [41; 42].

**TIAs**

**What are the most common focal neurologic signs of a TIA?**

TIAs are sometimes referred to as “ministrokes” because, like ischemic strokes, they are caused by inadequate cerebral blood flow. TIAs are also called warning strokes, as they often precede an ischemic stroke [43]. The superseded definition of a TIA was “a sudden, focal neurologic deficit that lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery” [44]. The 24-hour time limit was an arbitrary...
remnant of the time interval used in prospective surveys in the early 1970s [45]. Magnetic resonance imaging (MRI) and computed tomography (CT) have demonstrated that one-third of TIAs, including those that last only minutes, cause infarcts [46].

Because TIA and ischemic stroke are less distinct from one another than once believed, a new TIA definition was proposed, revised, and endorsed in 2009. The proposed definition states that TIA is “a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of acute infarction” [44]. This definition was designed to better reflect the ischemic pathogenesis of TIA, promote its early management, and support the use of diagnostic imaging techniques to ensure that the patient does not have infarction [44]. The definition was endorsed by the 2009 AHA/ASA guideline, with the omission of “typically less than 1 hour” (as infarction is not necessarily bound by a set period of time) and reads, “Transient ischemic attack (TIA): a transient episode of neurologic dysfunction caused by focal brain, spinal-cord, or retinal ischemia, without acute infarction” [10; 47].

Research shows that a TIA should be considered a dire condition that requires urgent treatment in order to prevent a more potent ischemic stroke; approximately 15% of ischemic strokes are preceded by a TIA [1]. However, there are several challenges to immediate treatment of TIAs [10]:

- A wide majority of the general population and many healthcare professionals believe that TIAs are generally benign.
- Individuals experiencing a TIA often believe they can postpone or forego professional treatment because clinical symptoms usually resolve quickly and without care.
- Due to the 24-hour arbitrary time limit in the previously accepted definition, healthcare professionals often choose to monitor a patient with a TIA rather than provide immediate treatment.

The risk of ischemic stroke is dangerously high in the period following a TIA. Research indicates that one-half of subsequent strokes occur within the first 48 hours, and a meta-analysis showed that approximately 5% of patients who have a TIA will have an ischemic stroke within 7 days of that event [11; 43]. The risk of stroke within 3 months after a TIA is approximately 10% to 20% and is 24% to 29% over the following 5 years [11]. Early initiation of treatment for TIA and minor stroke with existing therapies has been shown to reduce the risk of early recurrent stroke by 80% [48].

As with any stroke, the symptoms of TIA depend on the affected vascular territory. For instance, involvement of the carotid artery causes disturbances in the ipsilateral eye or brain [49]. Although the most common focal neurologic signs of TIA are sudden-onset unilateral weakness and numbness or tingling in a limb, a TIA can cause any of the following symptoms [49; 50]:

- Numbness of the face, hand, or leg, with or without weakness
- Paralysis
- Slurred speech
- Dizziness
- Double vision
- Hemianopia
- Transient monocular blindness
- Imbalance
- Aphasia
- Confusion
- Head pain

Transient graying or blurring of vision is also common. Occasionally, the line of sight will be shaded. Vertebrobasilar TIAs reflect vestibulocerebellar symptoms such as ataxia, dizziness, vertigo, dysarthria, vision abnormalities (e.g., double vision, hemianopia, bilateral vision loss), and unilateral or bilateral motor and sensory dysfunctions [10].

By the time of evaluation, however, most patients appear asymptomatic because TIAs usually resolve within 5 minutes [51]. A clinician should highly suspect a TIA if the patient says, “I don’t know why I’m here. Whatever it was, it is all better now” [52].

TIAs are caused by conditions similar to those leading to ischemic stroke [10]. Among the common causes are atherosclerosis of large vessels, cardioembolism, and atrial fibrillation (AF). Uncommon causes include hypercoagulable states, arterial dissection, sympathomimetic drugs (e.g., cocaine), and arteritis (caused by noninfectious necrotizing vasculitis, drugs, irradiation, or local trauma) [53].

The risk factors for TIA are also similar to those for ischemic stroke and include many modifiable factors, such as hyperhomocysteinemia, hyperlipidemia, smoking, obesity, and diabetes [10]. Risk can be reduced substantially by the treatment of vascular anomalies such as hypertension and AF, two conditions commonly associated with older age. Younger individuals (18 to 45 years of age) who have a TIA or ischemic stroke often have no detectable vascular risk factors [54].

Ischemic Strokes

Within minutes of the onset of ischemic stroke, the core of an infarct can begin to form at the least-perfused site. This site is encircled by an area partially altered metabolically and ionically by cytotoxic edema [55]. This area, the ischemic penumbra, is structurally intact and generally salvageable if reperfusion is achieved promptly. Because cerebral function deficits develop rapidly (within minutes to hours) as an ischemic stroke progresses, these brain attacks are a medical
emergency. Each minute that passes results in an average loss of 1.9 million neurons and 14 billion synapses; an ischemic brain ages 3.6 years for every hour that passes after the onset of stroke [56]. For this reason, stroke specialists use the mantra, “time is brain.” Although irreversible damage occurs, most individuals with stroke have recoverable penumbral tissue for at least 3 hours following the onset of symptoms [16].

The physical signs, symptoms, and sequelae of ischemic stroke are usually unilateral because of the circulatory anatomy of the brain (Table 3). Anterior circulation is composed of the paired internal carotid arteries and vessels that supply blood to the cerebral hemispheres [57]. Each common carotid artery bifurcates into the internal and external carotid arteries. The ophthalmic artery, posterior communicating artery, and anterior choroidal artery are supplied by the internal carotid artery (Figure 1). Most importantly, the internal carotid artery provides blood to the middle cerebral artery, the largest intracerebral vessel. The middle cerebral artery provides oxygen to the lateral, frontal, parietal, and temporal lobes and the basal ganglia. It also supplies the anterior cerebral artery, which is responsible for the medial part of the frontal and parietal lobes, most of the corpus callosum, the frontobasal cerebral cortex, deep structures, and the anterior diencephalon. The anterior choroidal artery supplies a portion of the thalamus and the posterior limb of the internal capsule.

Posterior circulation is primarily composed of the vertebrobasilar artery, the posterior cerebral artery, which it supplies, and other branching vessels [57]. The posterior cerebral artery provides blood to the occipital and medial temporal lobes, as well as regions of the midbrain, subthalamic nucleus, basal nucleus, thalamus, mesial inferior temporal lobe, and occipitoparietal cortices. The two main segments of the posterior cerebral artery (P1 and P2) are connected by the posterior communicating artery. The Circle of Willis links the anterior and posterior circulation at the base of the brain.

In general, ischemic strokes are categorized according to etiology: thrombotic and embolic [61]. In addition, they are classified into five subtypes according to a system developed by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [62].

**Thrombotic Stroke**

A thrombotic stroke occurs when a thrombus impairs cerebral blood flow by further narrowing or blocking an artery, typically around an atherosclerotic plaque. The stenosed or occluded artery may be a large vessel (e.g., carotid artery systems, vertebral arteries, the Circle of Willis) or a small vessel (e.g., branches of the Circle of Willis, the posterior circulation). Approximately 21% to 27% of ischemic strokes arise from atherosclerotic disease of the large vessels [63; 64]. The cerebral artery branch points, especially those of the internal carotid artery, are the most vulnerable [65]. Small-vessel
disease is associated with 21% to 25% of ischemic strokes [63; 64]. Thrombotic strokes caused by small-vessel disease are traditionally associated with lacunar infarcts, small, deep, subcortical lesions of 15 mm or less in diameter resulting from occlusion of a single penetrating artery [62; 66]. As many as 20% of older individuals who are otherwise healthy have asymptomatic lacunar infarcts unrelated to an ictal event [67]. These silent infarctions were previously believed to be benign with a good long-term prognosis. However, they now have been linked to increased risks of stroke and death and can lead to debilitating cognitive impairments such as vascular dementia [67; 68].

Independent risk factors for lacunar infarcts include hypertension, gender, age, diabetes, smoking, and a history of TIA [67]. Although hypertension is strongly associated with the development of small-vessel occlusion, lacunar infarcts also occur in individuals without hypertension. However, normotensive individuals with lacunar infarcts are typically 85 years of age or older, suggesting that hypertension accelerates the arteriopathy underpinning small-vessel disease. Diabetes is an independent risk factor for lacunar infarcts [69].

Embolic Stroke

An embolic stroke occurs when an embolus (i.e., any circulating clot or particle originating from a distal point) blocks an artery that supplies oxygen to the brain. Stroke registries indicate that 14% to 30% of ischemic strokes are embolic [70; 71; 72; 73; 74]. Emboli include blood clots, fatty deposits, atherosclerotic plaque fragments, and cancerous cells or infectious materials emanating from conditions such as atrial myxoma and endocarditis, respectively. Clinical symptoms of the resulting infarct correspond to the location of the embolus, not its type. The region of the middle cerebral artery is most frequently blocked by emboli [75].

AF is the most common cause of embolic stroke, increasing the risk of embolic stroke fivefold and doubling the risk of death [76; 77]. Patients with valvular thrombi, from endocarditis or prosthetic valves, or mural thrombi from myocardial infarction (MI), AF, severe heart failure, or patent foramen ovale, are at high risk for the development of emboli [78; 79]. MI is associated with a 2% to 3% incidence of embolic stroke, 70% of which occur in the first week after the event [77; 79].
The subtype of ischemic stroke influences treatment decisions, prognosis, and risk of recurrent stroke. The TOAST system was designed to facilitate decision making and standardize ischemic stroke research (Table 4) [62]. Most strokes are subclassified as a large-artery atherosclerosis (caused by either a thrombus or an embolus), a cardioembolism, or an occlusion of a small vessel (lacuna) [62]. Approximately 4% of individuals with stroke have coexisting large-vessel and small-vessel disease [61; 80]. Other determined causes are rare (approximately 3%), and registries have classified up to 33% of ischemic strokes as being of “undetermined etiology” [81].

**TOAST Classification**

The subtype of ischemic stroke influences treatment decisions, prognosis, and risk of recurrent stroke. The TOAST system was designed to facilitate decision making and standardize ischemic stroke research (Table 4) [62]. Most strokes are subclassified as a large-artery atherosclerosis (caused by either a thrombus or an embolus), a cardioembolism, or an occlusion of a small vessel (lacuna) [62]. Approximately 4% of individuals with stroke have coexisting large-vessel and small-vessel disease [61; 80]. Other determined causes are rare (approximately 3%), and registries have classified up to 33% of ischemic strokes as being of “undetermined etiology” [81].

**MORBIDITY AND MORTALITY**

Approximately 16% of men and 14% of women have a stroke by 85 years of age, and stroke is the fifth leading cause of death in the United States, accounting for nearly 133,000 deaths in 2014 [1; 3; 84]. Morbidity associated with stroke is also high, with at least 65% of stroke survivors having some sort of impairment [85]. At 3 months after a stroke, approximately 20% of survivors depend on long-term care. Between 15% and 30% of stroke survivors are permanently disabled [86]. A 6-month follow-up of ischemic stroke survivors (65 years of age and older) demonstrated that [87]:

- 50% had some degree of hemiparesis
- 35% had depressive symptoms
- 30% were unable to walk without some assistance
- 26% were dependent in activities of daily living
- 26% were in a nursing home
- 19% had aphasia

Fortunately, stroke mortality has been declining since the early 20th century. In the United States, stroke has fallen from the third to the fifth leading cause of death, representing a true mortality decline rather than a repositioning of causes of death [3; 84]. This decline is a result of reduced incidence of stroke and lower case-fatality rates, concurrent with cardiovascular risk factor control interventions (e.g., hypertension control). Other efforts (e.g., diabetes control, smoking cessation programs) likely have also contributed to the decline in stroke mortality. The effects of telemedicine and stroke systems of care require additional study but appear to be significant. The decline has occurred in both women and men, for all racial/ethnic and age groups, and represents a major improvement in public health and a reduction in years of potential life lost [88].

**Disparities in Prevalence and Mortality**

Age, gender, and race/ethnicity play major roles in the prevalence of stroke and its associated mortality.

**Age**

*What is the average age at the time of ischemic stroke?*

Prolonged damage of the aging cardiovascular system by various risk factors for stroke doubles the risk of ischemic stroke for each decade of life after 55 years of age [9]. Thus, clinicians should be sensitive to their patients’ modifiable risk factors, most notably hypertension, starting at an early age.
As many as 70% of strokes occur in individuals older than 65 years of age, and the average age at the time of ischemic stroke is 71 years in men and 75 years in women [1]. Stroke patients 85 years of age and older comprise 17% of all stroke patients [1]. Clinicians should be particularly aware of silent cerebral infarctions in older individuals, as these infarctions occur more commonly in this population [89].

Gender
Women have a higher lifetime risk of stroke than men [90; 91; 92]. According to estimates from the Framingham Heart Study, among people 55 to 75 years of age, the risk of stroke is 1 in 5 for women and 1 in 6 for men [93]. Age-specific stroke incidence rates are substantially lower among women than men, except in those 80 years of age and older, in which the incidence rate in women is approximately equal to or higher than the rate in men [90; 91; 94; 95; 96]. Among individuals 65 years of age and older, the median survival time after a first stroke is typically longer for women than for men. For both men and women, the median survival decreases with age (Table 5) [1]. However, the possibility of gender disparities in how health care is provided to individuals who present with stroke symptoms is also being evaluated.

Studies suggest that, compared with men, women are evaluated less frequently following a stroke and that any evaluation is more likely to be delayed [97; 98; 99]. This pattern results from women's presentation with nontraditional symptoms or without traditional symptoms and inappropriate worry by both clinician and patient about treatment-related risks (Table 6) [97; 98; 100; 101; 102]. Although studies to evaluate differences in strokes between men and women are in early stages, preliminary results indicate that emergency medical service (EMS) personnel and clinicians need an accurate understanding of symptom presentation patterns for men and women. The prevalence of nontraditional symptoms is higher among women than men; nontraditional stroke symptoms include headache, face and limb pain, nausea, and hiccups as well as symptoms typically believed to be unrelated to neurologic deficits (e.g., chest pain, shortness of breath, palpitations) [101].

Race/Ethnicity
The decline in stroke mortality has reduced, but not eliminated, the racial/ethnic gap in stroke mortality [88]. Racial/ethnic disparities in the incidence of stroke and its related mortality are substantial, and the factors contributing to the disparities are complex and poorly understood [1; 5; 6; 7; 8; 103]. The risk of first-time stroke among black and Hispanic individuals approaches twice that for white individuals in the United States [1]. The Northern Manhattan Study (NOMAS) showed that the age-adjusted incidence of first ischemic stroke per 100,000 individuals was 191 in the black population, 149 in the Hispanic population, and 88 in the white population [103]. Another study showed that the prevalence of stroke among these three groups also varied according to age [6]. In the black population, the prevalence of

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### COMPARISON OF MEDIAN SURVIVAL AFTER A FIRST STROKE ACCORDING TO SEX

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>55 to 64 years</td>
<td>7.8 years</td>
<td>13.1 years</td>
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<tr>
<td>65 to 74 years</td>
<td>7.7 years</td>
<td>6.2 years</td>
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<tr>
<td>≥75 years</td>
<td>2.3 years</td>
<td>2.1 years</td>
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*Source: [1]*

### COMPARISON OF PREVALENCE OF SELECT SYMPTOMS IN MEN AND WOMEN

<table>
<thead>
<tr>
<th>Symptom on Presentation</th>
<th>Prevalence</th>
<th>Prevalence</th>
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<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Overall nontraditional symptoms</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>Pain</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>12%</td>
<td>17%</td>
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<tr>
<td><strong>Traditional Symptoms</strong></td>
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<tr>
<td>Imbalance</td>
<td>20%</td>
<td>15%</td>
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<tr>
<td>Hemiparesis</td>
<td>24%</td>
<td>19%</td>
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*Source: [101]*

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CoMPArIsoN oF MeDIAN sur VIVAL AFTer A FIrsT sTroKe ACCorDING To seX

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<th>Age</th>
<th>Median Survival</th>
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<tr>
<td></td>
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Table 5

CoMPArIsoN oF PreVALeNCe oF seLeCT sYMPToMs IN MeN AND WoMeN

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<thead>
<tr>
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<th>Prevalence</th>
<th>Prevalence</th>
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<tr>
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<td>12%</td>
<td>17%</td>
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</table>

**Traditional Symptoms**

<table>
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<tr>
<td>Hemiparesis</td>
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<td>19%</td>
</tr>
</tbody>
</table>

Table 6
was 4.8% for individuals 45 to 64 years of age and 10% for individuals 65 years of age and older; the corresponding prevalences were 2.3% and 10% for Hispanic individuals and 2% and 9% for white individuals [6]. Intracranial atherosclerotic strokes were the most common type of strokes among the black and Hispanic populations [103].

According to the AHA 2016 update on statistics for heart disease and stroke, the prevalence of stroke is highest for the non-Hispanic black population and lowest for Hispanics (of any race) (Table 7) [1]. Data indicate variation among stroke-related mortality rates as well and show that stroke deaths have increased in minority populations while decreasing in the white population. Projections indicate a 20.5% increase in stroke by 2030, with the greatest increase (29%) in Hispanic men [1].

Data from 2012–2014 demonstrated an overall rate of 39.5 deaths per 100,000, with a rate of 53.7 for the black (non-Hispanic) population, 39.2 for the white (non-Hispanic) population, 32.8 for the American Indian/Alaskan Native population, 29.3 for the Hispanic population, and 27.1 for the Asian/Pacific Islander population [104]. Risk factors, such as hypertension, diabetes, and obesity, vary among these populations as well, but increased risks alone cannot completely explain increased prevalence or mortality [9].

**MODIFIABLE RISK FACTORS**

What risk factors for ischemic stroke are well-documented?

Several modifiable risk factors for stroke have been well-documented in the literature, and some have been less well-documented (Table 8). The well-documented risk factors include many associated with cardiovascular disease as well, and proper management of these factors can reduce both the risk of a first-time stroke and the development of a cardiovascular condition [7; 9]. Clinicians should discuss the potential for stroke associated with risk factors specific to patients and offer strategies to reduce or eliminate them [9]. Four lifestyle factors warrant brief review because of the substantial role the patient has in helping to manage risk: smoking, diet and nutrition, physical inactivity, and obesity and body fat distribution.

### MODIFIABLE RISK FACTORS FOR STROKE

<table>
<thead>
<tr>
<th>Well-Documented Factors</th>
<th>Less-Documented Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Atrial fibrillation (AF)</td>
<td>Inflammation and infection</td>
</tr>
<tr>
<td>Diet and nutrition</td>
<td>Migraine</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Sleep-disordered breathing</td>
</tr>
<tr>
<td>Obesity and body fat distribution</td>
<td>Elevated lipoprotein (a)</td>
</tr>
<tr>
<td>Cardiac conditions other than AF</td>
<td>Drug abuse</td>
</tr>
<tr>
<td>Asymptomatic carotid stenosis</td>
<td>Hyperhomocysteinemia</td>
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<tr>
<td>Sickle cell disease</td>
<td></td>
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<tr>
<td>Physical inactivity</td>
<td></td>
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</tbody>
</table>

*a* Listed in descending order of quality of documentation.

*b* Information on less-documented risks for stroke can be found in the American Heart Association (AHA) guideline, “Primary Prevention of Stroke.”

Source: [9] Table 8

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**RACIAL/ETHNIC VARIATIONS IN PREVALENCE OF STROKE AND HYPERTENSION**

<table>
<thead>
<tr>
<th>Population</th>
<th>Stroke Prevalence</th>
<th>Hypertension Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Black</td>
<td>4.5%</td>
<td>42.1%</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>3.0%</td>
<td>NA</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>2.5%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2.4%</td>
<td>24.7%</td>
</tr>
<tr>
<td>NA = Not available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: [1] Table 7
Diet and Nutrition

Increased consumption of fruits and vegetables reduces the risk of stroke in a dose-dependent manner. Risk is reduced 6% for each serving of fruits and vegetables per day [105]. Reducing sodium intake and increasing antioxidants, potassium, and calcium also mitigates the risk of stroke [9; 106; 107]. The AHA/ASA recommend that individuals with stroke residing in long-term care facilities be evaluated for calcium and vitamin D supplementation [21]. The Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in fruits, vegetables, and low-fat dairy products and which limits saturated and total fat intake, has been shown to lower blood pressure and likely reduce the risk of stroke [106; 107].

Cigarette Smoking

Overwhelming evidence shows an undeniable association between cigarette smoking and stroke [9; 108]. Smoking doubles the risk for ischemic stroke and increases the risk of hemorrhagic stroke 2 to 4 times [109]. Studies also indicate that repeated exposure to environmental (“secondhand”) smoke almost doubles the risk of stroke [110]. Using data from the National Health Interview Survey and death certificate data for 2000 through 2004, the Centers for Disease Control and Prevention estimated that smoking resulted in an annual average of 61,616 stroke deaths among men and 97,681 stroke deaths among women [111].

Individuals who smoke should be prescribed smoking cessation medications and be informed about cessation programs, counseling, and nicotine-replacement products. Epidemiologic studies show that, following smoking cessation, stroke risk decreases over time [9]. Individuals who do not smoke should be encouraged not to start.

Obesity and Body Fat Distribution

One study has found that in the body mass index (BMI) range of 25 to 50 kg/m², each 5 kg/m² increase in BMI was associated with a 40% increased risk of stroke mortality; in the BMI range of 15 to 25 kg/m², there was no relationship between BMI and stroke mortality [112]. Another large epidemiologic study showed that the risk almost doubled for overweight and obese men [113]. A meta-analysis of data from 25 studies involving more than 2.2 million people showed an increased risk of ischemic stroke of 22% in overweight individuals and 64% in obese individuals [114]. Studies have not yet addressed if losing weight reduces this risk [9]. However, it is well-documented that weight loss lowers blood pressure and cholesterol and positively affects other risk factors for stroke. Clinicians should encourage overweight patients to begin a weight-loss program that includes a healthful diet and exercise and provide patients with safe weight-loss strategies, such as those recommended by the AHA [9].

Body fat distribution has proven to be a fairly reliable indicator of stroke risk [115; 116]. While some studies support abdominal adiposity as a significant risk factor for stroke only in men, other research indicates that a high concentration of abdominal fat is a significant risk factor in both men and women, independent of BMI [9]. On the other hand, gynoid adiposity in women appears to be associated with a lower risk for stroke, even for women with a higher BMI [116]. A high hip-to-waist ratio may be a more important risk factor for vascular disease, including stroke, than BMI score alone [117].

Physical Inactivity

A large and generally consistent body of evidence indicates that routine physical activity prevents stroke [9]. A habitually sedentary lifestyle increases an individual’s chance of stroke. Physically active men and women generally have a 25% to 30% lower risk of stroke or death than the least active people [118]. Individuals should be strongly encouraged to engage in aerobic exercise at moderate intensity for 150 minutes or more weekly, at vigorous intensity for 75 minutes or more per week, or a combination of both that fulfills these requirements [9]. It should be noted that only moderate-to-vigorous intensity exercise has been found to reduce the incidence of stroke [103].

PREVENTION

PRIMARY PREVENTION

To decrease the incidence of first-time stroke in the United States, primary prevention should focus on individuals at high risk with modifiable risk factors. In areas of the United Kingdom, the incidence of major stroke has been reduced 40% through a reduction in the incidence of risk factors [119]. The AHA has established evidence-based recommendations for primary prevention of stroke and has developed public campaigns and educational materials to help raise awareness of stroke.

Evidence-Based Recommendations

For most individuals with nonmodifiable stroke risks, the probability of stroke can be decreased substantially with rigorous preventive measures and the treatment of modifiable risks [9; 16]. The AHA recommends addressing lifestyle risk factors, as discussed, and medically managing several risk factors, including hypertension, diabetes, AF, other cardiac conditions, dyslipidemia, and asymptomatic carotid stenosis [9].

Hypertension

According to the 2017 guideline, how often should an individual with a blood pressure of 124/85 mm Hg be screened for hypertension?

Hypertension is perhaps the most significant risk factor for stroke, and risk increases as blood pressure increases [9]. Fortunately, the prevalence of hypertension has plateaued over the past decade and remained stable, at 29%, between 2008 and 2017 [120; 121]. Control of hypertension (defined
as blood pressure less than 140/90 mm Hg) also has improved, with rates of control increasing from 27.3% in 1988–1994 to 50.1% in 2007–2008 [9]. These improvements are likely attributable to heightened awareness and treatment, with awareness among U.S. residents increasing from 69% in 1988–1994 to 81% in 2007–2008 [9]. Still, more than two-thirds of people 65 years of age and older are hypertensive [122].

The AHA and other professional organizations recommend that all adults 18 years of age and older be screened for high blood pressure [123]. The U.S. Preventive Services Task Force (USPSTF) recommends annual screening for all adults 40 years of age and older and for those who are at increased risk for high blood pressure. Increased risk is defined as [123]:

- High-normal blood pressure (130–139/85–89 mm Hg)
- Overweight or obese
- Black race
- Individuals 18 to 39 years of age with normal blood pressure (<130/85 mm Hg) who do not have other risk factors should be screened every 3 to 5 years. The USPSTF additionally recommends rescreening with properly measured office blood pressure. If the blood pressure is elevated, the diagnosis should be confirmed with ambulatory blood pressure monitoring [123].

The 2017 Guideline for High Blood Pressure in Adults recommends screening every 2 years for adults with a blood pressure less than 120/80 mm Hg and screening every 3 to 6 months for people with systolic blood pressure of 120 to 129 mm Hg or with diastolic blood pressure less than 80 mm Hg [124]. The AHA/ASA recommends that women be screened for high blood pressure before taking birth control pills, as the combination increases the risk of stroke [125].

Appropriate management of hypertension may also include dietary changes, other lifestyle modifications, and pharmacologic therapy. Studies have shown that management is possible for the majority of patients, but most will require treatment that includes two or more drugs [9].

**Diabetes**

The risk for stroke is 2 times higher among individuals with diabetes. In 2010, after adjusting for population age differences, hospitalization rates for stroke were 1.5 times higher among adults 20 years of age and older with diagnosed diabetes compared with those without diagnosed diabetes [126]. Type 2 diabetes is associated with an increased prevalence of atherogenic risk factors, such as hypertension, obesity, and dyslipidemia. The combination of hyperglycemia and hypertension is thought to increase the risk of stroke [9]. The AHA recommends that the target blood pressure for individuals with diabetes be less than 140/90 mm Hg [9]. Pharmacologic therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been shown to be safe and effective in this population [9]. In addition, lipid-lowering statins reduce the risk of first-time strokes in patients with diabetes, irrespective of the baseline lipid levels, pre-existing vascular conditions, and glycemic control [127].

**Atrial Fibrillation**

AF is associated with a fourfold to fivefold increased risk of ischemic stroke, and approximately 60,000 strokes occur among the 2.3 million individuals with AF annually [9]. According to the AHA/ASA, women older than 75 years of age should be screened for AF risk due to its link to greater stroke risk [125]. The AHA recommends that individuals with AF who have valvular heart disease (particularly individuals who have mechanical heart valves) should receive anticoagulant therapy [9]. Antithrombotic therapy with adjusted-dose warfarin or aspirin is approved for stroke prevention in individuals with nonvalvular AF based on their calculated risk of stroke and estimated risk of bleeding. The individual's preferences and access to high-quality anticoagulation monitoring should be considered. Warfarin therapy to maintain an international normalized ratio (INR) of 2.0 to 3.0 (target: 2.5) is strongly recommended for high-risk individuals (those with more than a 4% annual risk of stroke) with AF and no significant contraindications to oral anticoagulants [9; 128]. Despite the effectiveness of such treatments, anticoagulant therapy continues to remain underprescribed due to overestimation of the associated risks of warfarin (e.g., intracranial, extracranial hemorrhage) and underestimation of stroke risk [128]. Some physicians err on the side of caution and aim for an INR greater than the recommended target, with a corresponding reduction in therapeutic effectiveness.

**Other Cardiac Conditions**

The management of valvular heart disease, unstable angina, chronic stable angina, acute MI, and other cardiac conditions is a critical factor in stroke prevention. Strategies to prevent postoperative neurologic injury and stroke in patients undergoing surgical revascularization for atherosclerotic heart disease can be found in the American College of Cardiology coronary artery bypass graft surgery guidelines, which are approved by the AHA [9; 129]. The AHA states that it is “reasonable” to use warfarin for patients who have had ST-elevation MI and left ventricular dysfunction with extensive regional wall-motion abnormalities [9].

**Dyslipidemia**

The AHA recommends that statin therapy be prescribed for individuals with known coronary heart disease or high-risk hypertension (e.g., patients with diabetes), including those with normal low-density lipoprotein (LDL) cholesterol levels [9]. In addition, these individuals should be encouraged at every interaction to exercise, eat a healthful diet, and quit smoking. Niacin, bile acid sequestrants, ezetimibe, or fibric acid derivatives may also be considered for individuals with
known coronary heart disease and low levels of high-density lipoprotein cholesterol, such as people in whom target cholesterol levels cannot be achieved with statins or people who cannot tolerate statin therapy; however, their effectiveness in decreasing stroke risk has not been established [9].

**Asymptomatic Carotid Stenosis**

Individuals with asymptomatic carotid artery stenosis should be screened for other modifiable risk factors, and any risk factors identified should be controlled as soon as possible. Antiplatelet therapy with aspirin is recommended, unless contraindicated [9]. Preventive carotid endarterectomy performed by a skilled surgeon is an option for patients when it is determined that the morbidity/mortality risk is less than 3% to 6%; however, the reduction in stroke risk is modest at best [9; 10]. Comorbidities and life expectancy should be considered when determining if surgery is appropriate. In addition, thorough discussion with the patient and his or her family/caregivers is a necessity. Topics should include the possibility of surgery-related death, the risks and benefits associated with the procedure, and the patient’s preferences. For patients with a high surgical risk, carotid angioplasty/stenting may be considered. However, the periprocedural and overall 1-year event rates in some studies have dampened the AHA’s enthusiasm for the stenting option [9; 10].

The U.S. Preventive Services Task Force (USPSTF) recommends against screening for asymptomatic carotid artery stenosis in the general adult population. The USPSTF concludes that for individuals with asymptomatic carotid artery stenosis there is moderate certainty that the benefits of screening do not outweigh the harms. (https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/carotid-artery-stenosis-screening. Last accessed March 28, 2017.)

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

**Depressive Symptoms**

After publication of the AHA guidelines, the findings of a large study showed that depressive symptoms are an independent risk factor for stroke, especially for patients younger than 65 years of age [130]. Clinicians may consider managing depressive symptoms and mood disorders as aggressively as hypertension or diabetes, because mood disorders appear to increase risk for all types of stroke [131].

**PUBLIC HEALTH CAMPAIGNS**

What percentage of individuals with acute ischemic stroke receive thrombolytic therapy when they arrive at an emergency department within 3 hours after the onset of symptoms?

Although public knowledge regarding the warning signs and risks of stroke has improved, the majority of the general public is still unaware that early treatment can prevent severe disability and death [132; 133]. Estimates vary widely; however, the International Stroke Trial found that only 4% of patients with acute ischemic stroke arrive at the emergency department (ED) within 3 hours after the onset of symptoms, and a separate study found that 21% to 25% of individuals with acute ischemic stroke arrive at an ED within the same timeframe [134; 135]. Of these individuals, 2% to 4% receive thrombolytic treatment [136; 137]. It has been estimated that if all individuals called for emergency help at the onset of symptoms, as many as 29% could realistically receive treatment within 3 hours [136]. In addition, if all patients arrived at the ED within 1 hour after known symptom onset and received optimal treatment, the projected rate of thrombolysis would be 57%.

To improve the rate of early arrival in the ED, public education campaigns designed to help individuals recognize a stroke and seek early treatment often use the “five sudden warning signs” devised by the Brain Attack Coalition, or “FAST,” a mnemonic device created by study investigators on the basis of the Cincinnati Prehospital Stroke Scale [138; 139]. The AHA and the National Stroke Association and other organizations use FAST. Early signs and symptoms that comprise the five sudden warning signs include [139; 140]:

- Numbness or weakness of the face, arm, or leg (especially on one side)
- Trouble seeing from one or both eyes
- Severe headache
- Dizziness, difficulties with walking, and loss of balance and coordination
- Confusion and trouble speaking or understanding

FAST was designed to focus on fewer common signs of stroke onset (face numbness, arm numbness, and slurred speech) and to include an action component (time) for lay persons who may have trouble recalling the warning signs and the appropriate action. A retrospective study exploring the capacity of the FAST campaign to facilitate the recognition of stroke suggests that it leads to the identification of approximately 89% of individuals who have a stroke or TIA [139]. The most common stroke symptoms were related to the face, arm, and speech/language. The same study found that a modified version of FAST (with removal of the word “numbness”) decreased the number of TIAIs identified and targeted ischemic stroke more readily than hemorrhagic
stroke. Ultimately, it is unknown whether the general public is more likely to remember FAST or the five sudden warning signs.

In 1989, the United States Department of Health and Human Services Public Affairs launched a National Health Observance to help stimulate awareness of the risk factors, prevention, and early treatment of stroke. For more than 25 years, May has been recognized as National Stroke Awareness Month, with special campaigns to heighten awareness of stroke among the general public. Resources to aid community campaigns can be obtained from the National Stroke Association at http://www.stroke.org/stroke-resources/raise-awareness-stroke.

PATIENT EDUCATION

Patient education should be presented in several forms and focus on modifiable risk factors, patients' needs, lifestyle, and life stage. Healthcare professionals can be most effective in reducing the risk of stroke when they demonstrate an interest in a patient's lifestyle and psychologic status. For instance, if a patient depends on his or her spouse or companion for meals, optimum benefits will result from educating the spouse/companion about healthy diet practices. Clinicians should also consider cultural needs when addressing prevention strategies.

When a patient/caretaker does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A systematic review of the literature has shown that the use of professional interpreters provides better clinical care than the use of informal interpreters, with the former improving the quality of care for patients with limited English language skills to a level equal to that for patients with no language barriers [141]. Use of professional interpreters has been associated with improvements in communication (errors and comprehension), utilization, clinical outcomes, and satisfaction with care [141]. Individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [142].

Whether the education involves stroke prevention, stroke recognition, care after stroke, coping with the effects of stroke, or palliative care, written materials are as important as verbal communication. Several organizations supply general or specialized educational resources, and many also provide patients and family/caregivers with psychosocial, financial, and assisted-living information or aid (Table 9). Clinicians should attempt to obtain materials written in languages appropriate for their patient population and, if appropriate, that target patients in high-risk racial/ethnic populations, especially American Indian/Alaskan native and black individuals. Among new ways for clinicians to heighten awareness in their patients are electronic tips provided by the National Stroke Association that can be sent by e-mail to patients.

<table>
<thead>
<tr>
<th>ORGANIZATIONS PROVIDING PATIENT EDUCATION RESOURCES ON STROKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Heart Association</td>
</tr>
<tr>
<td>1-800-AHA-USA-1 (242-8721)</td>
</tr>
<tr>
<td><a href="http://www.heart.org">http://www.heart.org</a></td>
</tr>
<tr>
<td>American Stroke Association</td>
</tr>
<tr>
<td>1-888-4STROKE (478-7653)</td>
</tr>
<tr>
<td><a href="http://www.strokeassociation.org">http://www.strokeassociation.org</a></td>
</tr>
<tr>
<td>Brain Aneurysm Foundation</td>
</tr>
<tr>
<td>1-888-BRAIN02 (272-4602)</td>
</tr>
<tr>
<td><a href="http://www.bafound.org">http://www.bafound.org</a></td>
</tr>
<tr>
<td>Brain Attack Coalition</td>
</tr>
<tr>
<td><a href="https://www.brainattackcoalition.org">https://www.brainattackcoalition.org</a></td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td><a href="https://www.cdc.gov/stroke">https://www.cdc.gov/stroke</a></td>
</tr>
<tr>
<td>Internet Stroke Center</td>
</tr>
<tr>
<td>1-214-648-3111</td>
</tr>
<tr>
<td><a href="http://www.strokecenter.org">http://www.strokecenter.org</a></td>
</tr>
<tr>
<td>National Stroke Association</td>
</tr>
<tr>
<td>1-800-STROKES (787-6537)</td>
</tr>
<tr>
<td><a href="http://www.stroke.org">http://www.stroke.org</a></td>
</tr>
<tr>
<td>BrightFocus Foundation</td>
</tr>
<tr>
<td>1-800-437-2423</td>
</tr>
<tr>
<td><a href="http://www.brightfocus.org">http://www.brightfocus.org</a></td>
</tr>
<tr>
<td>Hazel K. Goddess Fund for Stroke Research in Women</td>
</tr>
<tr>
<td>1-561-623-0504</td>
</tr>
<tr>
<td><a href="http://www.thegoddessfund.org">http://www.thegoddessfund.org</a></td>
</tr>
<tr>
<td>National Aphasia Association</td>
</tr>
<tr>
<td>1-800-922-4NAA (4622)</td>
</tr>
<tr>
<td><a href="http://www.aphasia.org">http://www.aphasia.org</a></td>
</tr>
</tbody>
</table>

Table 9

PREDICTING RISK

What are the goals of risk assessment tools for stroke?

When determining the appropriate degree of risk management, information regarding an individual's risk of first stroke is valuable. The goals of risk assessment tools include [9]:

- Identifying patients who are unaware of their elevated risk
- Assessing the total risk of multiple factors
- Discerning the utility of modifications and treatments
- Projecting a quantitative risk in order to select appropriate treatments or stratification in clinical trials
- Guiding appropriate use of diagnostic tests

Source: Compiled by Author
The numerous nonmodifiable and modifiable factors that contribute to the risk of stroke have been discussed. Although many of these are independent risk factors, their interactions can affect predictions and management decisions in unexpected ways. No simple, validated stroke risk-assessment tool is currently available [9]. Although risk-assessment tools may have some utility, it is unknown if they improve primary prevention, especially when applied across subgroups according to age, gender, and race/ethnicity [9; 143].

Because TIA is a substantial risk factor for a subsequent stroke, clinicians in many EDs are stratifying such patients by degree of risk with use of the ABCD or ABCD2 assessments [144; 145]. The ABCD clinical tool is designed to predict 7-day risk of stroke through assessment of age (1 point for patients 60 years of age or older), blood pressure (1 point for a blood pressure greater than 140/90 mm Hg), clinical features (2 points for unilateral weakness with or without speech impairment or 1 point for speech impairment without weakness), and duration (1 point for 10 to 59 minutes, 2 points for greater than 59 minutes) [146]. The “2” designation in ABCD2 was added to represent the presence or absence of diabetes. The effectiveness of these screening tools is lessened by the fact that some individuals do not seek emergency care for a TIA or do not report a TIA to their clinician. However, the ABCD2 assessment has been shown to identify 21% of individuals with a high 2-day risk of having an ischemic stroke [144]. Individuals with high-risk TIA require the same intensity of evaluation and stroke prevention as individuals with ischemic stroke.

### EARLY MANAGEMENT

Because the temporal window for effective stroke treatment is short, it is imperative that evaluation and diagnosis are performed promptly and accurately. As noted, fewer than 25% of individuals with ischemic stroke present to an ED or a clinician’s office within the optimum 3-hour treatment interval [134]. The AHA has established several evidence-based recommendations for the diagnosis and early management of adult-onset ischemic stroke [16]. These recommendations address the evaluation of the individual before he or she arrives at an ED, diagnosis in the ED, the history and physical examination, laboratory tests, carotid ultrasonography, cerebral angiography, and imaging studies.

### PREHOSPITAL EVALUATION

The single most important factor influencing the treatment of stroke within 3 hours after the onset of symptoms is the rapid triage and transportation provided by EMS [147]. Stroke assessment should begin with the EMS dispatcher. When stroke or TIA is suspected, the dispatcher is responsible for notifying the appropriate EMS provider and coordinating with an appropriate acute stroke treatment facility (Table 10). Regardless of the degree of the neurologic deficits, an individual with suspected stroke or TIA should be dispatched and triaged as if he or she were a serious trauma patient [16]. If possible, the individual should be taken to a designated stroke center [16; 19].

After the individual’s airway, breathing, and circulation have been assessed and stabilized, the EMS personnel should initiate a prehospital evaluation [16; 148]. If the individual exhibits common signs of stroke and/or a stroke is indicated by a validated prehospital examination tool (e.g., Los Angeles Prehospital Stroke Screen, Cincinnati Prehospital Stroke Scale), EMS providers should notify the ED that an individual with suspected stroke is in transport [148; 149].
Any information about coexisting conditions and, most importantly, time of symptom onset should be provided in advance. A blood glucose level should also be determined, as symptoms of hypoglycemia may mimic those of a stroke [16].

Prehospital evaluation expedites the physician’s evaluation of the patient on arrival in the ED. If possible, a witness (preferably a close family member or companion) should be transported with the patient to assist with patient history, symptom onset, and contact information. If no witness was present, a family member should be contacted to go to the hospital and should be informed that he or she may need to provide consent for the patient’s treatment. History obtained by EMS providers should include [16]:

- Information about recent events (e.g., stroke, MI, trauma, surgery, bleeding)
- Comorbid diseases (e.g., hypertension, diabetes)
- Use of medications (e.g., anticoagulants, insulin, antihypertensives)

The patient’s medication containers should be transported to the ED as well, especially if medications include anticoagulant, antiplatelet, or antihypertensive drugs. Because 50% of individuals with suspected stroke do not use EMS for initial medical care access, ED staff should be alert to signs of stroke among individuals waiting to be seen in the ED [16].

**DIAGNOSIS IN THE ED**

Organization of the ED’s stroke team and assessment protocol is paramount to maximize the likelihood of early and successful management [16]. The acute stroke team should include physicians, nurses, and laboratory/radiology personnel. After the patient has been triaged and stabilized, the inaugural ED evaluation (history and physical examination), laboratory studies, and CT imaging should be performed concurrently. The multimodal approach has three goals [16]:

- Rapid and careful identification of people with stroke for treatment purposes
- Determination of the underlying cause of the stroke for secondary prevention
- Detection of stroke-mimicking conditions that may require immediate care

Within 1 hour of the patient’s arrival, the evaluation (including a neurologic examination) and treatment decision should be completed. The AHA recommends that all patients receive a standardized battery of tests and procedures, with alternative tests performed only if a particular condition is suspected or the patient’s history is incomplete (Table 11) [16]. Generally, diagnostic tests should be limited to save time. In addition, all diagnostic tests for stroke should be available 24 hours a day, 7 days a week.

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**IMMEDIATE DIAGNOSTIC STUDIES TO EVALUATE PATIENTS WITH SUSPECTED ISCHEMIC STROKE, AS RECOMMENDED BY THE AMERICAN HEART ASSOCIATION**

<table>
<thead>
<tr>
<th>Population</th>
<th>Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Cerebral computed tomography or magnetic resonance imaging (without contrast medium)</td>
</tr>
<tr>
<td></td>
<td>Blood glucose</td>
</tr>
<tr>
<td></td>
<td>Serum electrolytes/renal function tests</td>
</tr>
<tr>
<td></td>
<td>Markers of cardiac ischemia</td>
</tr>
<tr>
<td></td>
<td>Complete blood count, including platelet count</td>
</tr>
<tr>
<td></td>
<td>Prothrombin time/international normalized ratio (INR)</td>
</tr>
<tr>
<td></td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td></td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td></td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>Selected patients</td>
<td>Hepatic function tests</td>
</tr>
<tr>
<td></td>
<td>Toxicology screen</td>
</tr>
<tr>
<td></td>
<td>Blood alcohol level</td>
</tr>
<tr>
<td></td>
<td>Pregnancy test</td>
</tr>
<tr>
<td></td>
<td>Arterial blood gas tests (if hypoxia is suspected)</td>
</tr>
<tr>
<td></td>
<td>Chest radiography (if lung disease is suspected)</td>
</tr>
<tr>
<td></td>
<td>Lumbar puncture (only if stroke is suspected to be secondary to an infectious disease)</td>
</tr>
<tr>
<td></td>
<td>Electroencephalography (if seizures are suspected)</td>
</tr>
</tbody>
</table>

PHYSICAL EXAMINATION AND HISTORY

Which clinical signs suggest subarachnoid hemorrhage rather than ischemic stroke?

In addition to time of onset, other crucial historical data that should be obtained include [16]:

- Information about atherosclerotic and cardiac disease risk factors
- Prior and current drug abuse and history of migraine, seizure, infection, trauma, or pregnancy
- Eligibility for treatment of ischemic stroke

If a patient presents with classic signs of stroke and has one or more cardiovascular risk factors, the diagnosis of stroke can be straightforward. However, identifying more unusual cases may be a challenge. If fever and a cardiac murmur are present, the cause of the stroke may be infective endocarditis [151; 152]. Giant cell arteritis may be the cause if the patient is 50 years of age or older, has a headache, and has an elevated erythrocyte sedimentation rate. The presence of ptosis and miosis contralateral to the deficit may suggest carotid artery disease [150]. The findings of studies have suggested that the value of chest x-ray as part of the diagnostic workup is debatable, and the 2013 AHA guideline recommends a chest x-ray only if lung disease is suspected [16]. Although cardiac monitoring in patients with stroke has not been evaluated, the AHA recommends its use in the first 24 hours to monitor for AF or MI, either of which can lead to stroke or be a dangerous coexisting condition.

Blood pressure sustained at or above 180/120 mm Hg may signal hypertensive encephalopathy [122; 156]. Examination of the respiratory system and the abdomen may lead to the detection of additional conditions. The state of the skin and extremities may indicate systemic conditions, including coagulopathies, platelet disorders, or liver dysfunction [16]. An irregular pulse may be indicative of AF.

If only historical information and/or physical examination are relied on, up to 19% of stroke mimics are mistaken for stroke. Yet, a patient’s history and examination may also identify a condition masquerading as a stroke (Table 12) [16; 157]. The use of MRI or CT with laboratory studies enhances the accuracy of diagnosis, but detecting mimics with imaging techniques is a challenge if the patient has a history of stroke [16].

Another important component of the physical examination is assessment with the National Institutes of Health Stroke Scale (NIHSS). Although initially devised as a research tool to quantify neurologic deficits, this tool is now widely used to measure the severity of a stroke, devise an effective treatment plan that establishes a priority for patient safety, identify the potentially occluded vessel, and predict patient outcome [16; 158]. The NIHSS is standardized, reliable, and fast and facilitates communication among healthcare professionals. Any trained healthcare professional can use the scale at the bedside in 5 to 8 minutes. In addition, results are based only on patient evaluation; a history or information from others is not necessary. It is recommended that the scale be used to assess the patient during the ED evaluation and during treatment with recombinant tissue plasminogen activator (rt-PA) or other therapies and that it be repeated often in the first 24 hours. Further information about the NIHSS and a copy of the scale can be obtained from the National Institute of Neurological Disorders and Stroke [159].

LABORATORY TESTS

For all patients with suspected stroke, the battery of diagnostic tests should be carried out concurrently with laboratory tests, including blood glucose level (to rule out hypoglycemia as a stroke mimic), complete blood count (with platelet count), serum electrolyte levels, renal function studies, and cardiac ischemia biomarkers [16]. Determination of prothrombin time and partial thromboplastin time are of particular importance when considering thrombolysis. Generally, waiting for the results of a diagnostic test should not be a reason to delay thrombolytic therapy. The risk of increased neurologic
damage and death caused by ischemic stroke outweighs that of a secondary hemorrhage except when a bleeding or blood disorder is suspected, the patient was given warfarin or heparin, or the patient takes anticoagulant drugs.

**CAROTID ULTRASONOGRAPHY**

Carotid ultrasonography is a noninvasive vascular imaging technique used to measure arterial blood flow and determine the site and degree of stenosis/occlusion of cerebral vasculature. In particular, transcranial Doppler ultrasonography, which can be performed at the bedside, serves multiple purposes in the cerebrovascular setting. Its most common uses are to assess a patient's primary and secondary stroke prevention needs and to monitor a patient's progress during the early post-acute stroke phase [10; 16; 160]. Additional uses of transcranial Doppler ultrasonography in patients with stroke include [16; 160; 161]:

- Detection of intracranial and extracranial vascular disorders
- Assessment of recurrent stroke risk (e.g., microemboli detection)
- Identification of candidates for intensive prophylactic interventions (e.g., carotid endarterectomy, angioplasty/stenting)

- Intraoperative monitoring of carotid endarterectomy
- Detection of right-to-left shunts
- Identification of subclavian steal syndrome
- Measurement of a post-subarachnoid hemorrhage vasospasm
- Assessment of recanalization (spontaneous or thrombolytically induced)
- Prognosis of patients with stroke (performed during post-acute phase)

Despite the usefulness of this technique, its performance is highly operator-dependent [160]. Considerable anatomic and physiologic knowledge of the cerebral vasculature is required, as vessel images are not produced, and skill and experience are prerequisites for data interpretation [160; 162]. For these reasons, vascular imaging is not practical for the diagnosis of ischemic stroke in most cases. Data acquisition and interpretation tend to be time-consuming and may delay treatment. Thus, the 2013 AHA guidelines do not recommend the use of vascular imaging studies for patients in whom the onset of stroke-related symptoms is less than 3 hours [16]. The guidelines further suggest that carotid ultrasonography should be postponed until a patient has had acute treatment.

<table>
<thead>
<tr>
<th>COMMON NONCEREBROVASCULAR CONDITIONS THAT MIMIC STROKE</th>
<th>Differential Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain tumor</td>
<td>Gradual progression of symptoms</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>Altered mental status without focal findings</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>Neurologic findings in a nonvascular distribution Inconsistent examination Other psychiatric disorders</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Headache Delirium Significant hypertension Cortical blindness Cerebral edema Seizure</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>History of diabetes Low blood glucose level Decreased level of consciousness</td>
</tr>
<tr>
<td>Migraine with aura (complicated migraine)</td>
<td>History of similar events Preceding aura Headache Hemiplegia that outlasts the headache</td>
</tr>
<tr>
<td>Seizures/postictal paresis</td>
<td>Paresis History of seizures Witnessed seizure activity</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>History of lithium, phenytoin, or carbamazepine use</td>
</tr>
</tbody>
</table>

Source: [16; 157] Table 12
CEREBRAL ANGIOGRAPHY

Conventional catheter angiography is invasive, uses ionic radiation, and requires a nephrotoxic contrast medium [163]. It is particularly valuable for the detection of pathologic vascular disorders that lead to cerebral hemorrhage or ischemia, including aneurysm, vasculitis, arteriovenous malformation, atherosclerosis, and arterial dissection [10; 16]. Digital subtraction angiography (DSA), a type of catheter angiography, remains the standard criterion of conventional angiography for detection of many types of cerebrovascular lesions and diseases [164; 165; 166; 167]. Its sensitivity and specificity equal or exceed those of noninvasive techniques; however, it can cause serious complications, such as stroke or death [16].

Unlike catheter angiography, magnetic resonance angiography (MRA) is not an x-ray. This technique creates a map of blood flow, not a true image of the vasculature anatomy. Noninvasive time-of-flight MRA is performed without contrast medium, whereas phase-contrast MRA is performed with contrast medium and is minimally invasive (catheter insertion into a blood vessel is unnecessary). Although MRA provides a high-resolution image of many vessels, it cannot reliably resolve distal or branch occlusions of the intracranial vasculature [16]. Another major disadvantage of MRA is that it overestimates the degree and length of high-grade stenosis by signaling loss of flow when blood flow is turbulent, in-plane, or slow [168]. Although MRA continues to advance technologically, in large part through the improvement of contrast media, high-grade stenosis is still overestimated using this technique when compared with DSA [169]. MRA is helpful for detecting less common causes of ischemic stroke or TIAs (e.g., arterial dissection, venous thrombosis) [16].

Computed tomography angiography (CTA) is being investigated in the setting of acute ischemic stroke [16]. This procedure provides a means to rapidly and noninvasively screen intracranial and extracranial vasculature for stenoses and occlusions. Preliminary data suggest that CTA effectively detects large-vessel intracranial occlusions when compared with ultrasound and DSA; however, because it provides a static image of vascular anatomy, it is inferior to DSA for demonstrating flow rates and direction [16; 170]. Although CTA is fast and can be adapted to conventional CT, contrast medium is required and patients are exposed to additional radiation [16].

Transcranial Doppler (TCD) ultrasonography has been used to detect intracranial vessel abnormalities and to evaluate occlusions and stenoses in intracranial vessels. It is less accurate than CTA or MRA for steno-occlusive disease but can detect microembolic signals that indicate extracranial or cardiac sources of embolism [16]. TCD has been shown to predict and enhance outcomes with intravenous rt-PA [171]. Because the time between the onset of stroke and treatment should be limited, catheter angiography is not recommended by the AHA for the diagnosis of a suspected stroke [16]. In the case of a stroke, the utility of the imaging tool increases after a diagnosis has been made. As with transcranial Doppler ultrasonography, cerebral angiography is particularly useful for confirming the diagnosis, monitoring the progression of thrombolytic therapy, and assisting with the prognosis, particularly during the first 72 hours after a stroke [16].

IMAGING STUDIES

High diagnostic accuracy of stroke and treatment decisions is optimized by the use of imaging tools such as CT and MRI. Collectively, these neuroimaging options provide detailed information that influences stroke treatment decisions, including infarct age, severity, and distribution; intracranial vascular status; cerebral hemodynamics; estimated reversibility of ischemic damage; and hemorrhage type and distribution [16]. For instance, a widespread distribution of early infarction or edema increases hemorrhagic transformation risk following thrombolytic therapy. CT without contrast medium is readily sensitive to these conditions [16].

For prompt and accurate diagnosis, the use of noncontrast CT or diffusion-weighted MRI is recommended for suspected stroke [16]. Although noncontrast CT is less expensive, faster, and more widely available, diffusion-weighted MRI more readily detects small cortical, small subcortical, and posterior fossa infarcts and distinguishes chronic ischemia from acute ischemia. MRI is also sensitive to subclinical satellite ischemic lesions that characterize the pathophysiology of the stroke [16; 172]. Diffusion-weighted MRI can detect acute ischemic changes within minutes after the onset of stroke; CT may not detect ischemic stroke until up to 1 hour after the event [16]. However, not all patients with suspected stroke may benefit from MRI. Contraindications for MRI include claustrophobia, pacemakers, and metal implants.

If a patient is eligible for rt-PA, the AHA suggests that the CT or diffusion-weighted MRI should be completed within 25 minutes after arrival in the ED and interpreted within 45 minutes [16]. Thus, a physician with expertise in reading these images must be available. The multimodal CT approach (noncontrast CT, perfusion CT, and CT angiography studies) or MRI approach (diffusion-weighted imaging, perfusion-weighted imaging, MRA, gradient echo, and often fluid-attenuated inversion recovery or T2-weighted sequences) may provide additional information to improve the diagnosis of ischemic stroke. However, emergency treatment of stroke should not be delayed by waiting for the results of multimodal imaging [16].
Although CT and MRI are increasingly available in EDs, the AHA states that non-contrast-enhanced computed tomography (NECT) is sufficient to identify contraindications to fibrinolysis and to ensure that patients with ischemic stroke receive timely intravenous fibrinolytic therapy. The AHA recommends that NECT be obtained within 25 minutes after the patient’s arrival in the ED [16].

TREATMENT

Because strokes are highly heterogeneous, are associated with multiple medical complications, and are time-critical, their effective management depends on organized and comprehensive care. Such treatment is optimally provided in comprehensive stroke centers and stroke systems of care. In 2007, the AHA published evidence-based guidelines to provide recommendations for treatment. These guidelines were updated in 2013 [16].

STROKE SYSTEMS OF CARE AND COMPREHENSIVE STROKE CENTERS

What are the advantages of treatment at primary and comprehensive stroke centers?

Comprehensive stroke centers are designed to accommodate the needs of patients with complicated forms of stroke, intracranial hemorrhages, and subarachnoid hemorrhages, as well as patients in need of aggressive intervention measures and intensive care [19]. In general, primary and comprehensive stroke centers have been shown to be associated with better adherence to evidence-based guidelines and with an increased use of intravenous rt-PA [173]. Nationally, only 2% to 3% of individuals with stroke are treated with rt-PA, but the rate is typically greater than 10% at primary and comprehensive stroke care centers [19; 137]. Overall care may also be improved at comprehensive stroke centers [173; 174]. A formal certification process for comprehensive stroke centers has been established by the Joint Commission and the ASA. The Joint Commission has been certifying primary stroke centers since 2004, and it began providing certification for comprehensive stroke centers in 2014 [16]. Because patients are more likely to receive thrombolytic therapy at primary and comprehensive stroke centers, many states have enacted policies mandating the direct routing of individuals with suspected stroke (with onset of symptoms less than 3 hours previously) to either of these types of facilities. As of 2015, 1,505 of the 4,640 general hospitals and emergency rooms in the United States have been certified as primary stroke centers [175]. Seventy-four percent of the primary stroke centers have been certified by the Joint Commission and the AHA/ASA, 20% have been certified by state organizations, and 6% have been certified by other organizations. The highest proportion of primary stroke center certifications has occurred in the Northeastern United States [175]. Telemedicine for stroke (also called telestroke) and air transport are being increasingly used to serve individuals in rural areas that lack local stroke expertise [16; 174].

Stroke centers are commonly part of a comprehensive support network known as a stroke system of care [16]. The system seeks ways to coordinate the highest quality of stroke prevention, community education, EMS, acute care, and post-acute care. Without a system of care, these components often operate less effectively and in isolation. Implementation of a stroke system of care in underserved regions could substantially improve treatment statistics statewide or nationwide; for example, one study showed that the additional resources at as few as six target hospitals in the western part of North Carolina would increase patient access to stroke care by 61.5% throughout the state [176].

Guidelines for establishing a stroke system of care were developed by an ASA Task Force [20]. Because of the multidisciplinary aspects of a stroke system, Task Force members were experts in areas of stroke prevention, EMS, acute stroke care, rehabilitation, and healthcare policy. Overall, the recommendations promote the communication and collaboration of patients, clinicians, facilities, and agencies. General ASA recommendations for a stroke system of care are [20]:

- Coordinate providers of prevention, timely identification, transport, treatment, and rehabilitation of individual patients with stroke in a locality or region, and facilitate interactions among these individuals/agencies.
- Promote the use of an organized, standardized approach in each facility and component of the system.
- Identify performance measures (both process and outcomes measures), and include a mechanism for evaluating effectiveness through which the entire system and its individual components can improve.
- Provide patients and clinicians with the tools needed for effective stroke prevention, treatment, and rehabilitation.
- Ensure that decisions about protocols and patient care are based on what is in the best interests of patients with stroke.
- Identify and address potential barriers to successful implementation. Barriers may include costs of developing and maintaining a stroke system, geopolitical lines of service by EMS, adequate legal and political recognition of the system, competition for patients and market share among providers, tensions that may exist among academic and community-based institutions, variable commitment to acute stroke therapy, differences in corporate culture among different facilities and provider groups, and concerns about the adequacy of reimbursement. The involvement of policymakers and stakeholders may be necessary.
Customize systems for each state, region, or locality while maintaining universal elements to help ensure optimal prevention of stroke and the timely identification, transport, treatment, and rehabilitation of patients with stroke. For instance, the implementation of transportation services and telemedicine procedures may help individuals in rural areas gain access to needed services.

**EVIDENCE-BASED GUIDELINES**

Thrombolytic therapy with rt-PA is the only treatment approved by the U.S. Food and Drug Administration (FDA) for ischemic stroke [16]. Anticoagulant and antiplatelet agents are also used, but their appropriateness is a source of debate and ongoing research. Intra-arterial rt-PA may be beneficial for select patients; however, the drug is not FDA approved for this use [18]. Mechanical thrombectomy is a consideration as both a primary reperfusion strategy and in conjunction with pharmacologic fibrinolysis [16].

The AHA/ASA recommendations for the treatment of ischemic stroke are based on an exhaustive review of available studies and emphasize the importance of early management [16; 18]. Since publication of the 2013 guidelines, substantial new high-quality evidence on the clinical efficacy of endovascular treatments has become available. This new evidence is the basis of the AHA/ASA 2015 focused update to the 2013 guidelines and is included, where appropriate, in the recommendations that follow [18].

**Recombinant Tissue Plasminogen Activator (rt-PA)**

**What is the most common serious medical complication of rt-PA?**

The intravenous administration of rt-PA has been FDA-approved for the treatment of stroke since 1996. Rapid administration of rt-PA to appropriate patients remains the mainstay of early treatment of acute ischemic stroke [18]. Treatment with rt-PA is highly effective if administered within 3 hours. The earlier treatment is initiated, the higher the probability of a full recovery. Treatment within 90 minutes has been associated with a higher rate of favorable outcome at 3 months compared with treatment administered within 180 minutes [177]. For patients who meet national and international eligibility guidelines, intravenous rt-PA improves functional outcomes at 3 to 6 months when given within 4.5 hours after ischemic stroke onset and should be administered [18]. However, the therapeutic window may extend to 6 hours [178; 179]. Studies to determine the threshold of rt-PA benefits are ongoing. The AHA/ASA recommend that health systems set a goal of increasing their percentage of stroke patients treated within 60 minutes of presenting to hospital (i.e., door-to-needle time of 60 minutes) to at least 80% [16].

With a goal to improve functional outcomes, the American College of Emergency Physicians recommends that intravenous tPA should be offered and may be given to selected patients with acute ischemic stroke within three hours after symptom onset at institutions where systems are in place to safely administer the medication. The increased risk of symptomatic intracerebral hemorrhage should be considered when deciding whether to administer tPA. (https://www.guideline.gov/summaries/summary/49538. Last accessed March 28, 2017.)

**Strength of Recommendation: B (Recommendation based on moderate clinical certainty)**

The AHA/ASA have changed some of their recommendations regarding rt-PA treatment since their 2003 guidelines (Table 13) [16]. Administration of rt-PA is not recommended for patients who have a systolic blood pressure greater than 185 mm Hg or a diastolic blood pressure greater than 110 mm Hg [16].

Between 31% and 50% of patients treated with rt-PA have a 4-point or greater improvement on the NIHSS by 3 months after the stroke [16]. These clinical improvements do not recede for at least 1 year after the stroke. In general, the best response to rt-PA has been found for patients who are younger than 75 years of age, with a baseline NIHSS score of less than 20, and no history of diabetes or pre-existing disability [16].

The most common serious medical complication of rt-PA is secondary brain hemorrhage, which occurs in 6% of patients [16; 180]. Yet, the risk does not outweigh the benefits of rt-PA. Three months following rt-PA therapy, approximately 30% of patients are neurologically normal or near normal; 30% have mild-to-moderate neurologic deficits; 20% have moderate-to-severe deficits; and 20% have died [181]. Other dangerous complications of rt-PA, although rare, are angioedema, anaphylaxis, systemic hemorrhage, and, if rt-PA is administered soon after an acute MI, myocardial rupture [16; 182].
# Ischemic Stroke

## AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION

### RECOMMENDATIONS FOR THROMBOLYTIC THERAPY

### Class I Recommendations

Intravenous rt-PA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke (Class I, Level of Evidence A). Physicians should review the criteria outlined in the AHA guidelines to determine the eligibility of patients.

In patients eligible for intravenous rt-PA, benefit of therapy is time dependent; treatment should be initiated as quickly as possible. The door-to-needle time should be within 60 minutes from hospital arrival (Class I, Level of Evidence A).

Intravenous rt-PA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3–4.5 hours after stroke onset (Class I, Level of Evidence B). Physicians should review the criteria outlined in the AHA guidelines to determine the eligibility of patients.

Intravenous rt-PA is reasonable in patients whose blood pressure can be lowered safely (to less than 185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous rt-PA (Class I, Level of Evidence B).

In addition to bleeding complications, physicians should be aware of the potential side effect of angioedema that may cause partial airway obstruction (Class I, Level of Evidence B).

### Class II Recommendations

A patient with a seizure at the time of onset of stroke may be eligible for treatment as long as the physician is convinced that residual impairments are secondary to stroke and not a postictal phenomenon (Class IIa, Level of Evidence C).

The effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established (Class IIb, Level of Evidence C).

The usefulness of intravenous administration of tenecteplase, reteplase, desmoteplase, urokinase, or other fibrinolytic agents and the intravenous administration of anecrod or other defibrinogenating agents is not well established, and they should only be used in the setting of a clinical trial (Class IIb, Level of Evidence B).

The effectiveness of intravenous treatment with rt-PA is not well established (Class IIb, Level of Evidence C) and requires further study for patients who can be treated in the time period of 3–4.5 hours after stroke. Physicians should review the criteria outlined in the AHA guidelines to determine the eligibility of patients.

Use of intravenous fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered, and potential increased risk should be weighed against the anticipated benefits (Class IIb, Level of Evidence C). These circumstances require further study.

### Class III Recommendations

The intravenous administration of streptokinase for treatment of stroke is not recommended (Class III, Level of Evidence A).

The use of intravenous rt-PA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for more than 2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rt-PA (Class III, Level of Evidence C). Further study is required.

Source: [16]  
Table 13

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**Anticoagulants**

The AHA/ASA Task Force reviewed and discussed several studies addressing the use of heparin or low-molecular-weight heparin (LMWH) and danaparoid as an adjunct to a thrombolytic agent in the treatment of stroke [16]. In general, the Task Force concluded that early administration of heparin or LMWH and danaparoid is inadvisable partly due to the increased risk of bleeding complications, especially the hemorrhagic transformation of ischemic strokes. Additionally, early administration has not been shown to prevent recurrent stroke, lessen the risk of neurologic worsening, or improve patient outcome [16].

**Antiplatelets**

Although no new data regarding antiplatelet treatment have emerged since the 2003 version of the AHA/ASA guideline for ischemic stroke management, the AHA/ASA recommendations for antiplatelet therapy have changed (Table 14) [16]. Data combined from two large clinical trials suggest that administration of aspirin (325 mg) within 48 hours after the onset of stroke slightly reduces mortality and morbidity by preventing early recurrent stroke in some patients [183; 184]. The findings of these trials do not suggest the use of aspirin within 24 hours of thrombolytic administration or as a substitute for thrombolytic therapy. A review that...
summarized the results of nine randomized controlled trials confirmed these findings and demonstrated increased odds of complete recovery [185]. Other oral antiplatelet therapies (e.g., ticlopidine, clopidogrel, dipyridamole) have not been tested sufficiently in the setting of acute ischemic stroke. The efficacy of intravenous glycoprotein IIb/IIIa receptor blockers (GP IIb/IIIa inhibitors), such as abciximab, in combination with other interventions or alone is under investigation. Preliminary results from the Abciximab in Emergent Stroke Treatment Trial (AbESTT) indicate that intravenous GP IIb/IIIa inhibitors may accelerate spontaneous recanalization, improve microvascular patency, and offer an adequate safety profile [186; 187]. However, a systematic review of GP IIb/IIIa inhibitors as well as results of the AbcESTT-II (a phase III trial of abciximab) did not demonstrate either safety or efficacy of the drug for treatment of acute ischemic stroke and found an increased rate of symptomatic or fatal intracranial hemorrhage, with no reduction in death or disability in survivors [188; 189].

In patients with acute ischemic stroke or transient ischemic attack, the American College of Chest Physicians recommends early (within 48 hours) aspirin therapy at a dose of 160 to 325 mg.


Strength of Recommendation/Level of Evidence: 1A
(Strong recommendation, high-quality evidence)

Angioplasty and Stenting

Although emergent angioplasty and stenting are high-risk procedures, progressing strokes, which occur when patients’ moderate neurologic deficits deteriorate significantly within 72 hours after onset, are associated with very poor outcomes and high mortality rates [190]. Therefore, some case studies suggest that emergency angioplasty followed by immediate or delayed stenting is appropriate for patients with a progressing stroke caused by carotid artery occlusion or stenosis, respectively [191; 192].
Angioplasty and stenting may also be appropriate for patients with acute stroke secondary to carotid artery dissection [193]. In one study, emergency angioplasty and stenting of the internal carotid artery performed in conjunction with intra-arterial thrombolysis was associated with more favorable outcomes than pharmacologic treatment alone in patients with acute carotid artery occlusion and secondary artery-to-artery embolism to the middle cerebral artery [194]. In a larger study by the same group of investigators, treatment with urokinase followed by angioplasty and stenting increased recanalization [195].

The AHA/ASA assert that the use of angioplasty and intra-arterial thrombolytics in the emergency management of stroke should be limited to comprehensive stroke centers, which have the resources and physician expertise to perform them safely, and in the setting of clinical trials [16].

In addition to use in emergent angioplasty and stenting, mechanical thrombectomy is both a primary reperfusion strategy and an adjunct to pharmacologic fibrinolysis for achieving recanalization in patients with acute ischemic stroke [16]. Mechanical treatments include the use of catheters during angiography to directly deliver either a clot-disrupting or retrieval device to an artery-occluding thromboembolus [196].

The primary advantage of mechanical devices is their ability to remove a clot in a matter of minutes, compared with pharmacologic thrombolytics (even those delivered intra-arterially) that may take as long as two hours to dissolve the clot [197; 198]. A second advantage is that newer devices (e.g., retrievable stents) have shown higher recanalization rates and better outcomes than those seen with older devices (e.g., the Merci Retriever) [196]. The primary disadvantage of endovascular therapy is the delay in initiation of treatment because of the time required to mobilize the interventional team and, in many cases, the need to transfer the patient to another hospital [199; 200]. In the absence of sufficient trial data, it had been uncertain whether endovascular therapy, with or without the previous use of intravenous rt-PA, would be more effective than intravenous rt-PA alone [201]. However, newer trials (i.e., MR CLEAN, EXTEND-IA, ESCAPE, and SWIFT-PRIME) have demonstrated the efficacy of endovascular therapy using the newer, retrievable stents [202; 203; 204].

In addition to reviewing the results of these four trials, the AHA/ASA also reviewed the results of the REVASCAT trial [18; 205]. Of the five stent retriever trials, MR CLEAN, ESCAPE, AND SWIFT-PRIME permitted use of salvage intra-arterial fibrinolytic drugs, whereas EXTEND-IA and REVASCAT did not [18]. Every or nearly every patient in the trials first received intravenous rt-PA. All five studies enrolled participants 18 years of age and older. Four of the trials used NIHSS scores (>2, >5, and 8–29) as eligibility criteria, and the fifth trial enrolled patients with a similar distribution of NIHSS scores. Four of the five trials used a prestroke function eligibility criterion. All five trials required baseline nonenhanced CT or MRI and used different strategies of an imaging-based selection criterion in addition to nonenhanced CT or MRI. The overwhelming majority of patients in the trials had ICA or proximal MCA (M1) occlusion. All five trials allowed the inclusion of patients with proximal cervical carotid stenosis, and all but one trial (SWIFT-PRIME) allowed the inclusion of patients with complete atherosclerotic cervical carotid occlusion. General anesthesia and conscious sedation were the two most frequently used anesthetic approaches for patients with acute ischemic stroke receiving endovascular therapy. None of the trials established the usefulness of mechanical thrombectomy devices other than stent retrievers [18].

The AHA/ASA analysis of and conclusions about these five stent retriever trials form the basis of their 2015 focused update to the guidelines on the management of patients with acute ischemic stroke (Table 15) [18].

**Carotid Endarterectomy**

In the setting of acute ischemic stroke, justification for emergent (within the first 24 hours) or early revascularization with carotid endarterectomy (CEA) is based on reports of increased risk of recurrent stroke in patients undergoing medical therapy while awaiting revascularization. Some studies have found that CEA is most beneficial when performed within 2 weeks of the last cerebrovascular symptom and that the benefits decline rapidly after 3 weeks [185; 206]. However, the risk associated with emergency CEA is believed to be high, for several reasons, particularly in patients with an unstable neurologic status [207]. First, embolic and hemodynamic injuries can occur [208]. Second, detection of an arterial lesion and mobilization of an operating room staff is time-intensive. Lastly, hyperperfusion, which occurs in 0.3% to 1.2% of patients who have CEA, can lead to brain edema and hemorrhagic transformation [208]. Other complications may also develop.

For some patients, however, the benefit of CEA may outweigh the risk. For instance, patients with acute ischemic stroke who have already had previous CEA may be successfully treated with surgical revascularization. Some studies indicate that early CEA may also be appropriate for patients with small, nondisabling stroke in whom the goal is to reduce ongoing thromboembolism or flow-limiting ischemia [207; 209; 210; 211; 212; 213]. Results of other small studies have suggested that administration of an anticoagulant and delaying surgery until after the patient is stabilized is a better option [214]. Due to the limited and conflicting data, high perceived risk, and unestablished usefulness, the AHA/ASA have withheld a recommendation about the use of carotid endarterectomy for treatment of acute ischemic stroke [16].
# Ischemic Stroke

## American Heart Association/American Stroke Association Recommendations Regarding Endovascular Interventions for Ischemic Stroke

### Class I Recommendations

Eligible patients should receive intravenous rt-PA even if endovascular treatments are being considered (Class I, Level of Evidence A).

Patients should receive endovascular therapy with a stent receiver if they meet all the following criteria (Class I, Level of Evidence A):
- Prestroke mRS score 0 to 1
- Acute ischemic stroke receiving intravenous rt-PA within 4.5 hours of onset according to guidelines from medical societies
- Causative occlusion of the internal carotid artery or proximal MCA (M1)
- Age ≥18 years
- NIHSS score of ≥6
- ASPECTS of ≥26
- Treatment can be initiated (groin puncture) within 6 hours of symptom onset

As with intravenous rt-PA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset (Class I, Level of Evidence B).

Use of stent retrievers is indicated in preference to the MERCI device (Class I, Level of Evidence A).

The technical goal of the thrombectomy procedure should be a TICI 2b/3 angiographic result to maximize the probability of a good functional clinical outcome (Class I, Level of Evidence A).

Initial treatment with intra-arterial fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of less than 6 hours’ duration caused by occlusions of the MCA (Class I, Level of Evidence B). However, these data derive from clinical trials that no longer reflect current practice, including use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial rt-PA is not established, and rt-PA does not have FDA approval for intra-arterial use. As a consequence, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis of first-line therapy (Class I, Level of Evidence E).

### Class II Recommendations

When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the internal carotid artery or proximal MCA (Class IIb, Level of Evidence C). Additional randomized trial data are needed.

In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous rt-PA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa, Level of Evidence C). There are inadequate data at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for patients whose contraindications are time-based or nontime-based (e.g., prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).

Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (Class IIb, Level of Evidence C).

Although the benefits are not established in this age group, endovascular therapy with stent retrievers may be reasonable for some patients <18 years of age with acute ischemic stroke who have demonstrated large vessel occlusion in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset (Class IIb, Level of Evidence C).

Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated within 6 hours of symptom onset and who have prestroke mRS score of >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb, Level of Evidence B).

The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (Class IIb, Level of Evidence B).

The use of a proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial (Class IIa, Level of Evidence C). Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization.

Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be reasonable to achieve these angiographic results, if completed within 6 hours of symptom onset (Class IIb, Level of Evidence B).

Angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered, but the usefulness is unknown (Class IIb, Level of Evidence C). Future randomized studies are needed.

Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous rt-PA might be considered, but the consequences are unknown (Class IIb, Level of Evidence C).

It might be reasonable to favor conscious sedation over general anesthesia during endovascular therapy for acute ischemic stroke. However, the ultimate selection of anesthetic technique during endovascular therapy for acute ischemic stroke should be individualized based on patient risk factors, tolerance of the procedure, and other clinical characteristics. Randomized trial data are needed (Class IIb, Level of Evidence C).

Table 15 continues on next page.
What setting is associated with the best rehabilitation care for patients with ischemic stroke?

More than two-thirds of stroke survivors receive rehabilitation services after hospitalization, yet only a minority receive thrombolytic therapy and many have residual functional deficits, despite the development of designated stroke centers and improvements in stroke recognition and care delivery [21]. Effective stroke rehabilitation is likely to continue to be an essential component of the continuum of stroke care for the foreseeable future. Thus, in 2016 the AHA/ASA published a guideline for stroke rehabilitation and recovery [21]. This guideline spans the entire course of rehabilitation, from the early actions taken in the acute care hospital through the patient’s reintegration into the community. The guideline uses the framework (rating scheme) established by the AHA concerning classes and levels of evidence [21].

The likelihood of functional independence and survival is enhanced by organized multidisciplinary rehabilitation; five more patients for every 100 treated are able to live independently with such rehabilitation [215]. Early initiation of rehabilitation is a particularly strong predictor of improved outcome [21; 216].

Rehabilitation in a stroke unit has been associated with better outcomes than rehabilitation in a general healthcare facility, with improved quality of life, survival, and functional status at 5 years [17; 21; 217; 218; 219; 220; 221]. Yet the decision to refer a stroke patient to a particular setting after discharge is dictated by a complex set of demographic, clinical, and nonclinical factors that are also inevitably related to patient outcomes [21]. Variations in outcomes for inpatient stroke rehabilitation have been found among racial/ethnic populations [21; 222; 223; 224; 225; 226]. Black individuals have less functional improvement at discharge compared with white individuals and are more likely to be discharged to home despite worse functional independence measure (FIM) scores [227]. Asian individuals have functional improvements similar to those for white individuals but have less improvement at 3 months after discharge [227]. These disparities point to the need for focused attention on appropriate rehabilitation services for minority populations.

MULTIDISCIPLINARY REHABILITATION TEAM

Because the effects of stroke are multifaceted and unique to each patient, multidisciplinary and organized services play an important role in patient recovery [21; 218]. Post-acute stroke care settings include specialized inpatient rehabilitation hospitals, stroke rehabilitation units in acute care hospitals, outpatient therapy clinics, long-term care facilities, and patients’ homes. The findings of a systematic review showed that, of these settings, an inpatient specialized stroke unit is...
Ischemic Stroke

Best for providing care due to the presence of skilled nursing services, physician care, and variety of therapies [228]. However, the rehabilitation needs of some patients with mild or no disabilities may be addressed effectively in an outpatient facility (e.g., all-day care at a hospital) or in their homes [21; 229]. For select patients, early discharge to a community setting for ongoing rehabilitation may provide outcomes similar to those achieved in an inpatient rehabilitation unit. This “early supported discharge” model links inpatient care with community-based rehabilitation services and allows some patients to return home sooner [21]. In some cases, recovery may occur without the need for rehabilitation services.

For inpatient and outpatient rehabilitative intervention, the multidisciplinary teams typically consist of several or all of the following: physicians, physical therapists, occupational therapists, kinesiotherapists, speech and language pathologists, social workers, recreational therapists, and nurses [21]. Nursing care for patients in the post-acute phase is particularly intensive. Patients who are triaged to inpatient facilities receive great benefit from 24-hour care by nurses who specialize in stroke care [229; 230].

Depending on the patient’s and family’s/caregivers’ specific needs, a clinical psychologist, psychiatrist, dietitian, and other healthcare professionals may join a patient’s stroke rehabilitation team [21; 230]. However, a team’s exact composition is less important in maximizing a patient’s outcome than is early intervention and the use of a coordinated, interdisciplinary approach. Without communication and coordination, isolated efforts to rehabilitate the stroke survivor are unlikely to achieve their full potential [21].

The AHA/ASA recommendations for the organization of poststroke rehabilitation care and interventions specific to the inpatient hospital setting are summarized in Table 16 and Table 17 [21].

Stroke is an acute and harrowing event, and the emotions and deficits that follow are usually overwhelming to the patient and the patient’s family. The multidisciplinary rehabilitation team should therefore develop a treatment strategy to help individual patients based on a consensus model that incorporates family members and caregivers. Securing the family’s/caregivers’ active involvement early in the rehabilitation process optimizes the patient’s chances for recovery and community reintegration [21; 231]. After the rehabilitation team has formulated a plan of action for the patient, a team liaison should present its recommendations to the patient and family/caregivers through open discussions [232]. Providing patients and families/caregivers with both interactive and written materials is equally important [232]. Information to be presented should include:

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**AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION RECOMMENDATIONS FOR THE ORGANIZATION OF POSTSTROKE REHABILITATION CARE (LEVELS OF CARE)**

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organized, coordinated, interprofessional care is recommended for stroke patients who are candidates for postacute rehabilitation (Class I, Level of Evidence A).</td>
</tr>
<tr>
<td>Stroke survivors who qualify for and have access to inpatient rehabilitation facility (IRF) care should receive treatment in an IRF in preference to a skilled nursing facility (SNF) (Class I, Level of Evidence B).</td>
</tr>
<tr>
<td>Organized community-based and coordinated interprofessional rehabilitation care is recommended in the outpatient or home-based settings (Class I, Level of Evidence C).</td>
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<tr>
<th>Class II Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early supported discharge services may be reasonable for people with mild-to-moderate disability (Class IIb, Level of Evidence B).</td>
</tr>
</tbody>
</table>

Source: [21]  
Table 16

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**AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION RECOMMENDATIONS FOR REHABILITATION IN THE INPATIENT HOSPITAL SETTING**

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early rehabilitation for hospitalized stroke patients should be provided in environments with organized, interprofessional stroke care (Class I, Level of Evidence A).</td>
</tr>
<tr>
<td>Stroke survivors should receive rehabilitation at an intensity commensurate with anticipated benefit and tolerance (Class I, Level of Evidence B).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class III Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose, very early mobilization within 24 hours of stroke onset can reduce the odds of a favorable outcome at 3 months and is not recommended (Class III, Level of Evidence A).</td>
</tr>
</tbody>
</table>

Source: [21]  
Table 17
• Preferred setting and environment based on the patient’s projected recovery
• Treatment options, including suggested rehabilitation programs, estimated length of stay, frequency of therapy, and discharge criteria
• Information regarding the patient’s prognosis and the anticipated recovery process

Once rehabilitation has commenced, involving the patient’s family/caregivers in the rehabilitation sessions and training them to assist the patient with functional activities may aid patient recuperation [21; 233]. During rehabilitation, at least one or two informal meetings per week should be held with family/caregivers to reassess their concerns about the process [234].

Social and Family Caregiver Support
As stated, the stroke survivor’s family members and caregivers are integral to the poststroke treatment plan [21]. However, 12% to 55% of caregivers suffer from emotional distress, most commonly depression [21; 235; 236]. Untreated depression is associated with a lower quality of life for both the caregiver and the stroke survivor [21; 237]. A growing body of research is focused on treatment strategies to benefit both the caregiver and the stroke survivor and on educational programs that target issues such as supportive problem solving, physical care needs, financial and domestic assistance, respite, reassurance, and counseling [21; 238; 239; 240; 241].

PATIENT ASSESSMENT
For individuals who have had a stroke and are medically stable, rehabilitation assessment, prevention of medical complications, and secondary prevention become the focal points [10; 16; 21]. To begin, the rehabilitation team’s systematic evaluation of the patient addresses various issues, including the need for rehabilitation services; the risk of complications; physical functioning, cognition, and communication; and psychosocial conditions [21]. Next, the team works with the patient and family to implement a rehabilitation plan that includes a detailed exercise program and general as well as tailored strategies for secondary prevention [10]. Throughout, the team should strive to foster a climate of familial support [21].

Need for Rehabilitation Services
When a patient is medically stabilized, a rehabilitation physician is consulted to assess the patient’s rehabilitative needs and recommend the proper rehabilitation setting (Table 18) [17]. Additionally, the patient’s complete medical history is provided to the rehabilitation physician. If indicated, other rehabilitation specialists may perform specialized or more intensive assessments. Overall, rehabilitation assessments should be [21]:

• Multidisciplinary, to account for the heterogeneous effects of stroke.
• Well-coordinated and prompt, so patients can begin a rehabilitation program as soon as possible.
• Well-documented, to provide the patient’s rehabilitation team with accurate and detailed information.
• Conducted using formal standardized, validated measures.

The NIHSS is a strong prognosticator of functional outcome, rendering it a valuable tool for determining rehabilitation needs [242; 243]. It is the most widely used global assessment of impairment in the United States. It is a good predictor of short- and long-term morbidity and mortality and has been found to be sensitive to change in numerous studies [21]. Multiple assessments with the scale provide the rehabilitation team with a sense of the patient’s recovery trajectory as he or she enters the rehabilitation stage.
The NIHSS provides detailed information in addition to an overall stroke severity score. A score of less than 6 indicates minor or no functional disability, whereas a score of more than 16 suggests severe disability and an increased probability of death [242]. With the advent of stroke treatment, patients with a score of 6 to 15 are likely to benefit from rehabilitation without the need for a nursing facility [244]. Patients with a score of more than 15 may improve with rehabilitation; however, these patients will likely require long-term care. More than one-half of survivors with a baseline score greater than 20 are initially sent to some form of rehabilitation facility rather than directly discharged to a nursing facility or home [244].

Because the type of stroke affects the usefulness of the NIHSS, its results should be qualified by medical history, examination, and brain imaging data [245]. Specifically, the scale is better suited for predicting functional outcomes at 3 and 6 months after stroke for patients with subcortical lesions than for patients with cortical lesions [21; 246; 247]. Additionally, the reliability of the scale in predicting depressive symptoms and cognitive dysfunctions depends on the hemisphere affected [21; 247]. Because the NIHSS does not include evaluation of weakness of the distal part of the upper extremity, which is common in patients with stroke, a finger extension evaluation should be conducted in addition to the scale [248; 249].

Although new measurement tools are being developed, they are difficult to evaluate with the traditional criteria (e.g., validity, reliability) normally used in evidence-based reviews [21]. The AHA/ASA recommendations for the assessment of rehabilitation needs (Table 19) are based on traditional measurement models, such as the FIM [21].

Soon after patient assessment, family/caregivers should be educated about and referred to community resources [21; 250]. If it is recommended that the patient be discharged from an acute care facility to a nursing facility or the patient’s home, relevant contact and background information for nursing home facilities, assisted-living services, social support groups, and stroke-related organizations should be provided to facilitate familial decision-making. Viable options should be presented to the family, especially information about long-term care placement if a severely disabled patient is not a candidate for rehabilitation [21]. If the family/caregivers will be taking care of the patient at a private residence (with or without professional assistance), it is essential to foster discussions about the needs of the patient, challenges the patient and family/caregivers may face, and the benefits of social support programs for the patient and family/caregivers. Whenever possible, written materials should be provided, and they should be in the primary language of the family. Among the important topics to discuss and provide education about include [21]:

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### AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION RECOMMENDATIONS FOR DISABILITY ASSESSMENT AND REHABILITATION NEEDS

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that all individuals with stroke be provided a formal assessment of their ADLs and IADLs, communication abilities, and functional mobility before discharge from acute care hospitalization and the findings be incorporated into the care transition and the discharge planning process (Class I, Level of Evidence B).</td>
</tr>
<tr>
<td>It is recommended that all individuals with stroke discharged to independent community living from postacute rehabilitation or SNF receive ADL and IADL assessment directly related to their discharge living setting (Class I, Level of Evidence B).</td>
</tr>
<tr>
<td>A functional assessment by a clinician with expertise in rehabilitation is recommended for patients with an acute stroke with residual functional deficits (Class I, Level of Evidence C).</td>
</tr>
<tr>
<td>Determination of postacute rehabilitation needs should be based on assessments of residual neurologic deficits; activity limitations; cognitive, communicative, and psychologic status; swallowing ability; determination of previous functional ability and medical comorbidities; level of family/caregiver support; capacity of family/caregiver to meet the care needs of the stroke survivor; likelihood of returning to community living; and ability to participate in rehabilitation (Class I, Level of Evidence C).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class II Recommendations</th>
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</thead>
<tbody>
<tr>
<td>It is reasonable that individuals with stroke discharged from acute and postacute hospitals/centers receive formal follow-up on their ADL and IADL status, communication abilities, and functional mobility within 30 days of discharge (Class IIa, Level of Evidence B).</td>
</tr>
<tr>
<td>The routine administration of standardized measures can be useful to document the severity of stroke and resulting disability, starting in the acute phase and progressing over the course of recovery and rehabilitation (Class IIa, Level of Evidence C).</td>
</tr>
<tr>
<td>A standardized measure of balance and gait speed (for those who can walk) may be considered for planning postacute rehabilitation care and for safety counseling with the patient and family (Class IIb, Level of Evidence B).</td>
</tr>
</tbody>
</table>

ADLs = activities of daily living, IADLs = instrumental activities of daily living (tasks involving more complex domestic, community, and leisure activities), SNF = skilled nursing facility.

Source: [21] Table 19
• Secondary prevention and medication administration specifics
• Nutrition and hydration
• Symptoms of complications
• Specifics regarding assistance with activities of daily living (e.g., transfers, positioning, bathing, toileting, dressing, and grooming)
• Swallowing difficulties
• Feeding tube use
• Bladder catheter care
• Signs of mood disorders
• Strategies to improve cognitive skills and communication
• Exercises (range of motion)

Education about and referral to appropriate community resources can help to support the needs and priorities of the patient and the family or caregiver [21]. A systematic review and meta-analysis demonstrated that functional outcomes (i.e., motor, cognitive, and psychosocial function) can be improved or, at a minimum, maintained in stroke survivors when community interventions are available [21; 251; 252].

The patient’s psychosocial status will influence his or her willingness and approach to participating in a rehabilitation program. A psychosocial assessment enables the rehabilitation team to incorporate family/caregivers more effectively into the rehabilitation process [253]. In addition, how the team manages the patient’s care may be contingent on the patient’s life circumstances and personality profile. Some patients and their caregivers fail to discuss psychosocial issues with their providers [21; 236]. Cultural differences may also play a part in a patient’s willingness to discuss these issues [21]. Areas of emphasis for the psychosocial assessment should include:

• Medical history
• Coping style
• Therapeutic style and recovery expectations
• Demographic information
• Response to treatment
• Substance use and abuse
• Psychiatric/psychologic evaluation
• Emotional and mental status and history
• Education and employment
• Spiritual and cultural beliefs
• Family/caregiver relationship
• Preferred activities

When designing and implementing the patient’s treatment plan, the rehabilitation team should also take into account the residual effects of any difficulties the patient may have had before the stroke, such as drug or alcohol addiction; stress from recent life events, such as divorce, a loved one’s death, or retirement; or clinical depression [21]. Individual patients will vary in how well they respond to challenging and demanding therapeutic approaches. After a patient’s unique needs and circumstances are determined, relevant specialists will be incorporated into the team. All members of the rehabilitation team should be sensitive to the patient’s psychosocial needs.

Risk of Complications
Medical complications related to illness, being bedridden, or lack of proper care/attention can prolong hospitalization, impede rehabilitation, increase disability, or result in death. Living in an inappropriate post-stroke environment also substantially increases a patient’s risk for complications. Complications may develop in as many as 85% of hospitalized patients who have had a stroke [254]. Thus, medical examinations before and during a patient’s rehabilitation program should assess the most common risks of complications: skin breakdown, deep vein thrombosis (DVT), swallowing dysfunction, bowel and bladder incontinence, falls, and pain [21].

Skin Breakdown and Contractures
Pressure ulcers are a commonly encountered complication in hospital and long-term care facilities, occurring in approximately 10% and 25% of patients in those settings, respectively [254]. According to the National Pressure Ulcer Advisory Panel, a pressure ulcer is a “localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear” [255; 256]. Although ulcers typically occur proximal to osseous prominences (e.g., the sacrum, hips, ankles), skin breakdown at the ears is also common in certain settings [257; 258]. Most pressure ulcers are associated with deep tissue injury [259]. Regular assessment of skin and the use of objective risk scales (e.g., the Braden scale) may help prevent skin injury and should be followed by regular skin inspection with documentation [21; 260]. Risk factors for pressure ulcers include [254]:

• Immobility
• Poor hygiene
• Urinary incontinence and other sources of moisture
• Diabetes and other causes of poor circulation
• Peripheral vascular disease
• Lower body mass index
• Localized infection or trauma
• Edema
• Poor hydration and/or nutrition
Conditions secondary to pressure ulcers include pain, localized infection, cellulitis, osteomyelitis, sepsis, and even death [261; 262]. However, not all pressure ulcers, even those that are severe, will elicit a pain sensation [263].

Ulcers can be prevented or minimized with several measures, including proper positioning, turning, and transferring techniques; good hygiene; proper nutrition and hydration; and the use of barrier sprays, special mattresses, and protective dressings [21; 260]. Good pain management may be necessary to perform correct positioning and frequent turning. Patients should be monitored daily for skin breakdown [21]. Any sign of a pressure ulcer warrants daily treatment [21].

Following stroke with hemiparesis, contracture on the affected side will develop in approximately 60% of patients within the first year, with wrist contractures occurring most commonly in patients who do not recover functional hand use [21; 264; 265]. Contractures are painful and can make self-care difficult. Many clinicians recommend daily stretching of the affected limb(s); families and patients should be taught proper stretching technique [21]. The effectiveness of resting hand splints is not well established [21]. Contractures of the ankle/foot can affect gait quality and patient safety. Ankle-foot orthosis and the nighttime use of a resting ankle splint may be beneficial in preventing ankle contracture [21].

**Deep Vein Thrombosis**

DVT affects only 2% of patients with stroke; yet, its prevention is critical [254]. The American Academy of Family Physicians recommends that DVT risk be calculated with use of the Well’s DVT prediction model, and the results of this model will dictate subsequent DVT testing (Table 20) [266; 267]. For patients with symptoms in both legs, the more symptomatic leg should be tested. A score of 3 or more on the Well’s test indicates a high clinical probability of DVT; the probability is intermediate for a score of 1 or 2.

The D-dimer test alone is not recommended to rule out DVT in patients who have had a stroke. Patients with intermediate-to-high risk for DVT should be screened with use of ultrasonography. This imaging modality may not detect DVT in the calf, however, and repeat ultrasonography or venography should be used when DVT in the calf is suspected. Contrast venography was previously the most definitive test for the diagnosis of DVT, but today, Doppler ultrasound is the diagnostic study of choice [267].

Measures such as early mobilization and anticoagulation therapy are recommended to decrease the incidence of DVT after stroke. A patient’s risk can be substantially reduced by 50-foot walks daily (with assistance, if necessary), administration of subcutaneous, low-dose unfractionated heparin (5,000 units twice a day, unless contraindicated), and the use of graduated compression stockings (GCS) as an adjunct to medication [268]. GCS and intermittent pneumatic compression may be considered for prevention of post-stroke DVT, but their routine prophylactic use requires further study. The benefit of treatment should be weighed against the increased risk of skin complications [21; 269; 270].

**Swallowing Dysfunction**

Based on instrumental testing results, dysphagia may develop in 64% to 78% of patients with stroke [271]. This disorder is strongly linked to the development of malnutrition and pneumonia if not identified early and managed properly [21; 271; 272]. Patients with dysphagia often have problems with aspiration, which can cause serious consequences if the stroke has suppressed cough sensations. Although cerebral and cortical strokes can cause dysphagia, swallowing is most severely compromised by brain stem strokes [271].
The speech and language pathologist on the rehabilitation team should perform a brief swallow assessment on all patients with stroke before oral intake of food and fluids [21; 273]. A dysfunctional swallow should be further examined using a complete bedside swallow examination. If bedside swallow screenings indicate an affected swallow, or if the patient has a high risk for aspiration and/or dysphagia, performing a videofluoroscopy swallowing study or fiberoptic endoscopic examination is recommended [21; 273; 274]. The grade of dysphagia correlates with dysarthria, aphasia, low functional independence, and level of cognitive functioning [274]. The speech and language pathologist may best identify the specific physiologic problem and recommend the necessary management and interventions for treatment. A Cochrane review assessing the effectiveness of a variety of interventions (e.g., acupuncture, neuromuscular electrical stimulation, physical stimulation) on functional outcome found that behavioral interventions and acupuncture reduced dysphagia, and pharyngeal electrical stimulation reduced pharyngeal transit time. However, the authors concluded that data are insufficient to determine the effect of these and other interventions (e.g., nutritional/fluid supplementation) on functional outcome and death [272]. Authors of another review found that acupuncture may be effective for treatment of post-stroke dysphagia, but concluded that the reported benefits should be verified with further studies [275].

**Bladder and Bowel Dysfunction**

Upon admission to community-based facilities, approximately 50% of stroke survivors have urinary incontinence and 30% have fecal incontinence [276; 277]. Almost all patients with fecal incontinence (98%) also suffer from urinary incontinence. Urinary and fecal incontinence can lead to patient discomfort, skin breakdown, and sepsis. Fecal incontinence, in particular, reduces patient and family morale.

Large infarcts, aphasia, cognitive impairment, functional disability, lesions in the frontal cortex or frontoparietal lobes, and advanced age are associated with post-stroke urinary dysfunction [278]. Medications such as diuretics, alpha-adrenoreceptor blockers, and anticholinergic drugs can cause or exacerbate this complication [279; 280]. Hyporeflexia and hyporeflexia are the most common mechanisms of urinary incontinence in stroke survivors [281]. Detrusor sphincter dyssynergia, a cause of incomplete bladder voiding, is uncommon because its pathogenesis involves lesions between the brain stem and spine [280]. When assessing bladder function in patients with acute stroke, it is important to evaluate urinary retention with use of a bladder scanner or an in-and-out catheterization; urinary frequency, volume, and control; and the presence of dysuria. Patients who have urinary incontinence may benefit from bladder-training regimens and scheduled voiding [279; 282].

Fecal incontinence can be due to neurogenic impairments or leakage around a fecal impaction (overflow incontinence) [283]. If the underlying cause of fecal incontinence is neurogenic, the signs and symptoms would likely include reduced rectal sensation and tone, inability to voluntarily contract the rectal sphincter, and stool in the rectal vault [283]. A diagnosis of constipation with overflow incontinence is more likely if the patient has rectal sensation and tone.

Risk factors for impaction and constipation include immobility, inactivity, dehydration, some medications, mood disorders, and cognitive deficits [284; 285]. Multivariate analysis has shown that advanced age and diabetes are risk factors for fecal incontinence [285]. Patients with persistent constipation or fecal incontinence may benefit from bowel-management programs and psychosocial support [286]. Because of the risk of skin breakdown, the social stigma, and the burden of care associated with bowel and bladder incontinence, management is an essential component of the rehabilitation process [21].

**Falls**

Within 12 weeks after a stroke, approximately 25% of patients will fall [254]. Up to 70% of individuals with a stroke fall during the first six months after discharge from the hospital or rehabilitation facility [21; 287]. Individuals with stroke are also at risk of repeated falls that include injury [21; 288]. One study found that most falls occur at home in the first 3 months following post-stroke risk assessment [288]. Falls are a common complication for several reasons, including [283; 289; 290]:

- Unfamiliar environment and physical state
- Pain, fatigue, poor balance, and muscle weakness
- Incontinence
- Frequent positioning, turning, and transferring, especially in rehabilitative settings
- Cognitive impairments, mood disorders (including depressive symptoms), visual impairments, spatial neglect, and any other condition that can decrease a patient’s safety awareness

The Berg Balance Scale may be the most appropriate screen for patients who are likely to fall [291; 292]. This scale tests 14 specific functional movements of daily living of increasing difficulty [293]. The 56-point maximum score indicates adequate balance and low risk of a fall. A score of less than 45 is associated with a proclivity for falling [291; 293]. The score at 2 months post-stroke is useful for informing a patient’s risk of falls, but it does not account for the multifactorial nature of the problem and should not preclude risk management provided in conjunction with exercise interventions, such as rehabilitation that targets gait coordination, to improve mobility [288; 294]. If the patient is able to walk, the Stops Walking When Talking test may further help to identify the
risk for a fall [291]. With this test, the examiner initiates a conversation with the patient while walking; if the patient stops walking to respond, the risk of a fall is increased [295]. St. Thomas’ Risk Assessment Tool in Falling Elderly Inpatients (known as STRATIFY), a tool used commonly in the rehabilitation setting, has been shown to be a poor predictor of the risk for fall when screening patients with stroke [296].

In addition to the physical consequences associated with falls, there are also psychologic and social consequences. Impairments in balance, gait, motor control, perception, and vision contribute to a heightened fear of falling in the stroke survivor, with 30% to 80% reporting various levels of fear associated with falling and mobility [21]. This fear can cascade into reduced levels of physical activity and deconditioning, resulting in greater physical decline, loss of ability to perform activities of daily living, loss of independence, social isolation, and depression. Education in fall prevention, including balance training, is an essential component of the rehabilitation process [21].

Pain

Pain is one of the most frequently experienced complications. Almost one-half of all stroke survivors experience chronic pain, 65% of whom have shoulder pain [234]. Whether chronic or periodic, pain can delay functional recovery by masking motor function improvement, diminishing a patient’s motivation or willingness to perform rehabilitative tasks, or limiting the patient’s movement or requiring the use of a cane or wheelchair for ambulation [17]. Pain most often results from joint immobilization and the fixation of tendons and ligaments in one position [85]. In some patients, however, stroke-induced sensorimotor pathway damage leads to the sensation of pain in an affected extremity or side of the body. The most common pain syndrome of this type is central post-stroke pain, which affects 8% of patients, or at least 56,000 stroke patients in the United States each year [21; 297; 298]. Four percent of patients with central post-stroke pain experience it as shoulder pain. Central post-stroke pain can be difficult to manage, even with medications. Only amitriptyline and lamotrigine have been shown to be effective in placebo-controlled studies [299].

The AHA/ASA recommend patient and family education (i.e., range of motion, positioning) about shoulder pain and care following stroke [21]. A clinical assessment of the pain that includes musculoskeletal examination, evaluation of spasticity, identification of any subluxation, and testing for regional sensory changes is also recommended. Ultrasound may be considered for diagnosis of shoulder soft tissue injury [21]. Botulinum toxin injection or a trial or neuromodulating pain medications may be useful to reduce severe hypertonicity in hemiplegic shoulder muscles. Positioning and the use of supportive devices may help reduce pain [21].

Use of diagnostic criteria for central post-stroke pain can be helpful [21]. Additionally, initial medical examinations should thoroughly document suspected etiology of any pain, its location and characteristics (e.g., burning, tingling, stabbing, dull), its duration and intensity, and what aggravates or relieves the pain. Any pain that interferes with the rehabilitation process should be identified and treated accordingly. There is limited evidence on the efficacy of proposed treatments for central post-stroke pain. Combined pharmacotherapy (e.g., amitriptyline, lamotrigine) and therapeutic exercise may be reasonable. Few nonpharmacologic options exist [21].

Functional Outcome

Approximately 45% of stroke survivors have residual neurologic deficits that impair mobility, which is one of the most devastating sequelae of stroke [21; 87]. At 6 months, about half of ischemic stroke survivors who are 65 years of age or older have hemiparesis, nearly one-third require assistance with walking, and more than one-quarter need assistance with activities of daily living [87]. Although functional outcome primarily depends on the patient’s post-stroke neurologic damage and compensatory capacity, the multidisciplinary rehabilitation team plays a major role in recovery [218]. The team’s coordinated and customized efforts can help many stroke survivors adopt an active and social lifestyle. To tailor services to a patient’s needs, the team should assess his or her functional abilities during the immediate post-acute stroke phase before hospital discharge. Assessment relies on a physical examination and a systematic battery of tests that measure a patient’s ability to complete activities of daily living and that screens for cognitive/communication skills as well as visual/spatial neglect disorders [21]. Knowledge of the patient’s preferred activities is also helpful.

Several functions/activities are typically measured to assess comprehensive functional status initially and during the rehabilitation process (Table 21). Although many measurement tools can be used to objectively record a patient’s comprehensive functional acuity, the most widely used and trusted instrument in the stroke rehabilitation setting is the
ACTIVITIES MEASURED TO ASSESS COMPREHENSIVE FUNCTIONAL STATUS INITIALLY AND DURING THE REHABILITATION PROCESS

<table>
<thead>
<tr>
<th>Activities of daily living</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic capacity and endurance</td>
</tr>
<tr>
<td>Balance</td>
</tr>
<tr>
<td>Bladder and bowel management</td>
</tr>
<tr>
<td>Circulatory response to position changes and other functional tasks</td>
</tr>
<tr>
<td>Communication and social cognition</td>
</tr>
<tr>
<td>Gait</td>
</tr>
<tr>
<td>Joint integrity and mobility</td>
</tr>
<tr>
<td>Locomotion</td>
</tr>
<tr>
<td>Mobility</td>
</tr>
<tr>
<td>Motor function (agility, coordination, dexterity)</td>
</tr>
<tr>
<td>Muscle performance (activation, endurance, power, strength)</td>
</tr>
<tr>
<td>Pain response to functional tasks</td>
</tr>
<tr>
<td>Posture</td>
</tr>
<tr>
<td>Range of motion</td>
</tr>
<tr>
<td>Reflex integrity</td>
</tr>
<tr>
<td>Self-care ability</td>
</tr>
<tr>
<td>Sexual activity</td>
</tr>
<tr>
<td>Upper extremity activity/function</td>
</tr>
<tr>
<td>Use of assistive and adaptive devices</td>
</tr>
<tr>
<td>Visual and spatial neglect</td>
</tr>
</tbody>
</table>

Source: [21; 300] Table 21

FIM [300; 301]. Throughout the rehabilitation process, FIM-supported systematic screening can help the rehabilitation team to [21; 300]:

- Identify functional, cognitive, and visual/spatial deficits not previously detected
- Set realistic functional goals and document progression toward these goals
- Deduce discharge or extended care plans
- Ensure patients’ safety as they perform functional tasks and teach proper mechanics to reduce their risk of injury with continued performance

As stated, loss of mobility is a devastating poststroke outcome and restoration of gait-related activities (e.g., rising to stand, sitting down, climbing stairs) is often one of the primary goals of rehabilitation. Additionally, many patients will require assistive devices, adaptive equipment, and other items to maximize independent functioning after stroke [21].

In general, major rehabilitation goals are for patients to regain safe ambulation in their homes and community and to regain the ability to perform activities of daily living with minimal or no assistance. Thus, patients should be reassessed for daily tasks that are appropriate to their expected level of dependency [21]. If a return to independent community or home living is possible, domestic functioning should be evaluated [17; 302]. Skills needed to stay home alone include preparing a meal, using safety precautions, properly taking medications, and obtaining emergency services. Patients who may resume driving should be assessed thoroughly for driving-related physical, cognitive, and behavioral functions [21]. Driving is an instrumental activity of daily living for many individuals due to its impact on their ability to participate in activities outside the home. Between one- and two-thirds of poststroke survivors resume driving after one year, but because it is a highly complex activity requiring skills in cognition, perception, and emotional and motor control, the ability to drive is often affected by stroke. The AHA/ASA recommend that [21]:

- Individuals who appear to be ready to return to driving, as demonstrated by successful performance on fitness-to-drive tests, should have an on-the-road test administered by an authorized person and should be referred to a driver rehabilitation program for training if the test is failed.
- It is reasonable to assess individuals for cognitive, perception, physical, and motor abilities to determine readiness to return to driving. This may be achieved with a driving simulation.

Cognition and Communication

Healthy cognition and communication are considered to be essential parts of an individual’s well-being. However, stroke frequently has an adverse effect on cognitive and communicative abilities.
Cognition

What cognitive function shows the most improvement by 6 months after stroke?

Calculation, executive functioning (the integration of multiple and complex processes), and visual perception/construction are the cognitive arenas most often affected during the first several weeks after a stroke [303; 304]. Up to 88% of patients with a cerebellar stroke have cognitive deficits, such as impairments in abstract thought, attention, control, memory, planning, and speech [305]. In many cases, patients with stroke-associated right brain damage have anosognosia, a condition in which patients are rendered unaware of their contralateral sensory and motor neurologic deficits (hemiplegia, hemianesthesia, and hemianopia) [306]. Although many survivors regain some or all cognitive skills soon following a stroke, up to 38% remain cognitively impaired at 3 months [307]. Recovery rates may be as high as 80% within 6 months for stroke survivors, with visual perception and visual memory showing the most improvement and language and abstract reasoning showing the least [308; 309]. At 1 and 3 years after a stroke, cognitive impairment is one of the factors most strongly linked with poor physical and mental health status [310]. Cognitive status is an important determinant of post-stroke success. The AHA/ASA recommend that all stroke patients be screened for cognitive deficits before being discharged to home [21].

Stroke-induced damage to the brain’s cognition centers is second only to Alzheimer disease as the leading cause of dementia. Stroke-associated dementia manifests with the following symptoms [311]:

- Memory loss, especially short-term memory
- Attention deficits and difficulty following instructions
- Difficulty planning/organizing tasks or solving problems
- Confusion
- Poor judgment
- Behavioral changes, including inappropriate emotions and extreme mood fluctuations
- Mood disturbances and depression

Areas of cognitive and arousal ability that should be assessed before and during rehabilitation are learning and memory, attention, visual/spatial neglect and impairments, executive functioning, and apraxia (loss of the ability to execute skilled movements despite having the desire and the physical ability to perform them) [21]. In addition to its use in assessing functional ability, the FIM is effective as an initial screen of cognitive and functional communication deficits [312]. Because stroke-related cognition deficits are independently associated with left hemispheric stroke, visual field defect, and urinary incontinence, the presence of any of these conditions should heighten awareness of the possibility of the presence of the others [307].

Visual and spatial dysfunctions may be particularly difficult to identify during the initial post-stroke examination because multiple neuroanatomic systems can be affected to varying degrees. When a standard medical examination does not include the brief, systematic screening for visual and spatial neglects, more than 60% of these dysfunctions remain undiagnosed. However, the use of the FIM may increase their early identification [312]. Patients with neglect deficits are unknowingly inattentive to specific body parts and/or spaces in the external environment. For instance, patients may brush half of their teeth or only eat food on half of their tray. Unilateral neglect is present in almost 50% of patients with right hemispheric stroke [313]. Patients with unilateral neglect are also unaware of limbs contralateral to the site of the brain lesion(s). Neglect disorders are strongly associated with poor functional outcomes and safety issues. Patients with neglect are prone to falls and injuries as well as burns to the affected limbs [290]. Addressing visual and spatial deficits as early as possible in the rehabilitation process using multiple functional adaptation techniques (e.g., visual scanning, external cues) and patient/caregiver education may decrease a patient’s risk for injury [21].

Communication

As with cognitive difficulties, communication problems strain relationships between stroke survivors and their social system, impede rehabilitation, and lead to poor quality of life. Common communication-related stroke sequelae are aphasia, dysarthria, and apraxia of speech (motor speech disorder in which the muscles required for speech are less coordinated). Patients with communication disorders may also have dysphagia. How these disorders are manifested as well as their severity depends on the location and degree of the stroke. Interventions for apraxia of speech should be individually tailored and may include behavioral techniques and strategies that target [21]:

- Physiologic support for speech, including respiration, phonation, articulation, and resonance
- Global aspects of speech production (e.g., loudness, rate, prosody)
CHARACTERISTICS OF EXPRESSIVE AND RECEPTIVE APHASIA

Patients with expressive aphasia may:
- Use single words or short phrases
- Omit smaller words like “the,” “of,” or “and” (the patient’s message may sound like a telegram)
- Say words out of sequence
- Switch sounds or first letters of words (e.g., dishwasher becomes a “wish dasher”)
- Invent words
- Create meaningless sentences by fluently stringing nonsense words and real words together

Patients with receptive aphasia may:
- Require a significant amount of extra time to understand verbal communication, especially if the speech is fast
- Have difficulty following radio or television news
- Interpret figurative speech (e.g., “It’s training cats and dogs.”) literally

Patients frequently have global aphasia, with various combinations of expressive and receptive difficulties.

Source: [315]  Table 22

Augmentative and alternative communication devices and modalities should be used to supplement speech [21].

Aphasia affects one-third of stroke survivors and is one of the most common stroke-associated communication deficits [21; 314].

The three types of aphasia are expressive, receptive, and global (Table 22) [315]. Patients with expressive aphasia have difficulties using words and sentences, whereas patients with receptive aphasia struggle to understand what others are communicating to them. Global aphasia is a combination of these two types. Aphasia is typically related to lesions on the left side of the brain, as the language center is located within this hemisphere in most individuals [316]. In many cases, aphasia (mild aphasia in particular) can be an elusive diagnosis because patients may [315]:
- Be able to carry on normal conversations in many settings
- Have trouble understanding only when sentences are long or complex
- Have trouble finding the words to express an idea or may say, “the word is right on the tip of my tongue”

A variety of treatment approaches for aphasia have been developed, but no conclusions can yet be made about the effectiveness of one treatment over another [21].

An additional challenge in assessment is that members of the rehabilitation team typically do not have a clear sense of the patient’s communication skills before the stroke. Lastly, reading and writing skills are usually more affected than oral communication.

Well-trained and organized rehabilitation teams can use alternative methods of communicating to mitigate the effects of cognitive and communication disorders. Ideally, these problems should be recognized and managed early. However, arriving at a diagnosis can be challenging. The speech and language pathologist on the rehabilitation team is best suited to evaluate the patient for cognitive/communication disorders. In some cases, problems are initially undetected or develop after the evaluation. Training the rehabilitation team to recognize symptoms of cognitive and communication deficits early (especially those that are subtle) and report findings to the speech and language pathologist can serve as a “safety net” for patients [21]. For proper diagnosis, the speech and language pathologist should also seek the help of the patient’s family to gain an understanding of the patient’s cognition and communication history.

Through interviews, conversation, structured observations and other formal tests, the speech and language pathologist comprehensively evaluates the individual’s cognition and communication skills in the areas of speech, expression, social communication, and reading/writing (Table 23) [21; 317].

If necessary, the speech and language pathologist formulates remediation strategies to accelerate the patient’s recovery of affected communication skills, development of compensatory techniques, or use of residual skills [21; 317]. In many cases, patients with stroke-induced attention deficits, visual neglect, memory deficits, executive function deficits, and problem-solving difficulties can be retrained or taught compensation techniques [318]. Strategies to enhance communication with the patient should be taught to the rehabilitation team as well as the family/caregivers [21]. Any interventions should be individually tailored and designed to target the overt communication deficit as well as any deficits that accompany or underlie the communication deficit, including attention, memory, and executive functions. The use of drugs to improve cognitive impairments is not well established [21].
### SCREENING TOOLS FOR DEPRESSION

<table>
<thead>
<tr>
<th>Evaluation Instrument</th>
<th>Time Required</th>
<th>Benefits</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>10 minutes</td>
<td>Widely used, easily administered, norms available, good for somatic symptoms</td>
<td>Less useful in elderly and in patients with aphasia or neglect, high rate of false-positive results, somatic items may not be due to depression</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression (CES-D) Scale</td>
<td>&lt;15 minutes</td>
<td>Easily administered, useful in older individuals, effective for screening in stroke population</td>
<td>Not appropriate for patients with aphasia</td>
</tr>
<tr>
<td>Geriatric Depression Scale (GDS)</td>
<td>10 minutes</td>
<td>Easy to use with older or cognitively impaired individuals, as well as with individuals with visual or physical problems or low motivation</td>
<td>High rates of false-negative results in minor depression</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>&lt;30 minutes</td>
<td>Observer rated, frequently used for patients who have had a stroke</td>
<td>Multiple versions compromise interobserver reliability</td>
</tr>
<tr>
<td>Folstein Mini-Mental State Examination</td>
<td>10 minutes</td>
<td>Widely used for screening</td>
<td>Several functions with summed score, may misclassify patients with aphasia</td>
</tr>
<tr>
<td>Patient Health Questionnaire-2 (PHQ-2)</td>
<td>15 minutes</td>
<td>Widely used for screening, easily administered</td>
<td>Poor specificity in detecting major depression</td>
</tr>
</tbody>
</table>

*Source: [321; 322; 323]*  
*Table 24*
Psychologic Status
Following a stroke, it is understandable that patients and their families experience intense emotions. In many cases, the staff’s kindness and helpfulness, familial support, and the passage of time allow patients and their families to deal with the grief and other feelings precipitated by the stroke without medication or psychologic therapy. However, approximately 33% of patients experience post-stroke depression, and other mood disorders also manifest in stroke survivors [1; 319; 320]. In general, psychologic conditions can have a significant impact on the success of rehabilitation. Thus, all patients should be thoroughly evaluated for psychologic disorders as early as possible and on an ongoing basis [21].

Detecting post-stroke depression can be particularly challenging, as symptoms often appear to be typical post-stroke symptoms or are subtle. Patients may experience fatigue, sleeping difficulties, loss of appetite, tearfulness, and feelings of hopelessness. They may refuse to participate in therapy [21]. Additionally, cognitive deficits may prevent the patient from recognizing or having the ability to communicate depressive symptoms. Patients with an acquired flat affect may “sound sad” or indifferent to their situation without having post-stroke depression. Although several screening tools for depression in the older population are available (Table 24), a single, universally accepted evaluation tool for post-stroke depression has not been developed. Because little research in this area is available and the condition is underdiagnosed by nonpsychiatric physicians, the diagnosis of post-stroke depression should be based on information from multiple sources, including medical evaluation, patient self-report, observation of patient behavior, patient history, and staff reports of changes in behavior and motivation.

The accompaniment of post-stroke depression with other psychologic disorders is not uncommon [21]. Therefore, the medical evaluation should also screen for other categories of psychiatric symptoms [21]. Generalized anxiety disorder, which affects 20% of survivors, often coexists with post-stroke depression [324]. Generalized anxiety disorder delays the recovery of the ability to carry out activities of daily living and negatively affects social functioning [21]. Additionally, up to 15% of stroke survivors have pseudobulbar affect, characterized by uncontrollable laughing/crying [21].

Both post-stroke depression and pseudobulbar affect respond well to selective serotonin reuptake inhibitors [325]. Although these drugs carry some risk, they are safe in most patients who have had a stroke. However, these medications should not be administered prophylactically [326; 327]. Although studies are limited, the use of cognitive-behavioral therapy techniques and brief supportive therapy in conjunction with medication may be beneficial to those with post-stroke depression and other neuropsychiatric sequelae of stroke [21].

EXERCISE PROGRAM
Physical inactivity that typically occurs following a stroke can exacerbate muscle weakness (through atrophy and changes in muscle fibers), fatigue, cardiovascular and metabolic deconditioning, and poor balance [328; 329]. These complications have been shown to slow physical and social recovery and hinder brain activation over time [330]. Comprehensive fitness training may offset these effects (Table 25) [328; 331; 332]. Moreover, exercise programs can benefit a stroke survivor by reducing recurrent stroke and cardiovascular risks; reducing the risk and severity of post-stroke osteoporosis, preventing injuries and falls; increasing fitness, strength, flexibility, and functional activities; and promoting socialization [21; 328; 333]. However, exercise is not without risks. Training programs should be tailored to the patient’s capabilities and conditions to promote safety and reduce musculoskeletal injuries [334; 335]. For some patients, stroke severity and coexisting conditions may render exercise inadvisable. For instance, silent coronary artery disease, especially in sedentary patients, increases the chance of exercise-induced cardiac death. Because up to 75% of stroke survivors have cardiac comorbidities, the AHA suggests that the medical evaluation for an exercise program should include a graded exercise test with ECG monitoring [328]. Thorough screening, customized exercise program design, monitoring, and patient education should be performed during rehabilitation to maximize benefits and safety.

As with any rehabilitation program, the degree of a patient’s cognitive and communicative deficits can affect an exercise program’s success. The Neurobehavioral Cognitive Status Examination is a brief screening tool that provides a rapid and sensitive measure of the patient’s cognitive function. However, it, and other brief mental status scales, cannot adequately assess executive skills and other higher-level cognitive functions [21]. Personalized, tailored counseling interventions have demonstrated mixed results in improving adherence to an exercise program, whereas physical activity counseling has resulted in greater physical activity at 9 and 52 weeks post-stroke [328]. The crucial elements of a successful physical activity counseling intervention have not been identified definitively [328]. Barriers that may need to be addressed include lack of familial support, depression, fatigue, social integration, and cultural issues [328].

The consequences of inactivity may be most noticeable in patients with hemiparesis or other gait deficits. More than 50% of stroke survivors require rehabilitation to regain a functional level of ambulation [336]. Effects of neural damage underlying gait impairment, spasticity, and poor muscle performance are significantly compounded by muscle weakness, a lack of fatigue resistance, and the increased energy demands of rehabilitation [328]. Patients with mild-to-moderate conditions can benefit from treadmill training with partial body weight support [328]. As the patient walks on a treadmill,
his or her body weight is supported by harnesses to facilitate walking at a comfortable speed. This training augments conventional gait rehabilitation therapies by increasing gait speed, muscle performance, and fatigue resistance; however, its effect on long-term walking outcomes requires further study [336; 337].

Incorporation of progressive resistance training increases the generalizability of the fitness program and may improve the ability to carry out activities of daily living [338]. Although there are no accepted guidelines, the AHA suggests more repetitions with reduced loads (10 to 15 repetitions rather than 8 to 12), similar to programs recommended for patients recovering from MI [328]. Additionally, at least one set of at least 8 to 10 exercises should involve the major muscle groups (arms, shoulders, chest, abdomen, back, hips, and legs).

As technology continues to advance, rehabilitation programs may become enhanced with new ways to engage stroke survivors in exercise [21]. A study of virtual reality training sessions was shown to improve arm and hand movement skills in two patients with chronic hemiparesis [339]. The approach was also able to provide individualized, progressive practice based on the patient’s level of movement ability and rate of improvement [339].

### TRANSLATIONS IN CARE AND REHABILITATION CONTINUITY

The transition from inpatient care to home after a stroke can be difficult for both patients and caregivers. Ongoing rehabilitation, profound or permanent disability, or discharge to a long-term care facility affects not only the transition in care but also the continuity of that care. To ensure medical and rehabilitation continuity for the patient through the rehabilitation process and into the home or community, the AHA/ASA recommend individualized discharge planning in the transition from hospital to home that includes comprehensive assessment of activities of daily living, instrumental activities of daily living, and mobility assessments and discussion of sexual issues (e.g., safety, changes in libido), recreational and leisure activities, and return to work ability and timeline, where appropriate [21]. Patients for whom the discharge living setting is evaluated should

### SUMMARY OF EXERCISE PROGRAM RECOMMENDATIONS FOR STROKE SURVIVORS

<table>
<thead>
<tr>
<th>Mode of Exercise</th>
<th>Major Goals</th>
<th>Intensity, Frequency, Duration&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor specificity in detecting major depression</td>
<td>Increase independence in activities of daily living</td>
<td>40% to 70% peak oxygen uptake; 40% to 70% heart rate reserve; 55% to 80% maximal heart rate; rating of perceived exertion (RPE) 11–14 (6–20 scale)</td>
</tr>
<tr>
<td></td>
<td>Increase walking speed/efficiency</td>
<td>3 to 5 days/week 20 to 60 min/session (or multiple 10-min sessions)</td>
</tr>
<tr>
<td></td>
<td>Improve tolerance for prolonged physical activity</td>
<td>Complement with pedometers to increase lifestyle physical activity</td>
</tr>
<tr>
<td></td>
<td>Reduce risk of cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduce motor impairment; improve cognition</td>
<td></td>
</tr>
<tr>
<td>Strength (e.g., circuit training, weight machines, free weights, isometric exercise)</td>
<td>Increase independence in activities of daily living</td>
<td>1–3 sets of 10–15 repetitions of 8–10 exercises involving the major muscle groups</td>
</tr>
<tr>
<td></td>
<td>Increase muscle strength and endurance</td>
<td>2 to 3 days/week, with resistance gradually increased over time as tolerance permits</td>
</tr>
<tr>
<td></td>
<td>Reduce cardiac demands during lifting/carrying objects by increasing muscular strength</td>
<td></td>
</tr>
<tr>
<td>Flexibility/stretching</td>
<td>Increase range of motion (ROM) of involved extremities</td>
<td>2 to 3 days/week (Before or after aerobic or strength training) Hold each stretch for 10 to 30 seconds</td>
</tr>
<tr>
<td></td>
<td>Prevent contractures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease risk of injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase activities of daily living</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular (coordination and balance activities)</td>
<td>Improve level of safety during activities of daily living</td>
<td>2 to 3 days/week (Consider performing on same day as strength activities)</td>
</tr>
<tr>
<td></td>
<td>Improve balance, skill reacquisition, quality of life, mobility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease fear of falling</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Recommended intensity, frequency, and duration of exercise depend on each individual patient’s level of fitness. Intermittent training sessions may be indicated during the initial weeks of rehabilitation.

be considered candidates for community- or home-based rehabilitation when feasible. Providers should consider alternative methods of communication and support (e.g., telephone, visits, telehealth, online support), particularly for patients who reside in rural settings [21].

Rehabilitation services provided in the community can improve cardiovascular health, decrease the risk of cardiovascular events, and increase short-term survival rates for stroke survivors [21]. Among the benefits associated with community- and home-based rehabilitation programs are reduced costs, decreased length of stay in hospitals or institutional settings, increased opportunities for involvement by patient and family/caregiver, and less stress for family/caregiver. Patient satisfaction also is generally higher.

SECONDARY PREVENTION: EVIDENCE-BASED RECOMMENDATIONS

When is the risk for recurrent stroke highest?

In the United States, approximately 23% of stroke incidences are recurrent [1]. Due to the high risk of recurrent stroke and its consequences, secondary ischemic stroke prevention tends to follow a risk-stratified model of disease management [340]. Treatment of at-risk patients’ conditions is typically aggressive, as inadequate management can have serious implications.

A patient’s risk for a recurrent stroke is highest during the first year; 14% of survivors have a recurrent stroke within 1 year after the initial cerebrovascular event, suggesting that secondary prevention is time-critical and should be initiated during the rehabilitation process [341]. After the first year, the chance of recurrent stroke decreases to 4% per year [340]. Because TIA is an important determinant of stroke, the AHA secondary prevention guidelines for patients with TIA tend to be as aggressive as those established for ischemic stroke [10]. The guidelines focus on controlling several important modifiable risk factors.

CONTROLLING RISK FACTORS

A major component of secondary prevention is the treatment of modifiable risk factors and the underlying cause of the stroke. For patients who have had an ischemic event, the results of large studies have suggested that addressing hypertension, diabetes, smoking, alcohol consumption, and physical activity can reduce the risk of recurrent stroke [109].

Hypertension

The results of meta-analyses have indicated that lowering blood pressure reduces the risk of stroke 30% to 40% [342; 343]. The findings of longitudinal studies suggest that treatment with antihypertensive medications in hypertensive and normotensive patients reduces the incidence of recurrent strokes, MI, and other vascular events [344]. In particular, diuretics or diuretics combined with ACE inhibitors (e.g., ramipril, perindopril) most significantly reduce the risk of recurrent ischemic stroke [10; 344]. However, lifestyle modifications that include weight loss; increased intake of fruits, vegetables, and low-fat dairy products; habitual aerobic physical activity; and limited alcohol consumption are crucial components of controlling blood pressure [122]. Although most studies address the prevention of additional ischemic strokes, hypertension management has also been shown to reduce the risk of recurrent hemorrhagic stroke and is included in guideline recommendations published by the AHA/ASA [10; 344].

AHA Recommendations

- Initiation of blood pressure therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established blood pressure ≥140/90 mm Hg. Initiation of therapy for patients with blood pressure <140/90 mm Hg is of uncertain benefit.
- Resumption of blood pressure therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days.
- Goals for target blood pressure level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg. For patients with a recent lacunar stroke, it might be reasonable to target an systolic pressure of <130 mm Hg.
- The choice of specific drugs and targets should be individualized on the basis of pharmacologic properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (e.g., extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, diabetes).
- The optimal drug regimen to achieve the recommended level of reductions is uncertain because direct comparisons between regimens are limited.
- Lifestyle modifications are an integral part of a patient’s antihypertensive therapy.

Diabetes

Diabetes is a well-documented independent risk factor for recurrent stroke [345; 346]. Aggressive control of hypertension in diabetic patients, with a lower target of 130/80 mm Hg, has been shown to reduce the risk of stroke as well as other cardiovascular events [122]. Including ACE inhibitors in the treatment regimen of patients with diabetes effectively lowers blood pressure, slows the progression of renal disease, and reduces albuminuria [10; 347].
AHA Recommendations

- After a TIA or ischemic stroke, all patients should probably be screened for diabetes with testing of fasting plasma glucose, glycated hemoglobin (HbA1c), or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate postevent period.

- Use of existing guidelines for glycemic control and blood pressure targets for patients with diabetes is recommended for patients who have had a stroke or TIA.

Cigarette Smoking

Smoking doubles the risk of stroke [348]. Its cessation eliminates the elevated risk after 5 years and reduces the overall risk of stroke-related hospitalization [10; 349; 350]. Exposure to secondhand smoke also appears to increase the risk of stroke [10; 351]. The most effective combination of therapies for smoking cessation is nicotine replacement, social support, and counseling [10; 352].

AHA Recommendations

- All patients with TIA or stroke who smoke should be strongly urged to quit and to avoid passive smoke. The use of smoking cessation programs and nicotine-replacement therapy should be considered.

- It is reasonable to advise patients after ischemic stroke or TIA to avoid environmental (passive) tobacco smoke.

Alcohol Consumption

The results of a meta-analysis suggest that the risk of stroke is increased 69% for individuals who have more than five drinks (with one drink defined as 12 ounces of beer, 4 ounces of wine, or 1.5 ounces of liquor) per day compared with nondrinkers [353].

AHA Recommendations

- Patients with ischemic stroke or TIA who drink heavily should be strongly encouraged to reduce or eliminate their alcohol consumption to lessen risk factors that increase the likelihood of recurrent stroke.

- Light-to-moderate amounts of alcohol consumption (up to 2 drinks per day for men; up to 1 drink per day for nonpregnant women) may be reasonable; however, nondrinkers should not be counseled to start drinking.

Physical Activity

Habitual exercise clearly prevents stroke [333]. In addition, a sedentary lifestyle impedes functional recovery and places patients at a higher risk for stroke recurrence.

AHA Recommendations

- After successful screening and completion of formal stroke rehabilitation, an individually tailored exercise program is indicated to enhance cardiorespiratory fitness and reduce risk of stroke recurrence.

- At least three to four sessions per week, 40 minutes per session, of moderate-to-vigorous-intensity aerobic physical exercise is reasonable to reduce stroke risk factors in eligible patients. Moderate-intensity exercise is sufficient to break a sweat or noticeably raise heart rate (e.g., walking briskly); vigorous-intensity exercise includes activities such as jogging.

- Patients who are able and willing to initiate increased physical activity should be referred to a comprehensive, behaviorally oriented program.

- Consider supervision by a healthcare professional (e.g., physical therapist) on initiation of an exercise regimen for individuals with disability after ischemic stroke.

MANAGING DISEASE

For patients who have large-artery atherosclerosis, the specific underlying condition should be managed. Similarly, identification and treatment of cardioembolic stroke sources (e.g., AF, cardiomyopathy, acute MI and left ventricular thrombus, valvular heart diseases) is recommended. Patients with ischemic stroke and a high-risk source of cardioembolism generally benefit from anticoagulant therapy.

Extracranial Carotid Artery Disease

Carotid artery revascularization is recommended by the AHA for certain patients with stenosis greater than 50% [10]. However, surgery is not beneficial for patients with stenosis of less than 50%.

AHA Recommendations

- Carotid endarterectomy (CEA) is recommended for all patients who had a recent TIA or an ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis if the morbidity/mortality risk is less than 6%.

- CEA is recommended for certain patients (based on age, gender, and comorbidities) who had a recent TIA or an ischemic stroke within the past 6 months and ipsilateral severe (50% to 69%) carotid artery stenosis if the morbidity/mortality risk is less than 6%.

- When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularization.
• Carotid artery stenting (CAS) is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is found to be reduced by more than 70% on noninvasive imaging or more than 50% on catheter angiography or noninvasive imaging with corroboration and the anticipated rate of perioperative stroke or death is less than 6%.

• It is reasonable to consider patient age in choosing between CAS and CEA. For patients older than 70 years of age, CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for perioperative complications (e.g., stroke, MI, death) and long-term risk for ipsilateral stroke.

• CAS may be considered for patients with symptomatic severe stenosis (greater than 70%) if the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or other specific circumstances exist (such as radiation-induced stenosis or restenosis after CEA). In this setting, CAS is reasonable when performed by operators with established perioperative stroke and mortality rates of less than 6%, similar to those observed in trials of CEA and CAS.

• For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of extracranial to intracranial bypass is considered investigational.

• Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke.

Intracranial Atherosclerosis

The rate of stroke recurrence for patients with symptomatic intracranial atherosclerosis is approximately 9% [10]. The findings of retrospective studies have suggested that the greatest rate of recurrence is found among patients with this condition who do not have a response to antithrombotic therapy [354]. Although the results of some studies have indicated that angioplasty or stenting should be considered for such patients, the usefulness of these surgical interventions is unknown and considered investigational [10].

AHA Recommendations

With regard to patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery:

• Aspirin 325 mg per day is recommended in preference to warfarin.

• The data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone.

• Long-term maintenance of blood pressure <140/90 mm Hg and high-intensity statin therapy are recommended.

• Angioplasty and/or stent placement is not recommended, given the low rate of stroke with medical management and the inherent periprocedural risk of endovascular treatment.

• Extracranial-intracranial bypass surgery is not recommended.

With regard to patients with stroke or TIA due to 70% to 99% stenosis of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable.

Atrial Fibrillation

The anticoagulant warfarin has a narrow therapeutic margin and numerous food and drug interactions, and these factors (which necessitate frequent INR testing and dose adjustment), combined with the associated significant bleeding risks, have led to the underutilization of this drug despite having been shown to prevent recurrent stroke substantially in patients with ischemic stroke or TIA and AF and despite the adoption of performance measures and guidelines advocating its use in these patients [10; 355; 356]. Easy-to-use alternative therapies are required and include dabigatran, rivaroxaban, and apixaban [357; 358; 359]. Significant adverse effects (i.e., serious, sometimes fatal bleeding, acute coronary events) have been associated with some of these agents, making their use inappropriate for some patients [360; 361]. However, a 2011 focused update on dabigatran published by the American College of Cardiology, the AHA, and the Heart Rhythm Society recommends this agent as a useful alternative to warfarin for select patients [362].

Between 35% to 45% of patients with stroke and AF have coexisting conditions that may have caused the stroke [363]. In many cases, both the AF and the other condition (usually stenosis) will require treatment [10].

AHA Recommendations

• For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (for approximately 30 days) for AF is reasonable within 6 months of the index event.

• For patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent, or permanent AF, anticoagulation with a vitamin K antagonist (VKA) (target INR: 2.5; range: 2.0 to 3.0) is recommended.
• VKA therapy, apixaban, and dabigatran are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.

• Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF.

• The combination of oral anticoagulation (i.e., warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement.

• For patients unable to take oral anticoagulants, aspirin alone (75 mg to 100 mg per day) is recommended. The combination of clopidogrel plus aspirin, compared with aspirin therapy alone, might be reasonable.

• For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurologic symptoms. In the presence of high risk for hemorrhagic conversion (i.e., large infarct, hemorrhagic transformation, uncontrolled hypertension, hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days.

• For patients with AF at high risk for stroke (i.e., stroke or TIA within 3 months; Cardiac failure, Hypertension, Age, Diabetes, Stroke system [CHADS2] score of 5 or 6; or mechanical or rheumatic valve disease) who require temporary interruption of oral anticoagulation, bridging therapy with a LMWH administered subcutaneously is reasonable.

Noncardioembolic Strokes and TIA

The use of certain antiplatelet therapies rather than oral anticoagulation for noncardioembolic ischemic strokes and TIA has been shown to reduce the overall risk of recurrent stroke and decrease the incidence of fatal recurrent strokes [10]. Clopidogrel is appropriate for patients who are allergic to aspirin or for patients in whom dipyridamole-associated headaches occur.

AHA Recommendation

Aspirin (50 mg to 325 mg per day) monotherapy, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, or clopidogrel 75 mg monotherapy are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.

CASE STUDY

Patient M is an active woman, 70 years of age, who lost consciousness and collapsed at home. Her daughter, who was visiting her at the time, did not witness the collapse but found her mother on the floor, awake, confused, and slightly short of breath. The daughter estimated that she called EMS within 5 minutes after the collapse, and EMS responded within 10 minutes. EMS evaluated Patient M, drew blood for a glucose level, and determined that she may have had a stroke. They notified the nearest designated comprehensive stroke center that they would be arriving with the patient within 15 minutes. Patient M’s daughter accompanied her.

The triage and transportation of an individual with suspected stroke should be similar to that for an individual with serious trauma, and treatment is recommended within 3 hours after the onset of stroke. Because of the limited time available for assessment and diagnosis before optimal treatment, the EMS dispatcher should notify EMS personnel immediately and coordinate transport of the individual to the closest emergency facility, preferably one that is a designated primary (or comprehensive) stroke care center.

On presentation in the emergency department, Patient M is immediately triaged. Because Patient M is still somewhat confused, her daughter is asked to provide information on the patient's history. The daughter reports that her mother had had an episode of sudden-onset numbness and tingling in the right limb, with slight confusion and slurred speech, 3 days previously. The episode lasted only 5 minutes, and Patient M had not called her primary care physician. Additional information provided by the daughter indicates that Patient M has been treated for hypertension for 10 years but notes that she is often not compliant with her antihypertensive medicine, a diuretic. The patient has never smoked, drinks occasionally, and is of normal weight.

Patient M has two significant risk factors for stroke; one is a long history of hypertension. More than two-thirds of individuals older than 65 years of age are hypertensive, and it is important for individuals with hypertension to have regular blood pressure screening and to maintain a blood pressure of less than 140/90 mm Hg. Antihypertension therapy has been found to reduce the incidence of stroke by 30% to 40%. Patient M’s noncompliance with her antihypertensive medicine likely includes her among the 65% of known hypertensive individuals in whom blood pressure is not controlled.
Patient M's previous episode of numbness, confusion, and slurred speech appears to be evidence of a TIA, another substantial risk factor for stroke. Research has shown that approximately 5% of patients will have an ischemic stroke within 7 days after a TIA. In addition, the risk of stroke within 7 days is doubled for patients with TIA who did not seek treatment. As is the case for many individuals who have a TIA, Patient M did not seek medical attention because the clinical symptoms resolved quickly. However, research findings indicate that urgent treatment should be provided for TIA, as early treatment for TIA and minor stroke has been shown to reduce the risk of early recurrent stroke by 80%.

On physical examination, Patient M's blood pressure is 150/95 mm Hg. She has pain in her left arm and a slight headache. There are slight carotid bruits on the right. She is assessed with use of the NIHSS and found to have left hemiparesis and left visual/spatial neglect. The results of laboratory tests, including a complete blood count, prothrombin time, serum electrolyte levels, cardiac biomarkers, and renal function studies, are all within normal limits. CT of the brain indicates a thrombus in a branch of the right internal carotid artery, with approximately 50% occlusion due to atherosclerosis. There is an area of infarction in the right anterior hemisphere. There is no evidence of a subarachnoid hemorrhage. The diagnosis is made 2 hours after Patient M's arrival in the emergency department. She is treated with intravenous rt-PA at a dose of 0.9 mg/kg, and aspirin antiplatelet therapy is started at an initial dose of 325 mg, 24 hours after thrombolytic therapy, and a maintenance dose of 75 mg per day.

Many of the patient’s symptoms, including her loss of consciousness, shortness of breath, pain, and headache, are nontraditional symptoms of stroke. Studies have demonstrated that nontraditional symptoms are more prevalent among women, often leading to a delay in the evaluation for stroke. EMS personnel and clinicians should be aware of the potential for nontraditional symptoms in women and carry out a diagnostic evaluation addressing a suspicion of stroke.

Patient M is eligible for thrombolytic therapy with rt-PA according to evidence-based guidelines developed by the AHA/ASA: her blood pressure is lower than 185/110 mm Hg, the onset of symptoms is less than 3 hours prior to the start of treatment, and the laboratory values are within normal limits. Antiplatelet therapy with aspirin 325 mg daily (versus anticoagulant therapy with warfarin) is recommended for treatment of patients with stroke or TIA due to intracranial atherosclerosis with 50% to 99% occlusion. Antiplatelet therapy is not recommended as an adjunctive therapy within 24 hours of thrombolytic therapy.

When Patient M’s condition is stabilized, her primary care physician and consultant neurologist provide a referral for stroke rehabilitation, and a multidisciplinary rehabilitation team is formed to assess her rehabilitative needs, recommend the proper rehabilitation setting, and develop a treatment strategy tailored to her specific needs that includes daily antiplatelet therapy. Patient M is again assessed with the NIHSS, and the score is 12. The patient’s cognitive and communication skills are intact on evaluation with the FIM, with the exception of the previously documented left visual/spatial neglect. The assessment also includes evaluation of the patient’s risk for complications. Because of her spatial neglect, she is screened with the Berg Balance Scale and the Stops Walking When Talking test. The score on the Berg Balance Scale is 43, and Patient M does stop walking to engage in conversation. Psychosocial assessment includes screening with the Center for Epidemiologic Studies Depression (CES-D) Scale, as well as review of the medical history and conversations with the patient and her children; no signs of depression are present.

Patient M’s score of 12 on the NIHSS falls within the range (6 to 15) that indicates she is likely to benefit from rehabilitation. Evaluating a stroke survivor’s risk of complications is an important component of the overall assessment, and among the most common complications are falls, deep vein thrombosis, pressure ulcers, swallowing dysfunction, bladder and bowel dysfunction, and depressive symptoms. In assessing the risk of complications, the Berg Balance Scale appears to be the most appropriate screen for patients who are likely to fall, and a score of less than 45 is associated with a likelihood of falling. The risk of a fall is also increased when a patient stops walking to talk, as Patient M did, during the Stops Talking When Walking test.

Screening for signs of depression is also essential, as depression affects approximately 33% of stroke survivors. Signs of depression are subtle and may be vague. Several screening tools are available, but there is no universally accepted tool for use in the post-stroke setting. The CES-D was chosen in this case because it is easy to administer, is useful in older individuals, and has been found to be effective for screening in the stroke population, except for individuals who have aphasia. The diagnosis of depression in stroke survivors should be based on sources in addition to a formal screening tool, such as a medical evaluation, patient self-report, observation of patient behavior, patient history, and staff reports of changes in behavior and motivation.

The rehabilitation team discusses the results of the assessment with Patient M’s daughter and son, both of whom live about 45 minutes away from the patient. Together, the team and the family members explore options to determine the best approach to rehabilitation. A decision is made for Patient M to be discharged to an inpatient stroke unit, and a rehabilitation program is developed. The nurse on the team discusses the program with Patient M and her children and explains the course of rehabilitation and the expectations. Rehabilitation will focus on an exercise program consisting of aerobic exercise, strength training, stretching, and coordination and balance activities.
Early initiation of rehabilitation is a particularly strong predictor of improved outcome, and rehabilitation in a stroke unit has been associated with improved quality of life, survival, and functional status at 5 years compared with a general healthcare facility. No studies have demonstrated the superiority of one rehabilitation setting over another, and the inpatient setting was chosen primarily to ensure consistent care, given how far away Patient M’s children live, and the limited support she otherwise has for healthcare needs. Decisions about the setting and program for rehabilitation should be shared with family members, and family and other caregivers should be provided with educational resources about the rehabilitation process.

The exercise program developed for Patient M is designed to help her regain the ability to independently carry out activities of daily living safely and to regain a functional level of ambulation. The benefits of an exercise program include increasing fitness, strength, and flexibility; improving function; preventing injuries and falls; and reducing the risk of recurrent stroke.

Patient M gradually resumes the ability to function independently, and after more than 2 weeks in the stroke rehabilitation unit, she is able to walk with the assistance of a cane. Before she is discharged to her home, the rehabilitation team provides instructions for exercises to continue at home and recommends moderate physical activity as a secondary prevention measure. The team also educates Patient M about the importance of maintaining a normal blood pressure through use of her antihypertension medication and lifestyle modifications. At a follow-up visit with her primary care physician at 3 months, Patient M’s blood pressure is 135/80 mm Hg, and she reports that she has been compliant with her antihypertension medicine and antiplatelet therapy and is functioning well at home.

CONCLUSION

Ischemic stroke remains a significant contributor to morbidity and mortality in the United States. Stroke is associated with several modifiable risk factors, such as smoking, diet, physical inactivity, and obesity, and clinicians should encourage their patients to adopt healthy lifestyle habits, especially patients who are at highest risk. In addition, primary prevention of stroke involves the appropriate management of many medical conditions, such as hypertension, diabetes, dyslipidemia, and AF.

Early diagnosis and appropriate immediate treatment are key to recovery of neurologic function and survival after stroke, making it imperative for both healthcare professionals and the general public to recognize the symptoms of stroke and TIAs, a substantial risk factor for stroke. Clinicians, as well as EMS staff and ED staff, should be skilled in identifying possible stroke-related symptoms, especially noting that women are more apt to have nontraditional symptoms of both TIAs and stroke. Efforts to educate the public about the importance of seeking medical care for TIAs and about the warning signs of stroke are also essential.

Several evidence-based guidelines are available for the primary and secondary prevention of ischemic stroke, as well as for early management and rehabilitation. Adherence to these guidelines will help to reduce the prevalence of stroke and to decrease the morbidity and mortality for individuals who have stroke. Thrombolytic therapy with rt-PA is the cornerstone of treatment for ischemic stroke, and the AHA now recommends beginning antiplatelet therapy with aspirin 24 to 48 hours after the onset of stroke. Other antiplatelet agents, as well as anticoagulant therapy, are not recommended on the basis of the evidence to date.

Outcomes after stroke are improved when care is provided in a comprehensive stroke center and when rehabilitative care is provided by a multidisciplinary team. Effective rehabilitation begins with a systematic evaluation of the patient to determine the need for specific rehabilitation services, the risk of complications, the patient’s physical functioning and level of cognition and communication, and the patient’s psychosocial status. This evaluation allows for the development of a rehabilitation program that addresses an individual patient’s specific needs, with tailored strategies for secondary prevention. When all available resources are utilized, prevention and appropriate treatment of stroke will result.
Optimizing Opioid Safety and Efficacy

Includes 15 Pharmacotherapeutic/Pharmacology Hours

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

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

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

1. Define terms often used in discussion of opioid prescribing.
2. Analyze common myths related to opioid analgesic safety.
3. Recall the epidemiology of pain.
4. Outline the individual and societal impact of undertreated pain.
5. Describe risk factors for and comorbidities of chronic pain.
6. Evaluate barriers to adequate pain care.
7. Describe the endogenous opioid system and effects of opioid analgesia.
8. Discuss the classification and properties of the various mu opioid receptor full agonist agents.
9. Compare and contrast other types of opioid analgesics and antagonists.
10. Identify pharmacokinetic factors in opioid analgesic response.
11. Outline the Centers for Disease Control and Prevention’s (CDC’s) guidelines for opioid prescribing for chronic pain.
12. Recall other general recommendations for safe and effective long-term opioid use for chronic pain.
13. Identify patient factors that affect opioid analgesic response.
14. Describe issues that affect choices regarding opioid selection, rotation, and titration.
15. Discuss the identification and appropriate treatment of opioid analgesic side effects.

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

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

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

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.
Opioid analgesics are approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate or severe pain. However, individual patients differ greatly in clinical response (e.g., efficacy, side effects, safety) to different opioid analgesics, and patient populations show widely variable response to the same opioid and dose [1]. These response variations make opioid prescribing challenging. Scientific advances have improved the understanding of how opioid response is conditioned by genetic factors, comorbidity, drug interactions, and opioid dynamics and/or kinetics. Informed health professionals are now better able to match patients with a selected treatment option to maximize safety, efficacy, and tolerability when prescribing opioid analgesics.

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

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

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

DEFINITIONS

What is pseudoaddiction?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**PRESCRIPTION OPIOID ANALGESIC FATAL OVERDOSE RATES**

There is a misperception that overdose deaths from legally obtained prescription opioid analgesics continue rising, perpetuating an opioid epidemic. In fact, prescription opioid analgesic overdose deaths have steadily declined since 2012. This perception is in part the result of CDC data indicating 18,893 prescription opioid overdose deaths in 2014, up sharply from 16,300 deaths in 2013 [26]. However, the 2014 increase was the result of a change in reporting standards. Starting in early 2014, the CDC began classifying all fentanyl overdoses as prescription opioid analgesic deaths, because laboratory tests were unable to distinguish clandestine from pharmaceutical fentanyl [27]. Also in 2014, there was an influx of fentanyl into the illicit opioid market, largely from Mexico and often sold as heroin or oxycodone. This resulted in a significant increase in fentanyl overdose deaths.

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

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

**PRESCRIPTION OPIOID ANALGESIC PRESCRIBING RATES**

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

In late 2010, oxycodone ER was introduced as an abuse-deterrent formulation (ADF) to reduce abuse and overdose. After this product was released, there was a 39% prescribing decrease between 2010 and late 2012 [32]. In addition, oxycodone “doctor shopping” decreased 50% and overdose fatalities reported to the manufacturer decreased 65% [33]. Though it is still early, hydrocodone/acetaminophen combination product prescribing appears to be decreasing after it was rescheduled as a Schedule II controlled substance in 2014. After one year, there were 26.3 million fewer (-22%) prescriptions and 1.1 billion fewer (-16%) dispensed tablets [34]. Decreased hydrocodone/acetaminophen prescribing by primary care physicians during this period is also notable, with a 33% decrease from 2011 (144.5 million) to 2015 (97 million) [29; 35; 36].

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

**PRESCRIPTION OPIOID ANALGESICS AND HEROIN**

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

**EVIDENCE OF LONG-TERM OPIOID BENEFIT FOR CHRONIC PAIN**

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

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

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

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

**PRIMARY CONTRIBUTORS TO OPIOID ANALGESIC-RELATED FATALITIES**

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

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

**Methadone**

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

**Benzodiazepines**

In 2011, benzodiazepines were associated with what percentage of opioid analgesic fatalities?

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

**Alcohol**

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

**Prescriber Knowledge Deficits**

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

**EPIDEMIOLOGY OF PAIN**

**What is the most common anatomic location of pain in U.S. adults?**

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

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

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

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

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

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

CONSEQUENCES OF UNTREATED OR UNDERTREATED CHRONIC PAIN

What are the top two medical causes of suicide?

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

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

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

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

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

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

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

RISK FACTORS FOR CHRONIC PAIN

PSYCHOSOCIAL RISK FACTORS

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

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

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

Coping and Social Support

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

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

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

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

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

MEDICAL RISK FACTORS

Obesity

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

Past Surgeries

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

COMMON COMORBID CONDITIONS

Major Depressive Disorder and Anxiety Disorders

What is the single most important and prevalent chronic pain comorbidity?

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

Sleep Impairment

Disturbed phase 2/3 and rapid eye movement sleep decreases pain threshold, impairs immune function, decreases insulin sensitivity, and undermines pain treatment response. Roughly 50% to 70% of patients with chronic pain experience sleep disturbance, and pain, sleep, and mood are connected and mutually reinforcing—sleep disturbance exacerbates pain, and pain disrupts sleep. The bidirectional association results from lowered pain threshold, promotion of hyperalgesia, and increased release of inflammatory cytokines [8; 93]. Sleep recovery has an analgesic effect [85].
Medical Comorbidity
The presence of chronic pain is substantially elevated in patients with chronic respiratory disease, cardiovascular disease, or neurologic, metabolic, endocrine, and gastrointestinal (GI) disorders [94]. Among multi-morbid primary care patients older than 65 years of age, chronic low back pain was the most prevalent pain condition, significantly associated with cardiometabolic conditions in both sexes and depression in women [95].

**BARRIERS TO ADEQUATE PAIN CARE**

What groups are at risk for unrelieved pain due to stigma and bias?

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

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

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

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

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

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

**THE ENDOGENOUS OPIOID SYSTEM AND OPIOID ANALGESIC MECHANISMS**

What are the three primary opioid receptor types?

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

Naturally occurring opioid compounds are produced in plants (e.g., opium, morphine) and in the body (the endogenous opioids) [104]. Endogenous opioids are peptides that bind opioid receptors, function as neurotransmitters, and help regulate analgesia, hormone secretion, thermoregulation, and cardiovascular function. The three primary endogenous opioid peptide families are the endorphins, enkephalins, and dynorphins, and the three primary opioid receptor types are mu, kappa, and delta [105; 106]. A quick overview of this complex pain modulation system is helpful in understanding how opioid analgesics work.
ENDOGENOUS OPIOID PEPTIDES
Endogenous opioid peptides are neurotransmitter molecules in the opioid receptor complex that produce specific physiologic effects determined by neuronal distributions of the activated opioid receptor type [107]. The endogenous opioid peptides are cleaved from the pro-hormone precursors proenkephalin, pro-opiomelanocortin, and prodynorphin. The endogenous delta opioid receptor peptides are met-enkephalin and leu-enkephalin, cleaved from proenkephalin. Prodynorphin gives rise to kappa opioid receptor agonists dynorphin A and B. Pro-opiomelanocortin encodes the peptide beta-endorphin, which has agonist activity at all three classical opioid receptors. Some endogenous opioid ligands lack specificity for opioid receptor subtypes, such as beta-endorphin and the enkephalins [108; 109].

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

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

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

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

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

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

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

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

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

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

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

Spinal Level

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

Supraspinal Level

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

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

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

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

Neuropathic Pain

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

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

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

OPIOID ANALGESIC PHARMACOLOGY

Opioids have been a mainstay of pain treatment for thousands of years and remain so today. The opium poppy, Papaver somniferum, is the oldest and most prevalent source of opium and opioid analgesics. The opium poppy was grown in the Mediterranean region at least as early as 5000 B.C.E. and has since been cultivated in a number of regions throughout the world.
The first historical medical reference to opium dates back to the 3rd century B.C.E. by Arab physicians experienced in its therapeutic uses. In 1806, Friedrich Sertürner reported the isolation of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams [110]. Sertürner also published the first report of morphine toxicity in 1817. In this account, he discussed his experimentation of administering the alkaloid to himself, three young boys, three dogs, and a mouse. One of the dogs died, and the effects of morphine on Sertürner and his three young volunteers were described as “near-fatal.” In the 1850s, the first recorded morphine overdose fatality was reported by Alexander Wood when performing one of the first morphine injections on his wife, who subsequently died of respiratory depression [120].

Raw opium contains numerous alkaloids, but only morphine, codeine, thebaine, and papaverine have an identified use in medicine. Because the synthesis of morphine is difficult, the opium poppy plant remains the primary source of morphine [105]. Thebaine is a minor constituent of opium that chemically resembles morphine and codeine but produces a

<table>
<thead>
<tr>
<th>Category</th>
<th>Example Drugs</th>
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<tbody>
<tr>
<td>Analgesic Potency</td>
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<tr>
<td>Weak</td>
<td>Codeine</td>
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<tr>
<td>Intermediate</td>
<td>Buprenorphine</td>
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<td></td>
<td>Hydrocodone</td>
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<td></td>
<td>Pentazocine</td>
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<td></td>
<td>Oxycodone</td>
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<td></td>
<td>Butorphanol</td>
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<td></td>
<td>Nalbuphine</td>
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<tr>
<td>Strong</td>
<td>Morphine</td>
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<td></td>
<td>Oxycodone</td>
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<td>Hydromorphone</td>
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<td>Oxymorphone</td>
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<td>Levorphanol</td>
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<td></td>
<td>Fentanyl and analogs</td>
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<td></td>
<td>Methadone</td>
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<td></td>
<td>Meperidine</td>
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<tr>
<td>Chemical Classa</td>
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<tr>
<td>Phenanthrenes</td>
<td>Morphine</td>
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<td></td>
<td>Codeine</td>
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<td>Oxycodone</td>
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<td>Hydromorphone</td>
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<td>Levorphanol</td>
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<td>Oxymorphone</td>
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<tr>
<td>Benzomorphanes</td>
<td>Pentazocine</td>
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<tr>
<td>Phenylpiperidines</td>
<td>Meperidine</td>
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<tr>
<td>Diphenylheptanes</td>
<td>Methadone</td>
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<tr>
<td>Phenylpropyl amines</td>
<td>Tramadol</td>
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<td></td>
<td>Tapentadol</td>
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<tr>
<td>Functional Activityb</td>
<td></td>
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<tr>
<td>Full agonist</td>
<td>Morphine</td>
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<td></td>
<td>Codeine</td>
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<td>Hydromorphone</td>
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<td>Levorphanol</td>
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<td>Methadone</td>
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<td>Fentanyl and analogs</td>
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<td>Meperidine</td>
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<td>Tramadol</td>
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<td></td>
<td>Tapentadol</td>
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<tr>
<td>Partial agonist</td>
<td>Buprenorphine</td>
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<tr>
<td>Mixed agonist/antagonist</td>
<td>Pentazocine</td>
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<td></td>
<td>Butorphanol</td>
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<tr>
<td>Antagonist</td>
<td>Naloxone</td>
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<tr>
<td></td>
<td>Alvimopan</td>
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<td></td>
<td>Naltrexone</td>
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<tr>
<td></td>
<td>Methyl naltrexone</td>
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</tbody>
</table>

'^Under each class, the first listed opioid is the prototypical agent
'^At the mu opioid receptor

Source: [16; 104]  
Table 1
Thebaine is not used medicinally but is converted into oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, and buprenorphine [122].

The numerous synthetic derivatives of morphine and thebaine are produced by relatively simple modifications of the parent molecule. For example, morphine is transformed into codeine by methyl substitution on the phenolic hydroxyl group and into diacetylmorphine by acetylation at the 3 and 6 positions (to produce heroin). Structural alteration of opioid molecules has been performed with the goal of producing an opioid molecule with greater opioid receptor affinity, to alter drug activity from agonist to antagonist, to change lipid solubility, and to increase resistance to metabolic breakdown.

Although numerous opioid analgesics have been developed with clinical effects similar to morphine, morphine remains the criterion standard by which the analgesic efficacy of new opioids is measured [105].

There are several ways to classify the various opioids (Table 1). The traditional approach to opioid classification is grouping by analgesic potency into strong, intermediate, and weak subgroups [16]. Opioids may also be grouped into chemical classes, including phenanthrenes (the prototypical opioids), benzomorphans, phenylpiperidines, diphenylheptanes, and phenylpropyl amines [104]. A more pharmacologically and clinically relevant classification approach is grouping by functional interaction as mu receptor agonists,

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**Table 2**

<table>
<thead>
<tr>
<th>Opioid Analgesic</th>
<th>Opioid Receptor</th>
<th>Other Receptors</th>
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<tbody>
<tr>
<td></td>
<td>Mu</td>
<td>Kappa</td>
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<tr>
<td><strong>Agonists</strong></td>
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<tr>
<td>Codeine</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Morphine</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Fentanyl</td>
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<tr>
<td>Hydromorphone</td>
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<td>Oxycodone</td>
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<td>+</td>
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<tr>
<td>Oxymorphone</td>
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<tr>
<td>Methadone</td>
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<tr>
<td>Meperidine</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Levorphanol</td>
<td>+++</td>
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<tr>
<td>Tapentadol</td>
<td>+</td>
<td></td>
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<tr>
<td>Tramadol</td>
<td>+</td>
<td></td>
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<tr>
<td><strong>Partial agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>+</td>
<td></td>
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<tr>
<td><strong>Agonist-antagonists</strong></td>
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<tr>
<td>Pentazocine</td>
<td>-</td>
<td>++</td>
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<td>Nalbuphine</td>
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<td>+</td>
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<tr>
<td>Butorphanol</td>
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<tr>
<td><strong>Antagonist</strong></td>
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<td>Naltrexone</td>
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<td>+  = Low/moderate agonist</td>
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<td>+++ = High-affinity agonist</td>
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<td></td>
<td>--- = High-affinity antagonist</td>
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<tr>
<td>5-HT = serotonin, NE = norepinephrine, NMDA = N-methyl-D-aspartate.</td>
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</table>

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stimulant, rather than calming, effect. Thebaine is not used medicinally but is converted into oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, and buprenorphine [122].
partial agonists, mixed agonists-antagonists, or antagonists. For the purposes of this course, currently available opioids will be grouped and discussed by functional class.

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

**MU OPIOID RECEPTOR FULL AGONISTS**

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

**Morphine**

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

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

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

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

**Hydromorphone**

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

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

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

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

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

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

Oxycodone

How does oxycodone differ from morphine?

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

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

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

Oxymorphone

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

Oxymorphone is a semisynthetic derivative of the parent compound morphine and has a high affinity for the mu opioid receptor and negligible interaction with kappa and delta opioid receptors [134]. The potency is roughly 1.2 times that of morphine, but with less sedative effects [16]. Oxymorphone possesses less protein binding (10% to 12%) than morphine (30% to 35%) and oxycodone (45%), and its highly lipophilic properties provide ease in blood-brain barrier penetration [129]. The oral bioavailability of oxymorphone is approximately 10%, the lowest of the full agonists. In healthy volunteers, the half-life ranges from 7.2 to 9.4 hours, longer than that of morphine, hydromorphone, and oxycodone. Oxymorphone SA tablets may be given at six-hour intervals, whereas the ER formulation is dosed twice daily. Steady-state conditions are achieved after three to four days. Oxymorphone is subject to hepatic first-pass effects and is excreted by the kidneys. As such, this agent has a prolonged half-life and accumulates in patients with renal failure. In patients with hepatic insufficiency, increasing the dosing interval is recommended [103].

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

Hydrocodone

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

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

**Methadone**

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

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

Methadone is available in racemic form with a 50:50 mixture of two enantiomers: a levo-(R)-enantiomer and a dextro-(S)-enantiomer. The 1(R)-enantiomer produces opioid analgesia as a mu opioid receptor agonist, while the d(S)-enantiomer functions as an N-methyl-D-aspartate (NMDA) receptor antagonist and reuptake inhibitor of serotonin and norepinephrine. These pharmacologic properties expand indications for its use beyond those of most other mu receptor agonists [117]. Methadone produces analgesia similar to morphine, with greater potency. Analgesia is produced by activity as a mu, delta, and kappa opioid receptor agonist, NMDA receptor antagonist, and norepinephrine and serotonin reuptake inhibitor. The NMDA receptor antagonist potency of levorphanol is equivalent to ketamine and superior to methadone [49]. Single-dose analgesic duration is 6 to 8 hours, and the elimination half-life is 11 hours. This increases the potential for drug accumulation, and patients should be observed for toxicity during the initial two to five days. Roughly 50% of oral levorphanol clears first-pass metabolism and is bioavailable [140]. Initiate dosing every four hours, and every six to eight hours when steady state is reached (after one to two weeks) [15; 140].

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

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

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

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

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

Tramadol

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

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

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

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

Tapentadol

Tapentadol (Nucynta) is a novel synthetic opioid structurally related to tramadol that was approved in 2009. It was intentionally designed to overcome the barriers to efficacy associated with tramadol, such as the potential risk for serotonin syndrome [49]. Tapentadol has 18 times less affinity for mu opioid receptor than morphine and is 5 times less potent than oxycodone (i.e., 50 mg tapentadol is equivalent to 10 mg oxycodone) [146; 147]. Tapentadol has an oral bioavailability of 32%, and plasma protein binding is 20%. Time to maximum serum concentration is achieved in 1.25 to 1.5 hours, and the half-life is 24 hours [103].
Tapentadol has no active metabolites and primarily undergoes hepatic metabolism via phase II conjugation. Tapentadol selectively inhibits norepinephrine reuptake with affinity and potency comparable to venlafaxine, which increases efficacy and avoids the potential risk for serotonin syndrome. In a study of patients with chronic pain receiving tapentadol for up to two years, 88% did not experience opioid withdrawal symptoms on abrupt withdrawal and symptoms were mild-to-moderate among those who did [148].

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

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

**Meperidine**

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

The short analgesic duration (2.5 to 3.5 hours) makes meperidine impractical for persistent pain, although it is a useful analgesic in labor and delivery and uniquely effective in treating post-operative shivering. Accumulation of the neurotoxic metabolite normeperidine contraindicates its use for longer than 48 hours or at doses of 600 mg or greater over 24 hours in any context. Normeperidine accumulation is especially likely in patients with impaired renal function. The neuroexcitatory properties of this metabolite can cause tremors, muscle twitches, delirium, or seizures; multifocal myoclonus develops before seizures and can serve as a warning sign. Normeperidine toxicity is not reversible with naloxone.

Administration of meperidine to patients receiving MAOIs can lead to profound and possibly fatal autonomic instability [16; 110; 123]. Clinical use of meperidine has declined into virtual disuse in recent years [115].

**Propoxyphene**

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

**Levo-Alpha-Acetylmethadol**

Levo-alpha-acetylmethadol (LAAM) is a synthetic mu opioid receptor agonist closely related to methadone, but with a longer duration of action (48 to 72 hours). LAAM was originally developed by German chemists in 1948 and as early as 1952 was identified as an agent that could prevent opioid withdrawal symptoms for more than 72 hours. In 1993, the FDA approved LAAM for the treatment of opioid addiction, with the intent to build on the strengths and improve on the drawbacks of methadone [122; 152]. However, concerns over cardiovascular toxicity and subsequent under-utilization led to its withdrawal from the market in 2004 by the manufacturer, and LAAM is no longer commercially available in the United States [138].
The mu opioid receptor-binding kinetics of buprenorphine are unique. Receptor affinity is high, but buprenorphine associates and dissociates slowly (30 and 166 minutes, respectively) and incompletely (50%). This receptor saturation is particularly important with buprenorphine, because its high affinity and robust binding capacity make displacement by naloxone difficult or impossible. The relative resistance to naloxone antagonism requires higher doses for successful reversal [49].

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

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

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

**MIXED AGONIST/ANTAGONIST OPIOIDS**

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

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

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

**Pentazocine**

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

**Butorphanol**

Butorphanol (Stadol) is a morphinan congener with a pharmacologic profile similar to pentazocine. It is more suitable for acute than chronic pain. Side effects of drowsiness, weakness, sweating, sensation of floating, nausea, and psychotic-like effects are less frequent than with pentazocine. Physical dependence can develop from regular use [105]. Butorphanol was initially available as an injectable formulation (Stadol). More recently, a nasal spray (Stadol NS) became available, and the ensuing abuse and diversion of this product led to its designation as a Schedule IV controlled substance [122].
Butorphanol is a mu opioid receptor antagonist and kappa opioid receptor agonist, and the opioid receptor affinity ratio of 1:25:4 for mu, kappa, and delta receptors, respectively, indicates greater delta than mu opioid receptor affinity [158]. With parenteral administration, butorphanol has analgesic potency five to eight times greater than morphine. It has a rapid onset, with peak analgesia within 1 hour, plasma half-life of 2 to 3 hours, and elimination half-life of 4.5 to 5 hours. With oral administration, bioavailability is 17% that of a comparable IV dose. The intranasal formulation is commonly used in the treatment of migraine headache. The IV formulation is effective in moderate-to-severe pain and is typically used for postoperative pain and pain control during labor. With analgesia mediated by kappa and not mu receptor activation, butorphanol may be an effective analgesic option in patients with history of opioid use disorder [110]. At a dose of 10 mg IM, butorphanol induces respiratory depression similar to a comparable morphine dose, but the level of depression does not increase with dose escalation due to the ceiling effect [159; 160].

Nalbuphine

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

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

**OPIOID ANTAGONISTS**

**Opioid antagonists are FDA-approved for what indications?**

A fourth group of opioids, opioid antagonists, bind and inactivate opioid receptors. Naltrexone and naloxone have traditionally been used to reverse potentially fatal overdose from opioid receptor agonists such as morphine or heroin. Opioid agonist molecules on mu opioid receptor are displaced, agonist effects on mu opioid receptor are abruptly halted, and opioid-dependent patients rapidly experience full alertness, analgesic loss, and opioid withdrawal [164]. Clinical trials with low-dose naltrexone have found unexpected and paradoxical enhancement rather than blockade of analgesia when co-administered with morphine and other opioid agonists in postoperative pain or severe intractable pain. Other evidence suggests analgesic efficacy as monotherapy in Crohn disease, irritable bowel syndrome, and fibromyalgia [165]. These findings led to the development and introduction of the peripheral-acting mu receptor antagonists alvimopan, methylnaltrexone, and naloxegol for severe opioid-induced constipation [166; 167].

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

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

**Naloxone**

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

**Naltrexone**

Naltrexone (ReVia, Depade) has activity comparable to naloxone but with a longer duration of action and higher oral bioavailability (40%) [125]. Following oral administration of naltrexone, the peak plasma concentration occurs at 1 to 2 hours, the duration of action is up to 24 hours, and the half-life is up to 14 hours [165].
Methylnaltrexone
Methylnaltrexone bromide (Relistor) is a naltrexone derivative with high peripheral opioid receptor selectivity resulting from low lipid solubility and poor blood-brain barrier penetration into the CNS. Methylnaltrexone is indicated for opioid-induced constipation refractory to conventional therapies in patients with advanced illness receiving palliative care. It binds and antagonizes mu opioid receptors in the GI tract. With little oral bioavailability, methylnaltrexone is administered by subcutaneous injection [171].

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

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

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

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

ABSORPTION AND DISTRIBUTION
Most opioids, including morphine, oxycodone, hydromorphone, methadone, tramadol, tapentadol, fentanyl, sufentanil, buprenorphine, and codeine, possess high GI permeability and are completely absorbed from the GI tract following oral administration. However, fentanyl and buprenorphine, due to extensive hepatic first-pass metabolism, have very low oral bioavailability, rendering their oral use ineffective [1]. (This differs from sublingual and buccal administration.) To produce analgesic action in the CNS after absorption, opioids must penetrate the blood-brain barrier; highly lipophilic opioids possess a more rapid onset due to greater ease of blood-brain barrier transport [1]. The basis for the widely variable duration of effect among opioids is complex, not always explainable by the rate of plasma clearance and terminal half-life. For example, at equivalent analgesic doses, morphine produces longer analgesia than fentanyl but has a shorter half-life. This may be explained by morphine's relatively low lipid solubility and slower diffusion out of CNS tissue [104].

METABOLISM AND ELIMINATION
Many drugs, including opioids, must undergo biotransformation to be readily eliminated from the body. Opioid analgesic molecules that produce CNS effects must be lipophilic to cross cell membranes in the blood-brain barrier, and metabolism is performed to convert lipophilic opioids into hydrophilic metabolic products for elimination. This is achieved through hepatic enzymes. The metabolic process ends when the opioid byproducts are sufficiently hydrophilic for urinary excretion [174]. Medications can be substrates at multiple cytochrome (CYP) isoenzymes, inducing one while inhibiting another.
Hepatic enzymes facilitate two forms of metabolism: phase I and phase II [174]. Phase I metabolism consists of modification of the drug molecular structure through chemical reactions such as oxidation, reduction, or hydrolysis. The predominant catalysts for phase I drug metabolism are found in the CYP450 enzymatic superfamily [130]. Phase I metabolism of some opioids produces active analgesic metabolites, as with conversions of codeine into morphine, hydrocodone into hydromorphone, and tramadol into O-desmethyltramadol [175]. The CYP system is comprised of more than 50 isoenzymes, but more than 90% of opioid metabolism involves the 3A4, 2D6, or 2C9 isoenzymes [145].

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

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

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

ADVERSE DRUG INTERACTIONS

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

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

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

Morphine

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

Codeine

Analgesia requires the conversion of roughly 10% of codeine via CYP2D6 into morphine, which is then converted to M3G and M6G by glucuronidation. Codeine is also metabolized by CYP3A4 to the inactive metabolite norcodeine [103]. CYP3A4 inducers speed the conversion of codeine to the inactive norcodeine and decrease conversion to morphine. Although codeine undergoes phase II metabolism to codeine-6-glucuronide, UGT2B7 inhibition or induction does not result in codeine adverse drug interactions [130].

Oxycodone

Oxycodone undergoes a complex hepatic metabolic process. CYP2D6 catalyzes oxycodone to oxymorphine (10% of metabolites), and UGT2B7 rapidly inactivates oxymorphine by conversion to oxymorphine-6-glucuronide; the analgesic contribution of oxymorphine is minimal. CYP3A4 catalyzes oxycodone to noroxycodone, the primary (90%), but inactive, metabolite. In addition, CYP2D6 converts noroxycodone to noroxymorphine. These metabolites have varying mu receptor potencies and affinities [99; 176].
Many adverse drug interactions have been reported between oxycodone and other CYP3A4 substrates. CYP3A4 inhibitors can substantially increase oxycodone serum levels, reflected in the “black box warning” to not use oxycodone with CYP3A4 inhibitors due to the elevated risk of serious adverse effects, including potentially fatal respiratory depression. CYP3A4 inhibitors may elevate plasma oxymorphone to increase opioid effects, while CYP3A4 inducers may substantially decrease oxycodone (and potentially oxymorphone) serum levels, leading to analgesic failure. In general, concurrent use of oxycodone with CYP3A4 inhibitors or inducers is likely to result in adverse drug interactions.

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

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

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

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

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

Methadone
What pharmacologic property of methadone increases the risk of toxicity?

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

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

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

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

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

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

Toxicity risks of methadone can be mitigated with gradual titration and dose adjustment. Opioid-naïve patients should be started at a low dose, usually 2.5 mg every eight hours. The dose may be titrated by 10% to 20% increments, not less than three to four days apart except under inpatient or closely supervised settings. Once-daily methadone is ineffective for chronic pain; dosing at least every eight hours is required.
When rotating patients from another opioid to methadone, it is important to consult the latest product information for dose equivalence and conversion; do not use published equianalgesic tables [103; 175]. 

The increasing use of methadone treatment for chronic pain has led to high rates of fatal toxicity and concerns over its safe and appropriate use as an analgesic. Clinical practice guidelines have been developed to promote safer methadone prescribing for chronic pain [178]. The first step is careful patient assessment. From a thorough history, medical records review, physical examination, and possibly electrocardiography, stratify patients on risk for substance abuse, adverse reactions with other prescribed medications, and arrhythmia. Alternative opioids should be used in patients at high risk of QTc interval prolongation. If methadone is used, a low starting dose and slow titration are necessary, as are diligent monitoring and patient follow-up. All patients should receive education on methadone safety.

Levorphanol

No adverse interactions with CYP450 substrates have been noted with levorphanol. Interactions at glucuronidation enzyme sites are theoretically possible, but none have been substantiated [16].

Tramadol

CYP2D6 and CYP3A4 account for more than 70% of tramadol metabolism. CYP2D6 inhibitors reduce tramadol analgesia and concurrent use should be avoided. CYP3A4 inhibitors may increase exposure to tramadol, and their use should be avoided. CYP3A4 inducers can reduce plasma tramadol, and patients requiring CYP3A4-inducing medications should be monitored for inadequate analgesia [130].

Tapentadol

Clinically relevant drug interactions are unlikely with tapentadol [179].

PHARMACODYNAMIC DRUG-DRUG INTERACTIONS

Pharmacodynamic drug-drug interactions are possible with all opioid analgesics. Drugs with hypoventilatory or CNS depressant properties, such as benzodiazepines, sedative-hypnotics, and antihistamines, can act synergistically with opioids to increase sedation and risk of potentially lethal respiratory depression [174].

Some pharmacodynamic adverse drug interactions with opioids can be clinically advantageous. For instance, ibuprofen co-administration with hydrocodone or oxycodone potentiates the analgesia of the opioids in laboratory-induced moderate-to-severe pain, producing a 2.5-fold and 4.6-fold shift in the effective dose, respectively. Aspirin and ketorolac have no effect on hydrocodone analgesia, and ibuprofen has no effect on fentanyl or morphine analgesia [180].

CDC GUIDELINES FOR OPIOID PRESCRIBING IN CHRONIC PAIN

In 2016, the CDC published opioid prescribing guidelines for chronic pain by primary care physicians, not applicable to active cancer treatment, palliative care, or end-of-life care [42]. The CDC guidelines are expected to have a significant effect on opioid prescribing. Release of the draft and final CDC guidelines provoked controversy and alarm from pain professionals and pain patient advocacy groups and serious concerns by the American Medical Association (AMA), the American Cancer Society (ACS), the American Academy of Pain Medicine (AAPM), and other prominent organizations [56; 57].

The public health issue of opioid analgesics is complex; the ideal is balancing opioid control and access. Overemphasis on access in the 1990s and early 2000s led to over-prescribing, increased addiction, and overdose; now, excessive control has the potential to lead to restricted access and undertreated and untreated chronic pain. The well-intentioned but narrow public health focus on curtailing opioid prescribing and patient access is consistent with the CDC's orientation and agenda, but it may not be the most helpful approach in patient care [5; 57].

The CDC guidelines were based on a systematic review that rejected opioid studies greater than one year in duration without randomized controlled design. This made the pool of evaluable studies essentially unchanged from a 2009 systematic review of opioid analgesics, but conclusions of the 2009 review markedly differed from the 2016 review [43].

It is also important to note that the NPS, a comprehensive action plan to decrease the burden of undertreated pain, was also released in 2016. The NPS was developed in response to the 2011 IOM mandate for system-wide transformation of pain care but was largely overshadowed by the CDC guideline release [58].

The following recommendations are reprinted from the CDC guidelines and represent a simple approach to opioid prescribing for chronic pain. While this may be helpful for primary care providers, it does not take into account many of the nuances of opioid use for chronic pain, including patient-specific response, side effects, comorbidities, and pharmacokinetics and pharmacodynamics. These issues will be discussed in detail later in this course.
WHEN TO INITIATE OR CONTINUE OPIOIDS

According to the CDC guidelines for opioid prescribing in chronic pain, what should clinicians do before starting opioid therapy?

Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain [42]. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Before starting opioid therapy for chronic pain, clinicians should, for all patients:

- Establish treatment goals for pain and function.
- Consider how therapy will be discontinued if benefits do not outweigh risks.
- Continue opioid therapy only if clinically meaningful improvement in pain and function outweighs safety risks.

Before starting opioid therapy and periodically during the course of treatment, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

The American Society of Interventional Pain Physicians asserts that a robust agreement that is followed by all parties is essential in initiating and maintaining opioid therapy, as such agreements reduce overuse, misuse, abuse, and diversion.


**Level of Evidence:** Fair (Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.)

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

When starting opioid therapy for chronic pain, clinicians should prescribe SA instead of ER or long-acting (LA) opioid formulations. When opioids are started, clinicians should prescribe the lowest effective dosage but use caution at any dosage. It is important to carefully reassess evidence of benefits and risks when increasing dosage to ≥50 mg MED/day. Prescribers should avoid or carefully justify increasing the dosage to ≥90 mg MED/day.

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids. It is important to prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

Clinicians should evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should also evaluate benefits and harms of continued therapy with patients at least every three months. If benefits do not outweigh harms of continued opioid therapy, clinicians should taper and discontinue opioids or optimize other therapies and work with patients to taper opioids to lower dosages.

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms and incorporate into the management plan strategies to mitigate risk. Offering a naloxone kit should be considered when factors are present that increase opioid overdose risk, including:

- History of overdose or substance use disorder
- Higher opioid dosages (≥50 mg MED/day)
- Concurrent benzodiazepine use

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. The patient’s history of controlled substance prescriptions should be reviewed using state prescription drug monitoring program data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review prescription drug monitoring program data when starting opioid therapy for chronic pain, and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months.

When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy, and consider urine drug testing at least annually to assess for prescribed medications, other controlled prescription drugs, and illicit drugs. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorders.
According to the American Society of Interventional Pain Physicians, urine drug testing should be implemented from initiation of treatment with opioids along with subsequent adherence monitoring, in an in-office setting with immunoassay and confirmation for accuracy with chromatography in select cases, to identify patients who are noncompliant or abusing prescription drugs or illicit drugs, and urine drug testing may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.


**Level of Evidence:** Good (Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.)

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**CRITICAL RESPONSE TO CDC GUIDELINES**

Experts have argued that the dose levels established in the CDC guideline are arbitrary. Millions of Americans currently receive 90 mg MED/day for needed pain control [56]. The true risk factors for toxicity and overdose include organ dysfunction, pain control, tolerance, drug interactions, psychiatric disorders, history of substance use disorder, genetic variation, and concurrent benzodiazepine/other CNS sedative use [6]. Critics have also asserted that the guideline neglects the serious consequences from undertreated chronic pain [59].

In addition, the opioid dosing limits for acute pain were based on emergency department prescribing guidelines for non-traumatic, nonsurgical pain, to provide analgesia until the acute pain resolves or the patient sees his or her primary care provider [43]. As such, the recommendation is unlikely to be helpful in a chronic pain guideline.

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**GENERAL RECOMMENDATIONS FOR ANALGESIC PRESCRIBING**

**What are the contraindications to the use of opioid analgesics?**

As discussed, the CDC’s opioid prescribing guidelines are strictly focused on curtailment and, as such, are less useful for guiding analgesic selection or patient matching [5]. Instead, this information may be obtained from practice guidelines from the FDA, the Federation of State Medical Boards, and the AAPM. These organizations state that opioid analgesics are generally not used as first-line analgesic therapy; non-drug and non-opioid drug alternatives should be considered first.

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Opioids may be initiated when benefits are likely to outweigh risks, when other approaches to analgesia are ineffective or unlikely to be effective, and with a treatment plan reasonably designed to mitigate the risks of addiction, toxicity, and other adverse effects [20; 181; 182].

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Despite limited evidence for reliability and accuracy, screening for opioid use is recommended by the American Society of Interventional Pain Physicians, as it will identify opioid abusers and reduce opioid abuse.


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

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Opioid therapy should be presented as a time-limited trial to evaluate pain, functioning and quality of life benefits, and adverse effects. Opioid-naïve patients should be started at the lowest dose, with titration to effect. In general, it is best to begin opioid therapy with an SA formulation and rotate to an ER/LA formulation, if indicated. Opioid therapy may be continued beyond the trial period after careful evaluation of benefits versus adverse effects and/or potential risks [20; 182].

Fear of inducing respiratory depression has constrained opioid prescribing for patients with chronic pain, but this risk can be minimized by exercising caution and providing patient education regarding the risks of any concomitant use of CNS depressants, especially benzodiazepines and alcohol [20]. Caution should also be used with dosing and titration in patients with sleep apnea or end-stage respiratory disease. Emerging data suggest an association of chronic opioid therapy with central sleep apnea, but the direction and details of this association are unclear. Patients on long-term opioid therapy are at risk for hypoxia if respiratory infections or acute asthmatic attacks supervene; patients should be advised that opioid dosage adjustments may be necessary in the event of any intercurrent illness that affects breathing.

Previous assumptions that patients on chronic opioid therapy will invariably develop analgesic tolerance (i.e., decreasing pain control with the same dosage over time) have also constrained effective opioid prescribing practices. Chronic pain unresponsive to opioid dose escalation may reflect tolerance, but it may also be the result of disease progression, non-opioid responsive pain syndromes, or opioid-induced hyperalgesia. Tolerance is not usually an impediment to long-term opioid therapy [20].
PATIENT FACTORS AND OPIOID ANALGESIC RESPONSE

Clinicians have long observed wide response variation in patients receiving opioids for pain. Patient factors, including age, medical comorbidity, and genetic differences, substantially contribute to this variation. Understanding how these factors influence opioid response can facilitate opioid selection and prescribing that mitigates side effects and toxicity while attaining adequate pain control.

AGE

By 2025, the number of adults 65 years of age and older in the United States is projected to increase 80% from 2010 estimates, comprising nearly 20% of the population. Understanding age-related physiologic changes and the complexity of pain management in elderly patients is essential for optimal efficacy, safety, and tolerability [49].

Independent of disease morbidity, aging elevates the risk of adverse events and associated opioid toxicity (Table 3). The elderly account for 49% of all hospitalizations due to medication adverse effects [186]. A variety of age-related physiologic changes account for this, including diminished gastric secretions and intestinal dysmotility; vitamin D deficiency, loss of appetite, and poor nutrition; and decreased bone density. Increased arterial thickening and rigidity elevate cardiac risk, while decreased lung elasticity may exacerbate respiratory disorders. Neurons become less stress-resilient. Reduced hepatic and renal blood flow diminish metabolism and filtration, increasing the risk for toxic substance accumulation [186]. Patients with dementia and/or cognitive deficits may have communication problems or confusion that render expression of pain severity, therapeutic response, and/or side effects difficult [187].

In older adults, heightened sensitivity to adverse effects results from physiologic changes, drug interactions, and drug-disease interactions [189]. Aging is associated with higher steady-state concentrations of water-soluble drugs and increased half-life of fat-soluble drugs. Consequently, opioid use in older adults may necessitate a lower than usual dose or longer dosage interval in order to maintain an appropriate balance between analgesia and side effect risk [190]. Other functional changes and comorbidities that impact opioid pharmacokinetics may also influence patient response and tolerability. Therefore, the selection and prescribed dosage of opioids in elderly patients must be considered carefully [187].

Older adults are also more likely to be prescribed multiple medications for a variety of chronic and acute conditions. In some cases of multimorbidity and chronic conditions (e.g., hypertension), the use of multiple medications may be unavoidable if one is to follow best practice clinical guidelines; this is referred to as “appropriate polypharmacy.”
However, even when the prescription of multiple medications is warranted, it raises the risks of drug-drug interactions, compliance issues, and adverse effects.

Elderly adults are more likely than younger adults to experience significant chronic pain because of the higher prevalence of rheumatic diseases, orthopedic conditions, and other debilitating illnesses. In many cases, opioid therapy with optimum patient-treatment matching is the safest analgesic option for elderly patients compared with oral NSAIDs, acetaminophen, antidepressants, or anticonvulsants [49].

**MEDICAL COMORBIDITIES**

Comorbid medical or neuropsychiatric conditions can affect opioid response or tolerability by interfering with opioid metabolism, elimination, efficacy, and adherence. Many patients require polypharmacy, especially the elderly and patients with psychiatric illness, cancer, cardiovascular disease, diabetes, and other chronic illnesses. As discussed, polypharmacy elevates risks of drug interactions that reduce efficacy or increase toxicity [191].

Cardiovascular, cerebrovascular, and respiratory disease all impact susceptibility to respiratory depression, bradycardia, or hypotension. Neurologic or neuropsychiatric conditions such as dementia, brain injury, or psychiatric illness may render the patient more susceptible to adverse CNS effects from opioids, such as cognitive impairment or sedation [191]. The presence of significant cognitive or intellectual disabilities can accompany sensory or communication disorders to interfere with verbal or nonverbal communication of pain to healthcare providers. In these patients, chronic pain can manifest in behavioral challenges or gradual declines in function. Appropriate treatment can greatly improve patient quality of life and caregiver stress [71].

**Hepatic Dysfunction**

Opioid biotransformation occurs in the liver, and any significant impairment in hepatic function will delay the metabolism and prolong the effect of opioids and their metabolites. Generally, CYP-mediated metabolism is affected more than glucuronidation, although opioids solely metabolized by glucuronidation also show altered pharmacokinetics. Morphine clearance is reduced ≥25%, and hydromorphone plasma concentrations are increased four-fold [191]. As such, it is important to avoid using oxymorphone and tapentadol and to use hydromorphone and oxycodone with great caution in these patients. Fentanyl is the first-choice opioid in patients with serious liver disease. Buprenorphine is safe in patients with mild-to-moderate liver disease, and methadone can also be used safely [103]. All opioids should be used with extreme caution with lowest-dose initiation [191].

**Renal Dysfunction**

Renal impairment can interfere with clearance of opioids and metabolites, which may lead to serum concentrations rising to dangerous levels. Delayed morphine elimination can lead to respiratory depression, excitotoxicity, and/or neurotoxicity. In these patients, morphine, hydromorphone, tramadol, tapentadol, and codeine should be avoided. Oxymorphone and oxycodone may be used with great caution. Fentanyl should be considered as the opioid of first choice for patients with renal impairment, followed by buprenorphine and methadone [103]. All opioids should be started at a low dose and slowly titrated [191].
Cardiovascular Disease
In patients with heart failure, special care should be taken with methadone. Some patients prescribed methadone for chronic pain may be at increased risk for developing prolonged QT interval or may already have a congenital QT prolongation.

Tramadol is recommended ahead of NSAIDs for patients with significant cardiovascular risk, and the same can be argued for tapentadol. Fentanyl, morphine, or oxycodone should be considered for these patients, as none are significantly associated with QT prolongation [190].

GENETIC FACTORS
Morphine, oxycodone, hydromorphone, and fentanyl have comparable population level efficacy but widely variable analgesic efficacy and tolerability at the individual level; the same drug/dose may be toxic in some patients and have little or no effect in others. For example, up to 30% of patients with cancer-related pain show poor morphine response from inadequate analgesia or intolerability, but most achieve pain control with alternative opioids. Genetic factors account for at least 25% of this response variation to opioids [99; 192]. Genetic variations with greatest confirmation and relevance to opioid kinetics and dynamics include CYP450 enzymes, P-gp transporter ABCB1, catechol-O-methyltransferase (COMT) enzymes, and cytokine gene promoters (Table 4).

P-glycoprotein (P-gp) transporter ABCB1
The P-gp transporter ABCB1, encoded by the ABCB1 gene, regulates the cerebrospinal fluid and serum levels of drugs passing the blood-brain barrier. ABCB1 polymorphism alters P-gp transporter expression and activity at the blood-brain barrier to influence drug concentrations, CNS parent drug/metabolite ratios, and adverse effects. The impact of polymorphic ABCB1 varies with the particular opioid in use. With morphine, it is associated with increased systemic and CNS exposure and accumulation; with fentanyl, increased respiratory depression; and with oxycodone, greater pain reduction and adverse effects due to higher plasma concentrations [193].

Cytochrome P450 Enzymes
Which racial group is most likely to have polymorphic CYP2D6 resulting in intermediate (underactive) opioid metabolism?

As discussed, CYP enzymes influence the concentration of circulating opioids. Polymorphism of genes that encode CYP isoenzymes can affect opioid metabolism by determining isoenzyme activity level [194]. Polymorphic CYP2D6 is the most important genetic determinant of opioid response [1].

Phenotypic variations due to CYP2D6 polymorphism are classed into four functional groups: poor, intermediate, extensive, and ultra-rapid metabolizers [175]. In the general population, polymorphic CYP2D6 results in ultra-rapid metabolism in 7%, poor metabolism in 10%, intermediate metabolism in 33%, and extensive metabolism in 48%. In white individuals, 77% to 92% are CYP2D6 extensive metabolizers. However, racial differences are found in polymorphic CYP2D6 distribution, with greater effects seen in certain groups (Table 5) [194].
In patients with CYP2D6 polymorphism resulting in poor metabolism, the opioid cannot undergo metabolism and is eliminated unchanged. Absence of metabolic activity delays clearance and elevates plasma opioid concentration. This phenotype is hazardous and especially dangerous in opioid-naïve patients. Another effect is analgesic failure with pro-drugs, from the inability to convert to the active metabolite [175; 196].

Underactive Activity
In intermediate metabolizers, the isoenzyme functions at reduced activity level and the opioid is metabolized at a slower rate, delaying plasma clearance, elevating serum concentration, and increasing toxicity potential. In some patients, isoenzyme function is activated with high serum opioid concentration, but these patients have greater overall risk of adverse effects and require lower opioid dosing [175; 194].

Full Activity
The greatest proportion of the population has extensive (full) opioid metabolism ability. With isoenzyme activity fully functional, patients show expected opioid dose response and the expected rate of opioid metabolism [194; 197].

Overactive Activity
In overactive (ultra-rapid) metabolizers, accelerated opioid metabolism and clearance results in analgesic failure from serum concentrations not reaching analgesic threshold, leading to ongoing pain and frequent dose escalation to attain analgesia. Another effect is greatly reduced analgesic duration, as when an ER opioid normally providing 12 hours of analgesia is effective for only 4 hours [175; 194].

Mu Opioid Receptor-1 (OPRM1)
The mu opioid receptor is the primary site of action for opioid analgesics, encoded by the mu opioid receptor-1 (OPRM1) gene. The OPRM1 polymorphism most consistently associated with opioid response is A118G, which results in higher mu opioid receptor binding affinity of beta-endorphins. Studies show a pattern of less analgesia (i.e., higher dose requirements for morphine, tramadol, and fentanyl) and fewer CNS and GI side effects in patients with this polymorphism, reflecting reduced mu opioid receptor sensitivity and higher drug concentrations required to displace beta-endorphin from the mu opioid receptor [193]. A study of genetic influences on oxycodone response also found variations in mu and delta opioid receptor genes that may explain differences in patient responses [198].

Catechol-O-Methyltransferase (COMT)
The COMT enzyme is responsible for inactivating catecholamines. The most widely studied variant is a nucleotide substitution that changes the amino acid from valine to methionine at codon 158 (Val158Met). This alteration reduces the enzymatic activity of COMT, and low COMT activity is associated with increased mu opioid receptor system sensitivity to morphine [184; 192].

Cytokines
Cytokines are vital for coordination of immune and inflammatory response and are broadly classed as pro-inflammatory or anti-inflammatory mediators. Polymorphic cytokine gene promoters are associated with greater pain severity and greater morphine dose requirements [184; 192].

Clinical Relevance
As discussed, there is patient-to-patient variability in the rate at which opioids are metabolized based on genetic phenotype. Patients who are poor or intermediate metabolizers achieve a therapeutic effect at low doses and are at higher risk of toxicity at usual doses of opioid. Patients who are rapid metabolizers require higher and more frequent opioid dosing in order to achieve and maintain plasma concentrations in the therapeutic range. Importantly, with opioid pro-drugs like codeine and tramadol, phenotypic influence on the pharmacokinetics of the primary analgesic metabolite is reversed [197; 199].

Following poor metabolic response to an opioid pro-drug or ultra-rapid metabolic response to a conventional opioid, patients may insist on the need for higher doses due to analgesic failure [195]. Clinicians should avoid assumptions of addiction, abuse, or drug seeking until further investigation clarifies the underlying cause of analgesic failure. This patient...
behavior may reflect a polymorphic-mediated pseudoaddiction. In patients who rapidly metabolize opioids and who develop physiologic dependence with long-term use, forced or arbitrary opioid reduction can be hazardous—serum opioid concentrations may drop too rapidly to a low or zero level and produce severe opioid withdrawal, pain rebound, and cardiovascular hyperactivity that, in older patients, carries some risk for cardiac arrest or stroke [175].

**Codeine**

As an inactive pro-drug that requires metabolism by CYP2D6 into morphine for analgesia, poor and intermediate metabolizers gain little to no analgesia from codeine. In contrast, ultra-rapid metabolizers can have dangerously high serum morphine levels with standard-dose codeine, because the codeine-to-morphine conversion progresses more rapidly and a higher overall proportion of codeine is converted to morphine. This can result in severe or life-threatening side effects [197].

**Tramadol**

Tramadol is also a pro-drug, and clinical response is significantly lower in poor metabolizers, who require at least 30% greater tramadol dosing than patients with normal CYP2D6 activity [145]. Concurrent use of CYP2D6 inhibitors further contributes to metabolic interference. Poor metabolizers show poor pain control and a four-fold need for rescue medication with tramadol, while ultra-rapid metabolizers have shown intoxication, serious adverse effects requiring hospitalization, respiratory depression requiring naloxone, and near-fatal cardiotoxicity [196].

**Oxycodone**

The biotransformation of oxycodone involves CYP2D6 and CYP3A4; the two isoenzymes are prominently linked by activity and metabolic byproduct [176]. As such, polymorphic CYP2D6 significantly impacts oxycodone analgesia and toxicity. Ultra-rapid metabolizers experience significantly greater analgesic effect and toxicity, while poor metabolizers experience minimal therapeutic or side effects. Concomitant use of CYP3A4 inhibitors dramatically elevates analgesic efficacy and toxicity with oxycodone. This effect is further exaggerated in ultra-rapid metabolizers, who risk serious side effects and potentially fatal respiratory depression; an alternative analgesic should be considered in these patients [176].

**Hydrocodone**

Poor metabolizers with CYP2D6 polymorphism have a 10- to 20-fold lower rate of hydrocodone clearance and reduced production of the active metabolite hydromorphone [115]. Evidence suggests that there is a heightened risk of side effects and toxicity if these patients concurrently ingest CYP3A4 inhibitors [196].

**Methadone**

The CYP3A4 and CYP2B6 isoenzymes primarily contribute to methadone metabolism. So, methadone should be used with caution in patients concurrently taking CYP3A4 or CYP2B6 inhibitors [196].

**ANTICIPATING FACTORS THAT ALTER PATIENT RESPONSE TO OPIOIDS**

Basic guidelines have been established to prevent opioid toxicity and overdose due to factors that alter opioid pharmacokinetics [175; 190; 199]. Genetic testing to identify polymorphisms relevant to opioid analgesics is not commercially available or affordable. Instead, providers should screen all patients for CYP450 polymorphism before prescribing an opioid by taking a medication history with an emphasis on side effects, therapeutic failure, beneficial effects, drug sensitivity requiring a low dose, and insensitivity requiring a high dose. For example, a history of inadequate response or marked side effects to codeine suggests that selecting an opioid not metabolized by CYP2D6 (e.g., tapentadol, morphine, fentanyl, oxymorphone) is warranted.

With suspected CYP450 polymorphism or in patients requiring several non-opioid medications that interact with CYP2D6, CYP3A4, CYP2C9, or CYP2C19 isoenzymes, physicians should select an opioid with a metabolic pathway that mostly bypasses the CYP450 system. These include hydromorphone, oxymorphone, levorphanol, and tapentadol. Oxymorphone is perhaps the safest, as it lacks CYP450 metabolism and has no active or toxic metabolites.

All patients prescribed opioid analgesics should receive education on the dangers of co-ingesting benzodiazepines, antidepressants, and agents or drug classes that are known CYP450 enzyme inhibitors.

**OPIOID SELECTION, INITIATION, AND MANAGEMENT**

Analgesic response, safety, and tolerability are highly influenced by the complex interplay of opioid and patient factors. These factors should be considered before selecting an opioid agent and initiating treatment.

**OPIOID RESPONSIVENESS**

Opioid responsiveness is defined as the “degree of analgesia achieved as the opioid dose is titrated to an endpoint, defined either by intolerable side effects or the occurrence of acceptable analgesia” [200]. Poor pain response to opioids is the result of intolerable side effect(s), inadequate analgesia, or both, despite dose escalation. When poor analgesic response is identified, the clinician should consider using adjuvant analgesics, switching opioids, changing the route of administration, or using NMDA receptor antagonists [103].
An essential safety factor in opioid selection is current opioid exposure. Many ER/LA opioid formulations and transmucosal immediate-release fentanyl are explicitly prohibited from use in opioid-naïve patients due to the high risk of severe, potentially fatal respiratory depression [201]. Patients should be identified as opioid-tolerant before considering the use of these particular formulations.

The term “opioid-tolerant” differs from “opioid tolerance.” Opioid tolerance is the physiologic adaptation to opioid exposure over time that manifests in reduced drug effect [157; 202]. On the other hand, a patient is considered opioid-tolerant after continuous opioid use for at least one week of at least 60 mg/day oral morphine, 25 mcg/hour transdermal fentanyl, 30 mg/day oral oxycodone, 8 mg/day oral hydrocodone, 25 mg/day oral oxymorphone, or an equianalgesic dose of another opioid [181]. ER/LA opioid analgesic products and dose levels restricted to opioid-tolerant patients are shown in Table 6.

### Recent Opioid Exposure

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Doses Restricted to Opioid-Tolerant Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avinza</td>
<td>Morphine capsules</td>
<td>90 mg, 120 mg</td>
</tr>
<tr>
<td>Belbuca</td>
<td>Buprenorphine buccal film</td>
<td>&gt;75 mcg film/day</td>
</tr>
<tr>
<td>Butrans</td>
<td>Transdermal buprenorphine</td>
<td>7.5, 10, 15, and 20 mcg/hr</td>
</tr>
<tr>
<td>Dolophine, Methadose</td>
<td>Methadone tablets</td>
<td>Refer to full prescribing information</td>
</tr>
<tr>
<td>Duragesic</td>
<td>Fentanyl transdermal system</td>
<td>All doses</td>
</tr>
<tr>
<td>Embeda</td>
<td>Morphine/naltrexone capsules</td>
<td>100 mg/4 mg</td>
</tr>
<tr>
<td>Exalgo</td>
<td>Hydromorphone tablets</td>
<td>All doses</td>
</tr>
<tr>
<td>Hysingla ER</td>
<td>Hydrocodone bitartrate tablets</td>
<td>Single-dose ≥80 mg</td>
</tr>
<tr>
<td>Kadian</td>
<td>Morphine capsules</td>
<td>100, 130, 150, and 200 mg</td>
</tr>
<tr>
<td>MorphaBond</td>
<td>Morphine tablets</td>
<td>100 mg</td>
</tr>
<tr>
<td>MS Contin</td>
<td>Morphine tablets</td>
<td>100 mg, 200 mg</td>
</tr>
<tr>
<td>Nucynta ER</td>
<td>Tapentadol tablets</td>
<td>No product-specific concerns</td>
</tr>
<tr>
<td>OxyContin</td>
<td>Oxycodone tablets</td>
<td>Single-dose &gt;40 mg, daily dose &gt;80 mg</td>
</tr>
<tr>
<td>Targiniq ER</td>
<td>Oxycodone/naloxone tablets</td>
<td>Single-dose &gt;40 mg/20 mg, daily dose &gt;80 mg/40 mg</td>
</tr>
<tr>
<td>Xtampa ER</td>
<td>Oxycodone capsules</td>
<td>Single-dose &gt;40 mg, daily dose &gt;80 mg</td>
</tr>
<tr>
<td>Zohydro ER</td>
<td>Hydrocodone bitartrate capsules</td>
<td>Single-dose &gt;36 mg, daily dose &gt;72 mg</td>
</tr>
</tbody>
</table>

ER = Extended-release.

### Routes of Administration and Formulations

What route of administration is contraindicated for opioids because it is painful and lacks any pharmacokinetic advantage?

As discussed, opioids are available for many routes of administration, including oral, rectal, SC, IV, transdermal, transmucosal, and intraspinal. The oral route of administration is simple, cost-effective, and preferred, and SA and ER formulations are available for most oral opioids [103]. SA opioids are used to control pain until reaching a steady state. SC, IV, rectal, transdermal, transmucosal, or intraspinal routes of administration are used when patients cannot take oral medications. IM administration is contraindicated, as it lacks any pharmacokinetic advantage and is painful. SC delivery is relatively easy, effective, and safe. IV is useful when pain is severe or pain levels have acutely increased. Transdermal fentanyl preparations are effective for patients unable to take oral medications who have stable pain control. Transmucosal fentanyl is similar to IV administration in its rapid onset and is used for acute breakthrough pain. The intraspinal route of administration is either epidural or intrathecal. This is the most invasive mode of opioid delivery.
and requires specialist involvement, but it confers advantages in patients with significant dose-limiting adverse effects, because systemic exposure is circumvented. Intraspinal delivery allows adjuvant medications to be directly administered to the spinal cord [103].

**ER/LA Opioid Formulations**

Although SA opioids are effective for pain control in many clinical contexts, they are characterized by pharmacokinetic shortcomings that may interfere with achieving sustained analgesia. ER formulations were developed to circumvent these pharmacokinetic shortcomings. Transdermal formulations of fentanyl and buprenorphine avoid the extensive first-pass metabolism that limits bioavailability with oral opioids [1]. ER formulations also lack the acetaminophen or ibuprofen found in many SA codeine, hydrocodone, and oxycodone formulations. These non-opioid analgesics impose a daily dose ceiling because of toxicity risks [137].

Several high-potency oral opioids have been used for decades to treat moderate-to-severe pain, including morphine, oxycodone, hydromorphone, levorphanol, methadone, and oxymorphone [16]. Methadone and levorphanol are inherently long acting, while morphine, oxycodone, hydromorphone, and oxymorphone possess a short analgesic duration and plasma half-life that requires frequent administration to establish and maintain a satisfactory analgesic effect. Before the 1990s, high-potency opioids were primarily used in surgery and inpatient settings, because they required IV or IM administration [154]. Oral ER formulations of these opioids were introduced to fulfill the unmet need of outpatients with chronic or disabling pain who required continuous analgesia not achievable with SA formulations [204; 205].

The terminology used to describe delayed-release opioids can be confusing. Opioids formulated with a release-delaying mechanism have been designated as ER, continuous or controlled release (CR), or sustained-release (SR), but these terms lack specific definition. Methadone and levorphanol are termed LA opioids to distinguish their inherently longer analgesic duration from opioids reformulated with an ER mechanism [206]. Likewise, the original strong opioids with relatively brief analgesic duration have been termed immediate-release or IR, but SA is a more accurate designation. IR is better reserved for truly rapid-onset opioids such as transmucosal immediate-release fentanyl.

Absorption, distribution, and metabolism influence the duration and stability of opioid analgesia and are difficult to manipulate with SA opioids. ER formulations modify the kinetic behavior of the opioid without changing the pharmacodynamic characteristics in order to improve analgesia through prolonged plasma concentration, lower maximum and higher minimum concentration, reduced fluctuation in plasma concentration, and delayed time in reaching maximum concentration [207; 208]. These ER opioid kinetics are thought to allow pre-emptive pain control instead of attempting to control pain after it becomes established (i.e., “chasing the pain”). This reduces or eliminates gaps in analgesia when plasma levels decline before the next scheduled dosing; decreases sleep interruption, side effects, and early opioid withdrawal symptoms by improving adherence and decreasing dose frequency; and reduces abuse potential by decreasing reward and reinforcement from slower onset of effects [72; 154; 209].

Fluctuating analgesia levels achieved with SA opioids can result in a need to take the medications more frequently (for comfort). This can cause conditioned passive pill-taking behavior, which can discourage the patient from taking an active role in pain self-care. The enhanced analgesic coverage and adherence with ER opioids may improve assessment of changes in the underlying pain condition or the chronic pain state by reducing the confounding factor of analgesic fluctuation [137].

The theoretical advantages of ER over SA formulations have been difficult to demonstrate in randomized controlled trials. However, there have been some comparison trials that may give some insight into the basis for ER formulations. In one study, a patient adherence advantage was found with ER formulations versus SA opioids, which may translate into improved pain relief [206]. In patients with moderate or greater chronic pain, CR tramadol showed lower pain scores and higher patient and investigator efficacy ratings than SA tramadol [210]. In addition, the daily variations in pain control experienced with twice-daily morphine were not reported with once-daily dosing, and this correlated with stability in serum morphine concentrations [211].

Compared with three-times daily morphine, twice-daily morphine is superior in pain control, sleep quality, and physical and mental impairment. In one study, almost twice as many patients dropped out with three-times daily versus twice-daily morphine, with inadequate pain relief the primary reason [212]. Patients with moderate-to-severe cancer-related pain show significantly greater dropout rates with four-times daily oxycodone than with twice-daily oxycodone due to inadequate pain control and side effects [213]. Another study of patients with cancer pain reported significantly greater tiredness during initial titration with six-times daily morphine versus once-daily morphine [214].

A literature review found that ER formulations of morphine, oxymorphone, oxycodone, and tramadol promoted improvements in ability to fall asleep, sleep quality, sleep duration, and pain-related sleep disturbance compared with SA formulations [206]. Patients with osteoarthritis have shown significantly improved sleep quality scores with ER versus SA oxycodone and with once-daily compared with twice-daily morphine [215; 216].
The CDC recommends initiation of opioid therapy with an SA formulation, but no further discussion or guidance is given [28]. The FDA states that the use of ER/LA opioids is indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate [181]. To ensure that benefits outweigh risks and to reduce risks while preserving access to opioid analgesics, the FDA has implemented risk evaluation and mitigation strategies (REMS) for ER/LA opioid analgesics. The ER/LA REMS program consists of a core prescriber education component that stresses safe product use, patient safety information, and guidance on patient counseling. This REMS-compliant education is strongly encouraged but not mandatory [181].

**Contraindications to ER/LA Opioid Formulations**

Class-wide contraindications to ER/LA opioids include [181]:

- Concurrent alcohol use (can cause rapid opioid release and potentially fatal respiratory depression)
- Mild pain, short-term, or acute pain
- Use as pre-emptive analgesia
- Postsurgical pain
- As-needed use for intermittent pain
- Paralytic ileus
- Acute or severe bronchial asthma or hypercapnia
- Significant respiratory depression, unless resuscitative equipment and respiration monitors are available

In addition to contraindications for all ER/LA opioids, there are some agent-specific contraindications. For example, doses greater than 1,600 mg/day of morphine ER (Avinza) should be avoided due to the risk of severe liver toxicity from the fumaric acid excipient. Oxycodone/naloxone ER (Targiniq) should not be used in patients with moderate or severe hepatic impairment. Tapentadol ER (Nucynta) is contraindicated in the presence of current or past 14-day MAOI use.

With postoperative, acute, or chronic intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with SA hydrocodone, morphine, or oxycodone is more effective than ER formulations. SA opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [15; 207; 209].

Treatement of moderate-to-severe persistent pain in opioid-naïve patients should be initiated with an SA opioid, with subsequent upward or downward dose adjustment until reaching adequate and tolerable analgesia [28]. When satisfactory analgesia and dose stability are achieved, the patient should be switched to an ER formulation of the initial opioid (assuming patient tolerability) [15; 177].

When switching from SA to ER formulations, patients should be advised not to expect the relatively rapid onset of relief they may be used to with the SA opioid. Analgesic benefit will become evident over time, and taking a second tablet to speed the onset of pain relief may lead to delayed toxicity or overdose. These medications should be stored securely, never shared, never chewed or crushed, and properly disposed of when no longer needed, as they contain large amounts of opioid and are potentially lethal if ingested by someone without tolerance or tampered with to cause rapid release of the contents [137].

**DOSING**

In clinical practice, patients may require more frequent dosing intervals with LA/ER opioids than recommended in product labeling by the manufacturer. For example, the labeling for CR oxycodone recommends every-12-hour dosing, but some studies have found that patients need a dose interval of 7 to 8 hours and that the majority of such patients are prescribed CR oxycodone three to four times daily [217; 218; 219]. Other studies of patients with moderate-to-severe pain found the majority used CR morphine three to four times daily [220]. Transdermal fentanyl patch labeling recommends patch replacement every 72 hours, but in one study, close to 50% of patients required patch replacement every 24 or 48 hours [218; 220].

This disparity can be explained by how premarket drug evaluation studies obtain pharmacokinetic data used in postmarket product labeling. These data are usually obtained from phase I studies that evaluate kinetic behavior of the drug in younger, healthy volunteers free of medical and psychiatric comorbidity and other medication use. This eliminates most patient factors that alter the pharmacokinetics of the drug. Less often, analgesic pharmacokinetic data are obtained from clinical samples involving subjects with a given pain condition, free of other medical and psychiatric comorbidities and concurrent medication use. These tightly controlled conditions eliminate factors that could later confound postmarketing clinical data, but this limits applicability of the results to typical patients in real-world settings. No single opioid dosing protocol can fit the characteristics of all patients to determine analgesic response, tolerability, and required dose frequency [221].

The FDA permits marketing of generic drugs when bioequivalence is shown. This parameter is met when serum levels of the active constituent fall within 80% to 125% of the original branded drug. The allowable variation in serum levels can be problematic in agents with a narrow therapeutic index. An added complexity is that FDA mainly relies on self-reported bioequivalence evaluation by the generic drug makers [221; 222].
Dose Titration

Titration is the process of incremental dose change based on individual patient needs and responses. The dose is increased (escalated) or decreased (tapered) until a reasonable balance is reached between analgesia and tolerability. Gradual titration allows sufficient time to ensure that the patient obtains the fullest degree of analgesia possible at the current dosage before further escalation is considered [223]. Regardless of opioid or dose, titration should be individualized based on health and pain status, treatment goals, and previous opioid response. Side effects such as sedation or nausea can interfere with upward titration.

Opioid titration is slower with ER than SA formulations. When transitioning from SA to ER formulations of the same opioid, the dose is based on the equivalent total daily dose [157].

The American Society of Interventional Pain Physicians recommends titration of long-acting opioids should be carried out with caution.

Level of Evidence: Good (Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.)

Opioid Rotation or Switching

Pharmacologists formerly considered opioid analgesics interchangeable, on the basis of shared mu opioid receptor agonism, differing mainly by potency. In contrast, clinicians have long observed subtle but important pharmacologic differences in potency, efficacy, and tolerability [224]. It is now known that individual differences in mu opioid receptor expression and density contribute to this variation.

Opioid rotation exploits these pharmacologic differences and incomplete cross-tolerance among opioids and involves switching the current opioid or route of administration to improve efficiency and safety [173; 223]. Opioid rotation can be an effective strategy for overcoming analgesic failure, side effect intolerance, problematic drug interactions, opioid-induced hyperalgesia, change in clinical status, problems related to medication cost and/or availability, need for a different route of administration, and patient preference [173; 223; 225].

Equianalgesic-Dose Tables

Verbatim use of equianalgesic-dose tables for opioid rotation contributed to opioid analgesic deaths in the 2000s and prompted changes in opioid conversion methods to mitigate risk and improve safety [12]. These tables include calculations derived from single dosing in opioid-naïve patients and permit broad guidance only. To ensure safety, a new opioid should start 50% below the calculated comparable dose to compensate for variable opioid response and incomplete cross-tolerance. The new opioid is titrated using product-specific instructions, with SA opioids used for analgesic rescue in breakthrough pain until reaching up-titration [12; 20; 226].

Morphine is the reference against which other opioids are compared, and analgesic potency is calculated as dose equivalence to morphine (i.e., MED). Table 7 shows a typical equianalgesic-dose table with figures validated for acute pain in opioid-naïve patients and conversions for opioid-tolerant patients [181].
Breakthrough Pain Management

Breakthrough pain has been defined as a sharply increased pain episode with otherwise stable, well-controlled pain. The incidence of breakthrough pain in patients with chronic cancer and noncancer pain is 50% to 90%, even with pain appropriately managed with around-the-clock opioid analgesic coverage [228; 229; 230]. Breakthrough pain types include spontaneous, incidental, and end-of-dose failure. It is important to minimize the use of medications to address breakthrough pain in patients with chronic pain by titrating the baseline opioid dose or using adjunctive agents. If necessary, a reasonable dose for breakthrough pain is 10% to 15% of the total daily opioid dose [184]. Transmucosal immediate-release fentanyl products may be considered if prevention and control of breakthrough pain is not achieved.

Pharmacokinetic factors determine the options for breakthrough pain treatment. Analgesics for breakthrough pain are ideally selected according to the time it takes to reach maximum serum concentration. This period depends on the route of administration, usually attained by 1 hour with oral, 30 minutes with SC, and 6 minutes with IV routes [103].

Despite the self-limited duration (mean: 30 to 60 minutes), breakthrough pain is highly distressing to the patient and burdensome to families, caregivers, and healthcare systems. It is linked to decreased functional status, treatment dissatisfaction, and worse medical outcomes. Breakthrough pain may go unrecognized and is often undertreated due to lack of knowledge and undue concern regarding overmedicating [231]. Of patients with breakthrough pain, 60% describe pain intensity as severe but only half take medication to address it [117]. Breakthrough pain has an unpredictable onset and reaches peak pain intensity in 5 to 15 minutes, making SA morphine, hydromorphone, and oxycodone—with onsets of action 30 minutes after oral ingestion—ineffective [143].

IV fentanyl analgesia, with onset of action in 5 to 8 minutes and duration of 30 to 60 minutes, is ideal but not feasible for outpatient breakthrough pain management. Instead, transmucosal immediate-release fentanyl products overcome the limitations of SA opioids to deliver analgesia approaching the rapid onset of IV fentanyl [231]. Available products include [201]:

- Sublingual tablet (Abstral)
- Citrate oral transmucosal lozenge (Actiq)
- Buccal tablet (Fentora)
- Nasal spray (Lazanda)
- Buccal soluble film (Onsolis)
- Sublingual spray (Subsys)

Transmucosal immediate-release fentanyl products are shown superior in pain reduction to placebo at all time points from 15 to 60 minutes and to SA oral morphine in the initial 45 minutes. Among these products, intranasal fentanyl spray is possibly superior to the buccal tablet and oral transmucosal lozenges in the first 30 minutes of dosing [143].
Tolerance to opioids may develop in several ways. Short-term use inhibits the production and release of endogenous opioids (e.g., beta-endorphins), while long-term use may also inhibit mu-opioid receptor expression. Studies of long-term morphine use have found down-regulation in POMC gene expression and subsequent decrease in endorphin production; decreased mu opioid receptor density on beta-endorphin containing neurons in the hypothalamus; and mu opioid receptor uncoupling from ligand-gated voltage channels with decreased ion channel potency and efficacy [111]. Morphine analgesic tolerance may also result from increased production of the anti-opioid peptides that bind mu receptors to decrease opioid binding and activation of mu opioid receptors. These processes develop over time and correspond with patient requirements for increasing opioid dose to maintain analgesia [111].

Other mechanisms may contribute to the loss of opioid analgesia. Pharmacokinetic changes can accelerate opioid metabolism and elimination from up-regulation of enzymatic activity in the metabolic pathway for the opioid. With enzyme induction, plasma opioid concentration diminishes over time while dosing remains constant [233]. The addition of other medications can induce metabolizing enzymes, with accelerated breakdown and excretion of the opioid leading to loss of analgesia and the need for dose escalation to regain analgesia [235]. Pharmacodynamic processes that include activation of the NMDA receptor/nitric oxide cascade can also result in opioid hypoanalgesia. NMDA receptor or nitric oxide synthase blockade can prevent or reverse opioid tolerance [236; 237; 238].

Progression of the underlying pain condition can also increase pain intensity and require dose escalation to control the pain. This may be mistaken for pharmacologic tolerance [233]. In general, tolerance can be managed by opioid rotation, dose escalation, or adding a non-opioid analgesic [175].

**Opioid-Induced Hyperalgesia**

As noted, opioid-induced hyperalgesia is characterized by paradoxical pain amplification. Pain sensitivity is heightened in the absence of a new or exacerbated injury. Opioid-induced hyperalgesia should be suspected in the patient who reports an unusual or unexplained change in pain profile, a diffuse allodynia (i.e., pain from normally non-painful stimuli) not related to the original pain condition, or worsening pain in response to dose escalation [234; 239].

Opioid-induced hyperalgesia involves CNS and PNS sensitization that develops through multiple mechanisms, including NMDA receptor activation; increased spinal cord dynorphin levels that activate excitatory pro-nociceptive neuropeptides; and CNS glial cell activation [232; 233; 234; 240]. CNS pain facilitatory mechanisms contribute to hyperesthesia (i.e., exaggerated pain sensitivity) and allodynia. Pain abnormalities with opioid-induced hyperalgesia often reflect exacerbated pre-existing painful conditions, with pain intensity worse than before opioid therapy [232; 241]. However, patients often describe the pain as more diffuse, less defined in quality, and typically extending beyond the original painful areas. Many features of pain associated with opioid-induced hyperalgesia resemble the pain experienced during opioid withdrawal, and both share a common neurobiology [232].

The diagnosis of opioid-induced hyperalgesia is often made in association with an increase in the opioid dose. Pain reduction indicates opioid tolerance, while worsening pain indicates opioid-induced hyperalgesia. Conversely, reducing the opioid may alleviate opioid-induced hyperalgesia symptoms, although care should be taken to avoid inducing withdrawal symptoms, which can increase pain and cloud the clinical picture [232].

Opioid-induced hyperalgesia is managed by addressing the underlying mechanisms. Morphine has the highest risk of opioid-induced hyperalgesia and should be replaced, if appropriate, in these patients. Switching to an NMDA antagonist opioid (e.g., methadone, levorphanol) is one approach. Spinal dynorphin is a kappa opioid receptor agonist, and kappa receptor antagonism may reverse opioid-induced hyperalgesia. As such, the kappa receptor antagonist buprenorphine is uniquely helpful as an alternative opioid for opioid-induced hyperalgesia [232]. If neuropathic pain is the original condition, it will often preferentially respond to non-opioid analgesics such as amitriptyline or pregabalin, which can enhance analgesia and decrease opioid dosing [234].

The NMDA antagonist ketamine has been used successfully in outpatients with opioid-induced hyperalgesia and is perhaps the most effective agent [239]. There is also evidence that concurrent use of the opioid antagonists naltrexone or naloxone at ultra-low doses can prevent opioid-induced hyperalgesia and enhance analgesia [242].

**Oral Opioids and GI Malabsorption**

Malabsorption may also contribute to analgesic failure. Possible causes of oral opioid failure were studied in 95 patients with intractable pain [19]. Patients were initially screened to assess pain and functional improvement with oral opioids; 21.1% had three or more failed oral opioid trials. Malabsorption symptoms of nausea and steatorrhea were identified in 100%, and undigested medication in the stool detected in 70%. Pain relief from IV hydromorphone was experienced by 75%. The researchers concluded that patients with intractable pain and oral opioid failure may have a GI condition that interferes with absorption. These patients require non-oral routes until the GI dysfunction is resolved [19].

**Endocrinopathy**

Some patients with severe chronic pain lack analgesic response from lower-dose opioids; their complaints of analgesic failure may be dismissed despite severe impairment and debilitation. It is crucial to consider an underlying endocrinopathy as a possible cause. In one study of 61 patients with
refractory chronic pain, 80.3% showed at least one hormone abnormality and 11.5% showed severe pituitary-adrenal-gonadal deficiency [243].

Pain that is uncontrolled, intractable, or severe impacts the endocrine system. Pain is a potent stressor that initially elevates serum pituitary, adrenal, and gonadal hormones. Severe uncontrolled pain depletes serum hormone levels; this serves as a biomarker for endocrinopathies and indicates that enhanced analgesia and hormone replacement may be necessary. Adequate physiologic levels of specific hormones may be required for optimal analgesia, neuroprotection, and neurogenesis. Hormone replacement is not a substitute for opioids but can minimize dose requirements [243].

**Patient Nonadherence**

Many patients with chronic pain do not take their medication as prescribed or stop altogether. A review of 11 trials involving 2,473 patients found an overall discontinuation rate of 22.9%, including 11.4% with weak opioids and 34.1% with strong opioids [244]. Community-based studies have found that 21% to 38% of patients adhere to their prescribed opioid regimens [245; 246].

Treatment adherence is essential for optimal pain control, for quality of life improvement, and to reduce healthcare utilization and associated costs. Inconsistent adherence to strong opioid prescriptions is the most important risk factor for hospitalization in these patients [247]. Poor adherence is also linked to problematic side effects, depression, higher dosing frequency, and negative attitudes of relatives or partners toward the patient's need for opioids. Adherence may be improved by patient education regarding the pain condition, realistic treatment expectations, and perceived benefit from treatment. In addition, primary care providers can modify risk factors for poor adherence by decreasing the dose frequency and addressing treatment expectation and benefit, side effects, depression, and attitudes of relatives and partners [248]. A tailored approach to opioid selection and titration optimizes the balance between pain control and side effects, which often enhances therapy adherence [1].

## OPIOID ANALGESIC SIDE EFFECTS AND MANAGEMENT

All opioid analgesics have the potential for serious adverse effects when prescribed without careful consideration of patient factors. Even when prescribed with due diligence, patients may experience side effects that, if not anticipated or managed properly, can promote treatment discontinuation or analgesic failure from intolerance of therapeutic dosages. Side effects are generally adverse (with the possible exception of sleep-promoting sedation) and result from specific opioid pharmacology, patient age, comorbidities, genetic polymorphisms, and impaired hepatic or renal function [103].

Upon treatment with opioids, most patients report their pain is less intense, less distressing, or gone entirely, while other sensory perceptions are unchanged. A minority of patients experience euphoria, but it is more common for pain-free volunteers without a history of substance use disorder to describe morphine as unpleasant. Except in cases of acute intoxication, opioids, even highly potent mu agonists, seldom induce the loss of motor coordination or slurred speech characteristic of calming or sedating drugs [104; 249].

Clinicians should anticipate and monitor common opioid side effects and discuss these effects with patients before opioids are initiated. Many side effects are time-limited and lessen or resolve following stable dosing. Tolerance to opioid effects tends to develop at different rates, ranked below in descending order [175]:

- Euphoria (most rapid)
- Sedation
- Nausea
- Analgesia
- Constipation (late, if ever)

### SEDATION

Sedation is a dose-dependent and often time-limited side effect. Anticholinergic activity of some opioids may contribute to sedation and drowsiness, but alleviation of pain can itself promote relaxation and sleep. Excessive sedation can occur with higher-dose initiation or rapid dose escalation and may result in nonadherence or reduced quality of life [110]. Management approaches for opioid-induced sedation include reduction or elimination of nonessential sedating medication (e.g., benzodiazepines, antihistamines, some TCAs, muscle relaxants), opioid dose reduction, and/or opioid rotation [110].

### PRURITUS

Opioid analgesics can cause pruritus, which may be severe and difficult to manage, highly distressing to the patient, and among the top reasons for discontinuation. Pruritus is often misdiagnosed as an opioid allergic reaction, but true allergic and anaphylactic reaction to opioids is rare (<1%) and results from activation of central mu opioid, dopamine, serotonin, prostaglandin, and histamine receptors. Reactions related to histamine activation have been reported, most often with morphine. These reactions include urticaria, bronchospasm, and hypotension. When pruritus does occur, it typically involves the face, nose, and torso, and intrathecal administration is most associated with intense itching. Histamine release is most common with morphine [104; 250].
The goal of treating opioid-associated pruritus is to ameliorate the symptom without reversing analgesia with opioid antagonists. Options include anti-histamines (e.g., diphenhydramine, hydroxyzine) or H2 blockers (e.g., ranitidine, cimetidine). Naloxone infusion may be considered if other treatments fail and itching is severe. Opioid rotation to a different synthetic class (natural, semisynthetic, or synthetic) may also be successful. Epidural kappa opioid receptor agonists nalbuphine or butorphanol can reverse pruritus from mu agonists while maintaining analgesia [110; 250; 251]. If a true opioid allergy is identified, the offending opioid should be replaced by an opioid from a different chemical class to avoid antibody recognition [128].

**OPIOID-INDUCED CONSTIPATION AND BOWEL DYSFUNCTION**

GI symptoms are among the most common side effects reported with opioid use. Providers should be alert to the character and extent of patient distress resulting from these effects and the potential for non-adherence to therapy. Opioid-induced bowel dysfunction takes various forms, including dry mouth, nausea, vomiting, gastric stasis, bloating, abdominal pain, and opioid-induced constipation. Opioid activation of mu and kappa receptors in the neuronal plexus of the gut wall increases intestinal wall and sphincter resting tone and reduces biliary, pancreatic, and intestinal secretions. This results in dysrhythmic, non-propulsive contractions (bowel spasm), delayed passage and increased viscosity of intestinal contents, and the onset of constipation. Spasm and colic can also result from increased biliary tract tone [105; 107].

In order to prevent opioid-induced constipation, a laxative bowel regimen and bowel management education should be provided to all patients prescribed an opioid. In the event of laxative or stool softener nonresponse, patients may try [123; 171]:

- Mild osmotic agents (70% sorbitol solution, lactulose, milk of magnesia)
- Polyethylene glycol
- Bulk-forming laxatives (psyllium) with proper liquid intake
- Mild cathartic laxatives (senna, bisacodyl)

Saline or tap water enemas may be necessary to avoid fecal impaction.

Opioid switching from a hydrophilic agent (e.g., morphine, oxycodone, hydromorphone) to a lipophilic opioid (e.g., fentanyl, buprenorphine, methadone) may be helpful, as there is greater GI opioid receptor activity with hydrophilic opioids. Peripherally acting mu opioid receptor antagonists are indicated when other opioid-induced constipation treatments fail, including methylnaltrexone (50% to 60% efficacy in severe refractory opioid-induced constipation) or subcutaneous naloxegol injections [171].

**NAUSEA AND VOMITING**

Roughly 33% to 66% of patients receiving opioids experience nausea and vomiting, usually during initiation and titration. This often resolves by the first week of treatment, but can recur later with a significant dose increase. Nausea and vomiting results from reduced GI motility and constipation, delayed gastric emptying, and activation of opioid receptors, dopamine tracts, and other transmitters in the chemoreceptor trigger zone [123]. Some patients report a sharp exacerbation of nausea upon movement, suggesting a component of opioid-induced vestibular dysfunction [105].

Nausea and vomiting during opioid initiation should be controlled with antiemetics, and these agents should be available as needed after dosing is stabilized. Metoclopramide and domperidone are first-line options due to a mechanism that improves GI motility. Around-the-clock and/or transdermal prescribing may be considered, with extra doses for rescue. Extrapyramidal symptoms may occur, but are considered infrequent [123; 253].

Antihistamines block histamine receptors in the vomiting center and on vestibular afferents. They may be used when [123; 253]:

- Vestibular sensitivity mimics motion-induced nausea
- GI prokinetic agents are contraindicated due to bowel obstruction

Up to 91% of patients taking opioids experience constipation, the most common opioid-induced bowel dysfunction symptom. Opioid-induced constipation, often in combination with chronic nausea, can cause considerable distress, greatly diminished quality of life, and opioid discontinuation by as many as 33% of patients [252]. Most patients require constipation management for the duration of opioid therapy because complete tolerance rarely develops [123].
Ondansetron and other serotonin receptor antagonists are also effective in treating nausea and vomiting. Chlorpromazine is likely to produce significant sedation; prochlorperazine has greater antiemetic potency. However, potential extrapyramidal symptoms and anticholinergic side effects limit the clinical use of these agents [123; 253].

**RESPIRATORY DEPRESSION**

Therapeutic doses of morphine depress all phases of respiratory activity, including the breathing rate, minute volume, and tidal exchange. Respiratory depression results from decreased brainstem sensitivity to carbon dioxide build-up and is the primary lethal side effect of opioids [120]. Patients are most vulnerable to respiratory depression in the first five days of opioid initiation, especially the first 24 hours. Risk factors include obesity, sleep apnea, and pre-existing respiratory disorders (e.g., acute asthma, respiratory infection). Respiratory depression is antagonized by pain, and patients with substantial pain relief following uncontrolled pain are also at risk. Coingestion of any CNS respiratory depressant, including benzodiazepines or alcohol, elevates the risk of pronounced respiratory depression and fatality [104; 254].

Opioid use at appropriate prescribed doses seldom results in significant respiratory depression, even in patients with end-stage chronic obstructive pulmonary disease or dyspnea from advanced-stage cancer [255]. Patients on stable-dose, long-term opioid therapy have low risk of respiratory depression, although concerns remain prevalent among clinicians and patients [123]. It is important to note that respiratory depression may occur with a change in opioid analgesic, rapid dose escalation, development of renal failure or a serious pulmonary condition, or a single, large, inappropriate dose [254].

Sedation always precedes respiratory depression. With fatal respiratory depression, the process begins with sedation followed by reduction and finally cessation of breathing over the course of 5 to 15 minutes. Respiratory depression is characterized by rising peripheral carbon dioxide pressure, falling peripheral oxygen, and decreasing respiratory rate [255]. While these laboratory markers directly measure ventilation and ventilatory drive, they are often only available in an inpatient setting. In the outpatient setting, breathing rate and/or oxygen saturation are surrogate measures of ventilatory drive. In these cases, severe respiratory depression is defined by a respiratory rate less than 8 to 10 breaths per minute and oxygen saturation of <85% for more than six minutes per hour [120].

Naloxone can reverse respiratory depression caused by most opioids (though it is ineffective with meperidine). The extent and duration of naloxone reversal is determined by the specific opioid and dose, route of administration, concurrent medication(s), underlying disease, pain and state of arousal, and genetic factors [120].

When indicated for reversal of opioid-induced respiratory depression, naloxone (1:10 dilution) titrated in small increments or given by infusion should be administered to improve respiratory function without reversing analgesia [255]. The patient should be monitored carefully until the respiratory depression episode resolves [123].

Naloxone should be administered cautiously by slow IV infusion in opioid-dependent patients because it can abruptly induce acute opioid withdrawal syndrome and precipitate severe uncontrollable pain. Given this potential for abrupt, overwhelming physiologic and emotional stress with naloxone intervention, its use in respiratory depression should be strictly limited to patients unresponsive to physical or verbal stimulation or patients with shallow respirations, respiratory rate less than seven breaths per minute, or pinpoint pupils [120]. The 30- to 81-minute duration of naloxone is less than most mu opioid agonists, and re-administration is usually required.

The unique properties of nalbuphine make it effective in reversing opioid-induced respiratory depression or pruritus while maintaining analgesia. Nalbuphine can be a good analgesic option for patients susceptible to severe respiratory depression, pruritus, or nausea and vomiting with standard opioids [110].

**SEROTONIN SYNDROME**

Which opioid analgesic is associated with serotonin syndrome?

Serotonin syndrome results from overactivation of central and peripheral serotonin receptors, usually from concurrent use of multiple serotonergic agents. Serotonin syndrome can result from drugs that influence the reuptake, metabolism, synthesis, or release of serotonin; influence serotonin receptor activity; or interfere with CYP2D6 or CYP3A4 metabolism. The most commonly implicated agents are SSRIs, but other medications that may affect serotonin levels include serotonin-norepinephrine reuptake inhibitors, MAOIs, antipsychotics, analgesics, antiemetics, cough suppressants, and dietary supplements. In more severe cases, patients develop hyperthermia, autonomic instability, delirium, and muscle rigidity, with complications including seizure, rhabdomyolysis, arrhythmias, and respiratory arrest. Suspicion of serotonin syndrome requires urgent emergency management [256; 257].

Tramadol is the only opioid analgesic associated with serotonin syndrome. SSRIs inhibit CYP2D6, which decreases tramadol analgesic efficacy. Concurrent use of tramadol and paroxetine or venlafaxine has been reported to cause serotonin syndrome [256; 257]. Genetic susceptibility to serotonin syndrome has been identified and is influenced by a patient’s ability to produce different ratios of positive and negative tramadol enantiomers [257].
NEONATAL ABSTINENCE SYNDROME
Teratogenic effects from opioid exposure during pregnancy have not been identified. However, chronic opioid use during pregnancy can result in physical dependence in utero and potentially life-threatening opioid withdrawal in the neonate at birth and for up to 12 days after [104]. If signs of neonatal abstinence syndrome are present, the neonate should be taken to intensive care for observation and further assessment. Opioid replacement may be necessary to stabilize the patient, reverse the syndrome, and reduce complications of withdrawal. Additional medications may be necessary to control seizures and other symptoms.

MORPHINE AND CARDIAC RISK
Morphine is commonly used for chest pain in patients with a suspected acute coronary syndrome, but data suggest morphine use in patients with unstable angina and non-ST segment elevation myocardial infarction may increase mortality. It should be used with great caution or avoided entirely in this patient group [258].

NEUROPSYCHIATRIC EFFECTS
Hallucinations are more strongly associated with mixed agonist/antagonist opioids and rarely occur with mu opioid agonists, with few exceptions. In fact, a review concluded that mu receptor agonist opioids were not only free of psychoses risk, but probably possesses antipsychotic activity yet to be characterized [259]. Other adverse CNS effects, including cognitive impairment, delirium, and generalized myoclonus, are associated with meperidine, morphine, or hydromorphone use in patients with renal impairment. In these patients, opioid metabolites accumulate to neurotoxic levels. The metabolites have anticholinergic activity, which can result in cognitive changes and delirium [123].

There is little research that sufficiently addresses brain response to chronic opioid therapy. Positron emission tomography and magnetic resonance imaging studies show changes in brain response to long-term opioid therapy in patients with chronic pain. However, it is unclear whether these neuroimaging findings are the result of the chronic pain or the opioid medication use [260].

Differential diagnosis is necessary in patients with suspected opioid-induced delirium to rule out dehydration, other CNS medications, sepsis, and hypercalcemia. Tactile hallucinations and myoclonus suggest opioid toxicity. Immediate delirium management consists of neuroleptics to control agitation and perceptual or delusional disturbances. Haloperidol is the first-line option; methotrimeprazine and chlorpromazine are alternative options, especially when sedation is beneficial. For resistant delirium, midazolam is preferred; lorazepam is used for comorbid anxiety. In cases of cognitive impairment in the absence of delirium, methylphenidate or modafinil may be used. These agents are not recommended with evidence of perceptual or delusional disturbances [123].

Opioid toxicity from accumulating neurotoxic metabolites may present with generalized myoclonus, sedation, confusion, or chronic nausea. This is generally resolved by opioid switching [123].

IMMUNOLOGIC CHANGES
The traditional view of opioids as immunosuppressive has been challenged by evidence showing a more complex role of opioid receptors in immune function. Different opioids or routes of administration act through different mechanisms to produce immunosuppressive, immunostimulatory, or dual immune effects. The impact of specific opioids on immune function probably result from a combination of direct effects on immunocytes and indirect effects on centrally mediated mechanisms, systemic production, and release of immuno-modulatory mediators [261].

The interaction between opioids and the immune system is complex. Trauma and severe pain alone are immunosuppressive, which is reversible by sufficient pain control [262]. Exogenous opioid drugs can induce immunosuppression, while endogenous opioids appear to promote immunostimulation.

Opioid therapy has been shown to inhibit humoral and cellular immune responses, including antibody production, lymphocyte activity, cytokine expression, and phagocytic activity. Potential underlying mechanisms include HPA modulation, sympathetic nervous system stimulation, and activation of mu opioid receptor on immune cells [263; 264]. Opioids vary by immune system interaction. Compared with morphine, tramadol produces greater enhancement in natural killer cell activity, lymphocyte proliferation, and interleukin-2 release, while buprenorphine produces a negligible effect on immune response [249].

ENDOCRINE EFFECTS
Opioid therapy can result in HPA suppression and hypopituitarism, clinically expressed as hypogonadism, impotence, infertility, and/or osteoporosis [265]. Opioid-induced hormone dysfunction has been observed in men and women with oral, transdermal, IV, and intrathecal administration [249].

Opioids appear to differ in degree of adverse effect on hormonal function. In one study, men receiving buprenorphine maintenance therapy for opioid addiction showed significantly higher plasma testosterone levels and less sexual dysfunction than those receiving methadone [266]. Although long-term opioid therapy produces a dose-dependent decrease in total and free testosterone level, serum hormone levels return to normal in both sexes shortly after opioid cessation. Not all men experience androgenic suppression with long-term opioid therapy; body mass index and smoking status are thought to increase the risk of opioid-induced hormonal dysfunction [249].
If a patient on opioid therapy complains of changes in libido or sexual dysfunction, treatment is empirical, with knowledge that multiple factors may be involved in the pathogenesis of sexual dysfunction. In these cases, non-opioid analgesics should be added to reduce or, if possible, discontinue the opioid. In men, testosterone replacement is indicated if serum testosterone is low and not contraindicated. Sildenafil or another phosphodiesterase type 5 inhibitor may be used for men experiencing sexual side effects [121; 123].

For women taking opioids with complaints of sexual side effects, dehydroepiandrosterone is the first-line option. This is because adrenal gland suppression is a greater contributor to female androgen deficiency. In younger women, oral contraceptives with a relatively androgenic progestin component may be used [121; 123].

ACETAMINOHEN TOXICITY
Several codeine, hydrocodone, and oxycodone formulations include acetaminophen. In the United States, acetaminophen toxicity has replaced viral hepatitis as the most common cause of acute liver failure and is the second most common cause of liver failure requiring transplantation [227]. In 2009, the FDA imposed a daily dose ceiling for acetaminophen of 4,000 mg; however, doses less than 4,000 mg per day can produce subclinical liver toxicity. Concurrent alcohol use also increases the risk, and chronic alcohol use is a high risk factor for fatal acetaminophen toxicity [222; 225]. It is crucial to use caution when prescribing any opioid preparation containing acetaminophen to older patients or patients with hepatic or renal disease.

OPIOID USE DISORDERS
There is no adequately validated instrument to differentiate pain patients who are at risk of dependence from those who are not. Research suggests that patients, even alcoholics, with no history of opioid dependence are not at heightened risk of becoming addicted with short-term opioid exposure. However, those with a positive history of dependence would benefit from active recovery efforts while receiving such medications.

Despite the rise in prescription opioid analgesic use and misuse, definitive data on the rate of dependence among patients administered opioids for acute pain does not yet exist. There is, however, agreement on how to minimize the risk of iatrogenic dependence. These steps include screening for risk potential based on a family history of substance abuse and the exploration of different delivery systems that adequately treat pain but minimize abuse potential. Although a pattern of aberrant behavior may be grounds for caution, a history of opioid misuse does not necessarily preclude a patient from successful treatment with an opioid. Screening for psychologic disorders is also advisable, including psychosomatic causes of pain.

CONCLUSION
Safety is the foundation of effective pain control with opioid prescribing. Safety risks are mitigated by understanding that most opioid analgesic overdoses involve co-ingested CNS sedatives or alcohol, with side effects, tolerability and analgesic response largely determined by comorbidities, drug interactions, and genetic variation.
Course Availability List

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**POSTOPERATIVE COMPLICATIONS**

**#30762** • 15 ANCC / 1 Pharm Hour

**Purpose:** The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.

**Faculty:** Susan Engman Lazear, RN, MN

**Audience:** This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

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**ACUTE CORONARY SYNDROME: AN OVERVIEW FOR NURSES**

**#30991** • 15 ANCC / 10 Pharm Hours

**Purpose:** The purpose of this course is to reduce the widening gap between care according to guidelines and actual care delivered by providing nurses with knowledge necessary to implement the most appropriate approach to diagnosis and treatment.

**Faculty:** Karen Majorowicz, RN, ARNP; Lori L. Alexander, MTPW, ELS, MWC

**Audience:** This course is designed for nurses practicing in primary care, inpatient, outpatient, and home care settings to enhance their knowledge of the evidence-based guidelines related to the assessment, management, and secondary prevention of acute coronary syndrome.

**Additional Approval:** AACN Synergy CERP Category A

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**NEWBORN ASSESSMENT**

**#32262** • 10 ANCC Hours

**Purpose:** The purpose of this course is to provide an overview of a newborn assessment for all nurses, especially those who either presently care for newborns or those who come in contact with them occasionally.

**Faculty:** Nicole F. Keehn, RN, MSN, PsyD; Katrina Lieben, MSN, CNM

**Audience:** This course is designed for all medical-surgical nurses and ancillary nursing personnel involved in the assessment of newborns.

**Additional Approval:** AACN Synergy CERP Category A

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**RENAL DISEASE AND FAILURE**

**#34231** • 10 ANCC / 5 Pharm Hours

**Purpose:** The purpose of this course is to provide primary care clinicians with the information necessary to appropriately identify and treat renal disease, with the objective of minimizing the long-term effects and complications of the disease.

**Faculty:** Carol Whelan, APRN

**Audience:** This course is designed for nurses involved in the care of patients with kidney disease or failure.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

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**TREATING PRESSURE ULCERS AND CHRONIC WOUNDS**

**#34571** • 5 ANCC / 1 Pharm Hour

**Purpose:** The purpose of this course is to provide nurses with information regarding the process of wound healing and interventions that may advance or hinder it in order to support the use of evidence-based practice and improve patient health.

**Faculty:** Maryam Mamou, BSN, RN, CRN, CWOCN

**Audience:** This course is designed for nurses in all care settings who may care for patients with pressure ulcers or chronic wounds.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

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**DIABETES PHARMACOLOGY**

**#35322** • 10 ANCC Hours

**Purpose:** The purpose of this course is to meet the needs of nursing professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.

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

**Audience:** This course is designed for nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

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## Course Availability List (Cont’d)

### ALZHEIMER DISEASE
**#96152 • 15 ANCC Hours**

**Purpose:** In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

**Faculty:** Joan Needham, MSEd, RNC  
**Audience:** This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

### BORDERLINE PERSONALITY DISORDER
**#96220 • 15 ANCC / 2 PHARM HOURS**

**Purpose:** The purpose of this course is to provide health and mental health professionals with the information necessary to assess and treat patients with borderline personality disorder effectively and safely, while minimizing their own stress level and clinic disruption these patients are capable of producing.

**Faculty:** Mark Rose, BS, MA  
**Audience:** This course is designed for physicians, physician assistants, and nurses who are involved in the care of patients with borderline personality disorder.

**Additional Approval:** AACN Synergy CERP Category A

### SUICIDE ASSESSMENT AND PREVENTION
**#96440 • 6 ANCC HOURS**

**Purpose:** The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

**Faculty:** Mark Rose, BS, MA  
**Audience:** This course is designed for physicians, nurses, psychologists, social workers, therapists, counselors, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

**Additional Approval:** AACN Synergy CERP Category A

### CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT
**#97532 • 2 ANCC Hours**

**Purpose:** The purpose of this course is to enable healthcare professionals in all practice settings to define child abuse and identify the children who are affected by violence. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of New York for child abuse victims.

**Faculty:** Alice Yick Flanagan, PhD, MSW  
**Audience:** This course is designed for all New York physicians, physician assistants, nurses, and other professionals required to complete child abuse education.

**Additional Approval:** AACN Synergy CERP Category B

**Special Approval:** This course is approved by the New York State Education Department to fulfill the requirement for 2 hours of training in the Identification and Reporting of Child Abuse and Maltreatment. Provider #80673.

### HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW
**#98392 • 10 ANCC / 5 PHARM HOURS**

**Purpose:** Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals’ awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients’ medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

**Faculty:** A. José Lança, MD, PhD  
**Audience:** This course is primarily designed for physicians and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

**Additional Approval:** AACN Synergy CERP Category A

### INFECTION CONTROL: THE NEW YORK REQUIREMENT
**#98641 • 5 ANCC / 1 PHARM HOUR**

**Purpose:** The purpose of this course is to provide a review of current infection control practices and accepted standards, with an emphasis on the application of infection control standards and practices in outpatient and ambulatory settings.

**Faculty:** Lori L. Alexander, MTPW, ELS, MWC  
**Audience:** This course is designed for physicians, physician assistants, nurses, and other healthcare professionals in New York required to complete education to enhance their knowledge of infection control.

**Additional Approval:** AACN Synergy CERP Category A

**Special Approval:** This course is approved by the New York State Department of Health to fulfill the requirement for 3 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #TP02078.

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